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Serum Fibrinogen as marker of disease severity in Polymyalgia Rheumatica

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ABSTRACT

Objective: To determine the role of serum fibrinogen as marker of disease severity in Polymyalgia Rheumatic.
Study Design: Cross sectional study.
Place and Duration of Study: Rheumatology/General Medicine Department, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Jul 2019 to Feb 2020.
Methodology: Patient of polymyalgia rheumatica who fulfilled diagnostic criteria by European League against Rheumatism (EULAR)/American College of Rheumatology (ACR) published in 2012, for Polymyalgia rheumatica were included in study. fibrinogen levels in serum were determined in all the patients from laboratory of own hospital. Severity of disease was determined on the basis of Polymyalