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RESEARCH ARTICLE

REVISED Mean Platelet Volume (MPV) as an indicator of disease activity and severity in lupus [version 3; referees: 2 approved]

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Abstract

Background: Amongst the different clinical and laboratory parameters used to monitor disease activity in systemic lupus erythematosus (SLE), mean platelet volume (MPV) is a novel biomarker. Although MPV has been studied in other rheumatological conditions like rheumatoid arthritis, its role in adult SLE needs to be defined, especially in Pakistan. **Methods:** The aim of this study was to evaluate the role of MPV as a biomarker of disease activity in SLE. Fifty patients were recruited through a consecutive non-probability sampling technique for this cross-sectional study. On the basis of their SLE disease activity index (SLEDAI) score of greater or lesser than 5, these 50 participants were divided into two equal groups respectively; 25 patients with active SLE, and another 25 participants with stable, inactive lupus. MPV was measured in each group and compared using SPSS version 16. MPV was also correlated with SLEDAI and erythrocyte sedimentation rate (ESR). Independent sample t-test and Spearman's rho and Pearson's correlation tests were applied. Sensitivity and specificity of MPV were checked through ROC analysis. **Results:** The MPV of patients with active SLE (n=25, mean [M]=7.12, SD=1.01) was numerically lower than those in the inactive-SLE group (n=25, M= 10.12, SD=0.97), and this was statistically significant ($P<0.001$). MPV had an inverse relationship with both ESR (r=-0.93, $P<0.001$) and SLEDAI (r_s= -0.89, $P<0.001$). However, there was a strong positive correlation between ESR and SLEDAI (r_s=0.90, $P<0.001$). For MPV, a cutoff value of less than 8.5fl had a sensitivity of 92% and a specificity of 100% ($P< 0.001$). **Conclusions:** Higher disease activity in SLE is associated with a correspondingly low MPV.

This article is included in the Lupus nephritis and neuropsychiatric lupus channel.

Open Peer Review

Referee Status: ✓ ✓

	Invited Referees	
	1	**2**
REVISED **version 3** published 16 Mar 2017	✓ report	
REVISED **version 2** published 24 Feb 2017	? report	✓ report
version 1 published 10 Feb 2017	? report	? report

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Comments (0)

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Competing interests: No competing interests were disclosed.

> **REVISED** **Amendments from Version 2**
>
> This revised version has the following changes;
> 1: More details about sample size determination have now been included. Previous studies used for sample size calculation have been referred to.
> 2: Association between MPV and SLEDAI has been reassessed by using Spearman's rho correlation test. Moreover, discussion has been slightly rephrased at two points (see reviewer's report 2 and authors' response).
>
> **See referee reports**

Abbreviations

MPV: Mean Platelet Volume, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, SLE: Systemic Lupus Erythematosus, ESR: Erythrocyte Sedimentation Rate, CRP: C-reactive Protein, ACR: American College of Rheumatology.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that can affect any organ system of the body. It has an annual incidence of 5 per 100,000 of the general population[1]. There are racial and ethnic variations, with higher rates reported in Black and Hispanic peoples[2]. Usually, this disease with protean manifestations has a remitting relapsing course; however, it has a tendency to vary from acutely progressive to chronic indolent forms[1,2].

The clinical manifestations of SLE range from constitutional symptoms, such as fever, sweats, weight loss, joint pains and skin rashes (including the classic butter fly rash), to more serious features, including the involvement of the central nervous system and kidneys. However, to make a clinical diagnosis of SLE, simultaneous or sequential presence of 4 out of a total of 11 criteria, proposed by the American College of Rheumatology (ACR), must be present[3,4].

Considering the remitting relapsing nature of most cases of SLE, it is important to have a biomarker to monitor its disease activity. Although, the most effective and reliable tool to measure SLE disease activity is still open to debate, there are fortunately many validated measures, including the Systemic Lupus Activity Measure, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Lupus Activity Index, European Consensus Lupus Activity Measurement, and British Isles Lupus Activity Group[5]. These tools have been found to be beneficial in day to day practice[6,7].

Notable issues, apart from some other technical limitations, with the aforementioned severity assessment indices are that, these validated instruments are confusing, lengthy and time consuming. However, very recently, mean platelet volume (MPV) has been shown to be a very good and easily accessible marker of disease activity in lupus as well as in antiphospholipid syndrome (APS)[8–10]. Moreover, a recent study not only demonstrated an inverse relationship between MPV and disease severity in lupus, but also suggested serum albumin as another effective indicator of prognosis in such people[11]. Although MPV has been studied well as a simple but reliable inflammatory biomarker in several diseases, such as rheumatoid arthritis, scleroderma, rheumatic fever, ankylosing spondylitis and even chronic obstructive pulmonary disease, there is still a relative scarcity of its role as a disease severity indicator in lupus[12–16]. Therefore, we performed the present study to find out whether MPV does or does not correlate with SLEDAI and whether it can be used a predictor of lupus severity and activity.

Methods

Patient characteristics

This cross-sectional study was conducted in the Department of Medicine of Khyber Teaching Hospital (KTH; Peshawar, Pakistan) between January 2015 and July 2016. Medical records, intranet of our hospital and referrals by the general practitioners were the sources of recruitment. Patient information sheet, letters and direct contact by the investigators, who were directly involved in the provision of healthcare to potential subjects, were the chief methods of recruitment. This study was approved by the Ethics Review Committee of the hospital and a written informed consent was obtained from every participant (approval number, KTH/2015/Med-A/86C). The patient sample was collected using a consecutive-non-probability sampling technique. Nevertheless, as is true of cross-sectional studies, confounding and sample selection bias may be limitations to the generalization of our results.

Patients from both genders in the age range of 18–70 years, and those with both either newly diagnosed or pre-existing SLE were included in the study. In order to avoid bias, only those patients with a normal platelet count were included. This is because, MPV is influenced by the number of platelets in circulation. The ACR criteria for the diagnosis of SLE was used as a diagnostic tool.

Individuals who had history of smoking, acute or chronic infectious diseases, hemoglobin >16.5 g/dl, thrombocytopenia (platelets <150,000/mm^3), hypertension, angina pectoris, myocardial infarction, diabetes mellitus, hypo- or hyperthyroidism, anti-phospholipid syndrome, recurrent miscarriage, amyloidosis, thrombosis and acute or chronic renal failure were excluded from the study. Patients who had either clinical, biochemical or serological evidence of an autoimmune disorder other than SLE, such as rheumatoid arthritis, Sjogren's syndrome or scleroderma, were also excluded from the study. All these aforementioned conditions influence platelet number and/or size. As these conditions act as potential confounders, their inclusion would have caused a selection bias in our study results.

The sample size was calculated by using the frequency of low MPV in patients with actively flaring lupus from the previous studies, along-with a 5% margin of error and 95% CI on the WHO's formula for determination of sample size in health studies (http://www.who.int/chp/steps/resources/sampling/en/). Moreover, based on recent published data regarding the association of MPV with disease activity in SLE[9–11], sample size was doubly checked by using comparisons of means. Sample size calculation was performed by using $\alpha = 0.05$, $\beta = 0.20$, and two tails. It was demonstrated that, a sample size of 50 (25 participants per group) would yield a statistically significant study with a power of 80%. A total of 64 patients were assessed initially. However, only 50 of them satisfied the inclusion and exclusion criteria. The

50 participants recruited were divided into two equal groups, 25 subjects each in the active-SLE and the inactive-SLE groups, as detailed below.

SLEDAI

The participants were divided into two groups, active and inactive SLE groups. The division of the patients into two groups was based on their final score from using the Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2000)[17]. The previously published literature demonstrated a mean cut-off score of 5 or higher on SLEDAI-2000 as an effective indicator of actively flaring lupus[17]. Considering a mean cut-off score of 5 or more on SLEDAI-2000 as significant indicator of disease activity in lupus, those who scored 5 or higher were classified as active-SLE, while those with a final mean score of less than 5 were regarded as patients with inactive-SLE. Patients with active-SLE, fulfilling the inclusion criteria (SLEDAI-2000), were admitted to any one of the five medical wards of KTH for further workup and treatment. However, those with stable inactive disease were recruited in the study from the Outpatient Department of KTH.

Measurement of MPV

A total of 5ml of venous blood was taken in an EDTA tube from every participant for the measurement of complete blood count, including hemoglobin, white blood cells, platelets, MPV, and erythrocyte sedimentation rate (ESR). All the blood samples were analyzed within less than one hour after sampling. The complete blood count, including all the hematological parameters, was performed using the same hematology analyzer, Medonic. The tests were performed and read by the same laboratory technician of KTH.

Data analysis

All the data was entered on a structured questionnaire specifically designed for this study (Supplementary File 1). Data was transferred to and analyzed using SPSS version 16. Means and standard deviations were determined for quantitative variables. Independent sample t-test was run to compare means of MPV between the two groups. ROC analysis was performed to estimate cutoff values for sensitivity and specificity of MPV. Spearman's rho correlation test was used to assess any association of MPV and ESR with SLEDAI. Similarly, MPV was correlated with ESR through Pearson's correlation test. P value of less than 0.05 was considered as significant.

Results

Of the 50 participants, 84% were female and 16% were male. There were 4 males and 21 females in each of the active- and inactive-SLE groups, respectively. Other demographic details are shown below (Table 1). The overall mean age of all the participants was 27.94±2.52 years. The mean age of the patients in the active-SLE group (M=27.84, SD=2.06) was comparable to the inactive-SLE group (M=29.60, SD= 2.38). The clinical features of patients with active- and inactive-SLE are shown in Table 2 and Table 3, respectively. In the active-SLE group, 11 (44%) patients had evidence of clinically significant proteinuria; details of the histological sub-type of lupus nephritis are given in Table 4.

Table 1. Demographic details of patients in each group (n=25).

Characteristic	Active-SLE (n=25)	Inactive-SLE (n=25)
Males	16%	16%
Females	84%	84%
Pregnant Females	16%	24%
Outdoor workers (sun exposed)	28%	24%
Indoor workers (least sun exposed)	72%	76%
History of recurrence	20%	36%
Pakistanis	84%	88%
Afghans	16%	12%

Table 2. Overview of clinical characteristics of patients with active-SLE.

CLINICAL FEATURES	PATIENTS, N (%)
Polyarthritis	22 (88)
Butterfly rash	16 (64)
Photosensitivity	20 (80)
Patchy alopecia	15 (60)
Pleurisy	14 (56)
Pericarditis	2 (8)
Neuropsychiatric problems	13 (52)
Oral ulcers	20 (80)
Proteinuria (>0.5gm/day)	11 (44)
Anti-dsDNA antibodies	24 (96)
Antinuclear factor	23 (92)

Table 3. Overview of the clinical characteristics of patients with inactive-SLE.

CLINICAL FEATURES	PATIENTS, N (%)
Non-specific aches and pains	17 (67)
Malaise	14 (54)
Dyspepsia	13 (53)
Anorexia	10 (40)
Photosensitivity	6 (23)
Non-scarring alopecia	5 (19)

Table 4. Overview of the renal histology in 11 patients with active-SLE and proteinuira.

Histological type of lupus nephritis	Patients, N (%)
Focal proliferative glomerulonephritis	3 (27)
Diffuse proliferative glomerulonephritis	7 (64)
Membranous glomerulonephritis	1 (9)

The MPV of patients with active-SLE (n=25, M=7.12, SD=1.01) was numerically lower than those in the inactive-SLE group (n=25, M= 10.12, SD=0.97). An independent sample t-test was run to compare the means of the two groups. The assumption of normality was tested by Kolmogorov-Samirnov test and was found tenable (*P*> 0.05). Moreover, similar results were obtained on Skewness and Kurosis testing (skewness=0.01, kurtosis= -1.06). The assumption of homogeneity of variances was tested using Levene's test and was found tenable (F (48) = 0.23; *P*= 0.63). The results of the independent t-test showed a statistically significant difference between the mean values of MPV of the two groups(t (48) = 10.69; *P*<0.001; Cohen's D= 3.02). The 95% Confidence Interval (CI) was -3.56 to -2.44. Receiver operator characteristic (ROC) curve was used to check the specificity and sensitivity of MPV (Figure 1). The ROC curve had an area under the curve of 0.98. At a value of 8.5fl for MPV, the sensitivity and specificity were 92% and 100%, respectively, (*P*<0.001;95%CI -0.96 to +1.01). At a cutoff value of 8.5fl, MPV has a maximum sensitivity and specificity. Therefore, we recommend that, at an MPV value of <8.5fl, the probability of SLE increases remarkably.
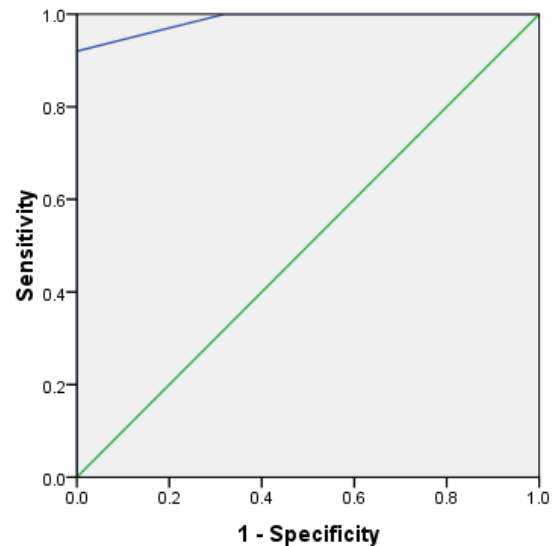
The SLEDAI scores between the two groups, active-SLE (M=16.36, SD=4.48) and inactive-SLE (M=3, SD=0.82), varied at a statistically significant level of *P*<0.001. The ESR was higher in patients with active SLE (M=49.52, SD=12.93) than those with stable disease (M=13.76 SD=1.72)(*P*<0.001). The details of the different hematological parameters are given in Table 5.

Pearson's correlation test was run to assess any relationship between MPV, and ESR in the active-SLE group. The results showed a statistically significant, negative correlation of MPV with ESR (r= -0.93, *P*<0.001). The spearman's rho correlation demonstrated that, MPV had a strong but inverse correlation with SLEDAI, (r_s= -.89, *P*<0.001). However, it showed a strong but positive correlation between ESR and SLEDAI (r_s=0.90, *P*<0.001). Hence, it can be argued that increased disease activity of SLE is associated with both a higher ESR and SLEDAI score, and a correspondingly low MPV (*P*<0.001).

Figure 1. ROC analysis for sensitivity and specificity of mean platelet volume.

Table 5. Comparison of different test variables between the two study groups. SLEDAI, Systemic Lupus Erythematosus Disease Activity; MPV, mean platelet volume; ESR, erythrocyte sedimentation rate; WBC, white blood cells; Hb, hemoglobin.

Variable	Active-SLE		Inactive-SLE		P value
	Mean	SD	Mean	SD	
SLEDAI	16.36	4.48	3.00	0.82	< 0.001
MPV (fl)	7.12	1.01	10.12	0.97	< 0.001
ESR (1st hour)	49.52	12.93	13.76	1.72	< 0.001
Platelets×10³/mm³	259.72	1.10	259.68	1.03	0.89
WBC/mm³	5422.00	396.68	5896.00	79.53	< 0.001
Hb (gm/dl)	11.64	1.04	13.56	0.87	< 0.001

Discussion

SLE, which is more common in Black women, has a female to male ratio of approximately 9:1[12]. Our study group comprised of 84% female and 16% male population. Furthermore, most of the participants in our study were in the third decade of life. Participants with active-SLE were younger than those with the stable form of the disease. These findings are comparable to international statistics[18,19]. We observed that MPV was significantly lower in patients with active lupus than those without a flare. Similarly, we found that, MPV had a tendency to be lower with a correspondingly higher ESR in individuals with actively flaring SLE and vice versa. Moreover, MPV had a significant inverse correlation with both SLEDAI and ESR. Thus, it can be argued that, as an indicator of disease activity in patients with SLE, MPV may be a

breakthrough hematological biomarker to monitor disease activity along-with both ESR and SLEDAI-2000.

Gasparyan *et al.* concluded that high MPV correlated with a variety of diseases, like cardio- and cerebrovascular disorders, venous and arterial thrombosis and low-grade inflammatory conditions[20]. However, it was observed that, high intensity inflammatory disorders, such as active rheumatoid arthritis or relapses of familial Mediterranean fever, had low values of MPV, which could be reverted with anti-inflammatory medications[21–23]. Although we did not check the effect of anti-inflammatory medications, like corticosteroids, on MPV, we observed a strong inverse relationship of MPV with lupus severity and activity. Therefore, we recommend MPV as one of the markers of disease activity in patients with SLE.

Apart from MPV, ESR has traditionally been used as a marker of disease severity in patients with inflammatory conditions, and SLE, specifically[24]. Similarly, SLEDAI was promulgated in 1985 as a tool to assess disease activity in lupus. This was later modified in 2002 and re-introduced as SLEDAI-2000[25]. SLEDAI-2000 has been validated against classic SLEDAI and is an important predictor of prognosis and mortality[26]. High disease activity will increase ESR and SLEDAI-2000 score[24,26]. Our study demonstrated that, MPV correlated inversely with both ESR and SLEDAI-2000. Thus it can be stated that, actively flaring lupus in a given patient will be characterized by a higher ESR and SLEDAI-2000 score and a correspondingly lower MPV.

Why is MPV low in active SLE? The answer cannot be clearly stated. However, previous studies have shown that, in active inflammatory conditions, especially rheumatoid arthritis, large and activated platelets are consumed preferentially at the site of inflammation, leaving small platelets behind[21,22]. This may also explain lower MPV values in actively flaring SLE patients in our study group as well as in other studies which demonstrated lower MPV values in patients with active lupus[11].

Considering active-SLE as a state of severe inflammation, those with active disease in our study were treated with 1g daily dose of methylprednisolone for three days, followed by a maintenance dose of 1mg/Kg oral prednisolone for another 4–6 weeks. Although, all participants with active lupus achieved dramatic symptomatic and clinically obvious improvement, MPV was not studied after the completion of steroid therapy. However, in other studies, where pre-treatment MPV was compared with post-treatment MPV, it was observed that, after successful treatment with anti-inflammatory medications, MPV reverted back to normal[22–27]. Considering this data, we would advocate future studies focusing on comparing pre- and post-treatment MPV in patients treated with corticosteroids for acute flare of SLE.

It is noteworthy that; although, most of the studies found an inverse relationship between active-SLE and MPV in adults, a positive association was observed between MPV and disease activity in juvenile lupus erythematosus[10]. A similar observation was demonstrated in an Indian study by Sarkar RN *et al.*[28]. These findings of positive correlation between MPV and disease activity in lupus are in sharp contrast to the results of our and similar previous studies[8,9].

Notably, the results of this study were in accordance with the expectations of authors. Moreover, considering recent research studies showing a link between low MPV and disease activity in SLE patients, our study will add further evidence. However a limitation to the conduct and results of this study was a small sample size. This is because, SLE is not very common in Pakistan. Therefore, in order to highlight the actual role of MPV as a biomarker of lupus severity, we recommend that, cohort studies should be done in future, both in Pakistan and abroad.

Conclusions
MPV is an excellent biomarker to assess disease activity in SLE, as higher disease activity will reduce MPV. Moreover, MPV has an inverse relationship with both ESR and SLEDAI. At a cutoff value of less than 8.5fl, MPV has an excellent sensitivity and specificity for determining disease activity in SLE.

Ethics approval and consent
This study was approved by Ethics Review Committee of Khyber Teaching Hospital, Peshawar, Pakistan (approval number, KTH/2015/Med-A/86C). Informed written consent was obtained from every participant.

Data availability
Dataset 1: Raw data of disease severity indicators in lupus. This file contains data regarding disease severity indicators and demographics of patients with SLE. This coded data was stored on SPSS version 16. Group: 1, active-SLE; 2, inactive-SLE. Gender: 1, male; 2, female. SLEDAI, systemic lupus erythematosus disease activity index; MPV, mean platelet volume; ESR, erythrocyte sedimentation rate; WBC, white blood cell (thousand/mm^3); Hb, hemoglobin (gm/dl); platelets, platelet count $\times$ 10^3. doi, 10.5256/f1000research.10763.d151064[29]

Supplementary material

Supplementary File 1: Lupus severity and disease activity questionnaire. This questionnaire was used to gather data from the partici-pants. SLEDAI, systemic lupus erythematosus disease activity index; MPV, mean platelet volume; ESR, erythrocyte sedimentation rate; WBC, white blood cell (thousand/mm³); active SLE, SLEDAI >5 points; inactive SLE, SLEDAI <5 points.

Click here to access the data.

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Data Source

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Current Referee Status: ✔ ✔

Version 3

Referee Report 20 March 2017

✔ **Guillermo Delgado-García** (iD)

National Institute of Neurology and Neurosurgery, Mexico City, Mexico

It has been a pleasure for me to review your valuable work. I applaud again your academic openness and your critical spirit. I want to add the following:

5. This point was appropriately addressed.

8. This point was appropriately addressed.

10. This point was appropriately addressed.

12. This point was addressed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: Last year our team published an article on this same topic (Rev Bras Reumatol. 2016 Nov-Dec;56[6]:504-8). No financial competing interests.

Version 2

Referee Report 14 March 2017

✔ **Alina Dima** (iD)

Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Dear authors,

Thank you for all changes made.

Best regards,

AD

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 28 February 2017

doi:10.5256/f1000research.11885.r20506

Guillermo Delgado-García (iD)

National Institute of Neurology and Neurosurgery, Mexico City, Mexico

First of all I want to thank Abidullah Khan (Pakistan) for his punctual answers, and in the same way I take this opportunity to applaud his openness to academic debate. I want to add the following:

1. This point was appropriately addressed.

2. This point was appropriately addressed.

3. This point was appropriately addressed. However, I am not sure if we are falling into a conflict of interest by including an article written by the reviewer under the suggestion of the same reviewer. If possible, I would like to leave this decision to another reviewer in order to avoid any conflict of interest.

4. This point was appropriately addressed.

5. Taking into account that you also used a formula to determine the appropriate sample size for detecting a difference between the means of two samples, I think it would be good to cite the previous report on which this calculation was based (i.e., the article from where you got the values to make your sample size estimation). Likewise, I think it would be good to know how much is "more than 0.8" (power).

6. This point was appropriately addressed.

7. I agree with your proposal, so lets leave them in two separate tables.

8. The final SLEDAI score is an ordinal variable [1], so I consider that it would be more appropriate to evaluate the correlation between this variable and MPV using Spearman's rho.

9. This point was appropriately addressed.

10. I do not know if you are close to the word limit. If this is not the case, perhaps it would also be worth mentioning the studies in adults [2] that yielded results similar to the study in patients with juvenile lupus [3].

11. This point was appropriately addressed.

An additional final comment:

12. The following lines in the Discussion seem particularly bold to me, perhaps it would be worth rephrasing them:

a) "Thus, it can be argued that, as an indicator of disease activity in patients with SLE, MPV was **as effective** as both ESR and SLEDAI-2000".

b) "Therefore, we recommend MPV as a global marker of disease activity in patients with SLE".

References

1. Lew RA, Liang MH, Doros G: Statistical considerations for stopping systemic lupus erythematosus clinical trials earlier.*Arthritis Res Ther*. 2015; **17**: 345 PubMed Abstract | Publisher Full Text
2. Sarkar RN, Bhattacharya K, Banerjee M: Mean platelet volume as an indicator of disease activity in systemic lupus erythematosus.*J Assoc Physicians India*. 2016; **64** (1): 68-69 PubMed Abstract
3. Yavuz S, Ece A: Mean platelet volume as an indicator of disease activity in juvenile SLE.*Clin Rheumatol*. 2014; **33** (5): 637-41 PubMed Abstract | Publisher Full Text

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: Last year our team published an article on this same topic (Rev Bras Reumatol. 2016 Nov-Dec;56[6]:504-8). No financial competing interests.

Author Response 06 Mar 2017

Abidullah Khan, Khyber Teaching Hospital/ Khyber Medical College, Peshawar, Pakistan

Thank you again very much for your precious time and tremendous energy in revisiting our manuscript critically. We have made the following changes in response to your remaining invaluable reservations.

5: Taking into account that you also used a formula to determine the appropriate sample size for detecting a difference between the means of two samples, I think it would be good to cite the previous report on which this calculation was based (i.e., the article from where you got the values to make your sample size estimation). Likewise, I think it would be good to know how much is "more than 0.8" (power).
Reply: This has been amended as advised.

8: The final SLEDAI score is an ordinal variable [1], so I consider that it would be more appropriate to evaluate the correlation between this variable and MPV using Spearman's rho.
Reply: Spearman's rho has been used to assess any relationship of MPV and ESR with SLEDAI. However, the relation of MPV with ESR has been assessed through Pearson's correlation test.

10: The Indian study has now been referred to. The study by Yavuz S et al had already been cited.

Additional comments: The final two sentences pointed to (a and b), have been rephrased.

I hope it works this time. Thanks again.

Competing Interests: No competing interests were disclosed.

Version 1

Referee Report 17 February 2017

Alina Dima (iD)

Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

1. **Title**: I don't find the term "monitoring" appropriate as it is presented a cross-sectional study with only one MPV determination and I so think that the use of assessment or determination could be tried.
   Also the term MPV (as possible marker of SLE disease activity) should be included in title.

2. **Abstract**: First two phrases of the abstract are too general, not directly related to this article subject. I think that for the background the idea MPV – activity – Inflammation – SLE is enough.
   In the method we understand that 25 patients with active vs. 25 inactive were chosen ... it should be clear noted; e.g. cross-sectional, prospective, successively inclusion and then how the two subgroups were defined.
   I don't think that the details of statistic should appear in the abstract - methods, maybe a more detailed conclusion.

3. **Introduction**: As for the abstract, I find the first two paragraphs are too general, not directly related to the article topic.
   For the classification criteria, instead of classification criteria up-dated ACR 1997 (that should be cited properly) I would propose the use of SLICC 2012 or both criteria sets; but anyway, the diagnosis would be the same as the last criteria set is more sensitive.

4. **Methods/ Results**: There are many exclusion criteria presented, maybe there could be some words in introduction or discussion about these factors influence on MPV (as it was discussed for thrombocytopenia) and reasons of exclusion.
   I understand from methods that it was a cross-sectional study with random, consecutive inclusion and then the lot was split in two groups according to SLE disease activity (assessed by SLEDAI). How was the SLEDAI cut-off of 5 points determined? This cut-off appears in previous published research, it is the mean value (as I understand all variables turned out to be parametric), or the group was split in two groups of similar patients number?
   And then, the bivariate correlations were realized only in the group with active SLE, so the results are applicable only in this subgroup of patients.
   I would propose a logistic regression for the entire lot (50 patients), with MPV, ESR (and adjusted for age and gender) as predictors for high SLEDAI.
   However, the degree of correlation obtained is very high and so it sustains the research

conclusion.

5. **Discussion**: the phrase "SLEDAI was as effective as both ESR and MPV" should be written differently (MPV was correlated with/ is an effective marker of ...) as the research is about MPV, disease activity was assessed by SLEDAI and ESR was noted as parameter known to correlates with disease activity.
    In the third paragraph, I don't find a relation between the discussion on CRP and the same paragraph last phrase. Of course, data on ESR usefulness as marker of SLE disease activity should be discussed in order to understand why SLEDAI and ESR as standard. And maybe also data on ESR and MPV in lupus or other diseases, if there are.

6. **Conclusion**: I think that the first phrase of conclusion should be reformulated. The term "monitor" I already discussed; "higher disease will reduce MPV" could be more specific; and "vice versa" I'm not sure that this can be concluded as the study does not discuss distinctly the relation between higher MPV with lower activity in the subgroup of inactive lupus patients (of course, it looks logical). I think also that the present last phrase of conclusion should be ended " sensitivity and specificity for ..." and in active SLE, without APS ...

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: An article in which I am co-author was cited in the present research. No financial competing interests.

Author Response 21 Feb 2017

Abidullah Khan, Khyber Teaching Hospital/ Khyber Medical College, Peshawar, Pakistan

We are really grateful to Alina Dima for her invaluable comments on our article. Please find below a point-wise response to the comments.

1. **Title**: "I don't find the term "monitoring" appropriate as it is presented a cross-sectional study with only one MPV determination and I so think that the use of assessment or determination could be tried. Also the term MPV (as possible marker of SLE disease activity) should be included in title."
    Reply: This suggestion has been incorporated.

2. **Abstract**: "First two phrases of the abstract are too general, not directly related to this article subject. I think that for the background the idea MPV – activity – Inflammation – SLE is enough. In the method we understand that 25 patients with active vs. 25 inactive were chosen ... it should be clear noted; e.g. cross-sectional, prospective, successively inclusion and then how the two subgroups were defined. I don't think that the details of statistic should appear in the abstract - methods, maybe a more detailed conclusion."
    Reply: Abstract has been re-phrased as suggested. However, we believe that, the statistics should appear in the abstract, as they give an overall idea to the researcher of what we did and what s/he may expect to find in the results?

3. **Introduction**: As for the abstract, I find the first two paragraphs are too general, not directly related to the article topic. For the classification criteria, instead of classification criteria up-dated ACR 1997 (that should be cited properly) I would propose the use of SLICC 2012

or both criteria sets; but anyway, the diagnosis would be the same as the last criteria set is more sensitive.

Reply: We have intentionally left the first two paragraphs as general looking. This is for the purpose of education of the young researchers and to give an impression as, how does SLE behave normally ?

4. **Methods/ Results**: There are many exclusion criteria presented, maybe there could be some words in introduction or discussion about these factors influence on MPV (as it was discussed for thrombocytopenia) and reasons of exclusion.
Reply: Sentence has now been added regarding the influence of the set exclusion criteria on MPV and the study results.

I understand from methods that it was a cross-sectional study with random, consecutive inclusion and then the lot was split in two groups according to SLE disease activity (assessed by SLEDAI). How was the SLEDAI cut-off of 5 points determined? This cut-off appears in previous published research, it is the mean value (as I understand all variables turned out to be parametric), or the group was split in two groups of similar patients number? And then, the bivariate correlations were realized only in the group with active SLE, so the results are applicable only in this subgroup of patients. I would propose a logistic regression for the entire lot (50 patients), with MPV, ESR (and adjusted for age and gender) as predictors for high SLEDAI. However, the degree of correlation obtained is very high and so it sustains the research conclusion.
Reply: The recommended changes have been made.

5. **Discussion**: the phrase "SLEDAI was as effective as both ESR and MPV" should be written differently (MPV was correlated with/ is an effective marker of ...) as the research is about MPV, disease activity was assessed by SLEDAI and ESR was noted as parameter known to correlates with disease activity. In the third paragraph, I don't find a relation between the discussion on CRP and the same paragraph last phrase. Of course, data on ESR usefulness as marker of SLE disease activity should be discussed in order to understand why SLEDAI and ESR as standard. And maybe also data on ESR and MPV in lupus or other diseases, if there are.
Reply: Discussion has been modified at points suggested by the respectable reviewer.

6. **Conclusion**: I think that the first phrase of conclusion should be reformulated. The term "monitor" I already discussed; "higher disease will reduce MPV" could be more specific; and "vice versa" I'm not sure that this can be concluded as the study does not discuss distinctly the relation between higher MPV with lower activity in the subgroup of inactive lupus patients (of course, it looks logical). I think also that the present last phrase of conclusion should be ended " sensitivity and specificity for ..." and in active SLE, without APS ...
Reply: The conclusion has been amended as recommended by the reviewer. Moreover, the term 'vice versa' has been removed.

Thank you once more for your time and precious comments.

Competing Interests: No competing interests to declare.

Referee Report 13 February 2017

Guillermo Delgado-García iD

National Institute of Neurology and Neurosurgery, Mexico City, Mexico

In this study, Khan et al explored the relationship between SLE disease activity and mean platelet volume (MPV). After reading this article, I have the following suggestions:

1. I think it would be good if the title were more specific (perhaps including such terms as "platelet size" or "platelet volume").

2. Contrary to what is mentioned in the last paragraph of the Introduction, Rupa-Matysek et al.[1] did not include SLE patients in their study.

3. Our team also published an article on this topic[2], which is not mentioned in the Introduction, even when it appeared online before that of Yolbas et al[3].

4. I would like to know if the sampling technique was consecutive or random. I'm inclined to think that consecutive (i.e., non-random) sampling was used.

5. I'm not sure if this STEPS Sample Size Calculator was the ideal one to estimate the sample size in the present study. I would like to know what other values were used in this calculation (level of confidence measure, MOE, baseline levels of the indicators, Deff, etc). I would also like to know which outcome was used to estimate the sample size. MPV? If so, why was not used a formula to determine the appropriate sample size for detecting a difference between the means of two samples?

6. One merit of this study when comparing it with others is that all the blood samples were analyzed within less than one hour after sampling, since MPV increases over time in EDTA tubes.

7. I think that the bar chart is not ideal to display demographic information. Perhaps one table could be just enough.

8. I suggest the first two tables could be merged into one.

9. When calculating the correlations it is important to remember that the SLEDAI is an ordinal variable [4].

10. In the discussion, when addressing the issue of pathophysiological mechanisms that could explain the decrease in MPV, two articles are cited. However, contrary to what is mentioned, neither of these articles deals with SLE patients.

11. It would be worthwhile to further discuss the findings of this study by comparing them more specifically with the other studies on this same topic.

12. There are some grammatical errors that would be worth correcting (e.g., an unnecessary semicolon in the second paragraph of the Methods).

References

1. Rupa-Matysek J, Gil L, Wojtasińska E, Ciepłuch K, Lewandowska M, Komarnicki M: The relationship between mean platelet volume and thrombosis recurrence in patients diagnosed with antiphospholipid syndrome.*Rheumatol Int*. 2014; **34** (11): 1599-605 PubMed Abstract | Publisher Full Text

2. Delgado-García G, Galarza-Delgado DÁ, Colunga-Pedraza I, Borjas-Almaguer OD, Mandujano-Cruz I, Benavides-Salgado D, Martínez-Granados RJ, Atilano-Díaz A: Mean platelet volume is decreased in adults with active lupus disease.*Rev Bras Reumatol Engl Ed*. **56** (6): 504-508 PubMed Abstract | Publisher Full Text

3. Yolbas S, Yildirim A, Gozel N, Uz B, Koca SS: Hematological Indices May Be Useful in the Diagnosis of Systemic Lupus Erythematosus and in Determining Disease Activity in Behçet's Disease.*Med Princ Pract*. 2016; **25** (6): 510-516 PubMed Abstract | Publisher Full Text

4. Lew RA, Liang MH, Doros G: Statistical considerations for stopping systemic lupus erythematosus clinical trials earlier.*Arthritis Res Ther*. 2015; **17**: 345 PubMed Abstract | Publisher Full Text

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: Financial competing interests: No competing interests were disclosed. Non-financial competing interests: Last year our team published an article on this same topic (Rev Bras Reumatol. 2016 Nov-Dec;56[6]:504-8).

Author Response 21 Feb 2017

Abidullah Khan, Khyber Teaching Hospital/ Khyber Medical College, Peshawar, Pakistan

We thank Guillermo Delgado-Garcia from Mexico for reading our manuscript thoroughly and for pin-pointing various discrepancies. We have now corrected the shortcomings and we believe that, the changes made in the light of recommendation of our honorable reviewer will add a lot to the science of our article. Please find below, a point-by-point response to the reviewers comments;

1. The title of the article has been modified as suggested.

2. "*Contrary to what is mentioned in the last paragraph of the Introduction, Rupa-Matysek et al. did not include SLE patients in their study*".
   This has been rephrased. Thank you for identifying this.

3. The article published by your team is very informative and has now been referred to.

4. The sampling technique was consecutive. The sentence has been rewritten. Sorry for the mistake in version 1.

5. *"I'm not sure if this STEPS Sample Size Calculator was the ideal one to estimate the sample size in the present study. I would like to know what other values were used in this calculation (level of confidence measure, MOE, baseline levels of the indicators, Deff, etc). I would also like to know which outcome was used to estimate the sample size. MPV? If so, why was not used a formula to determine the appropriate sample size for detecting a difference between the means of two samples?"*
   We used both the methods. However, we mentioned the WHO sample size calculator only.

All the missing info has now been added.

6. Thanks for your appreciation of the merits of our study.

7. Bar chart has now been replaced with a table as suggested.

8. ***"I suggest the first two tables could be merged into one".***
   Merging the two tables will make the tables look lengthy and possibly confusing. Therefore, we believe that, illustration of the clinical features of the two groups in separate tables will be better read and understood.

9. "***When calculating the correlations it is important to remember that the SLEDAI is an ordinal variable."***
   We understand that SLEDAI is an ordinal variable. However, we used the final SLEDAI score rather than the overall conclusion (active/inactive) while running the correlation tests. As the SLEDAI score is continuous and in our case, was normally distributed, we believe running a correlation test was tenable.

10. "***In the discussion, when addressing the issue of pathophysiological mechanisms that could explain the decrease in MPV, two articles are cited. However, contrary to what is mentioned, neither of these articles deals with SLE patients."***
    This area has been rephrased. Thank you for pointing it out.

11. In our opinion, discussing the study further, will unnecessary lengthen the text of this article.

12. Every effort has been made to correct the English and grammar.
    We thank you once more for your efforts.

Competing Interests: No competing interests to declare.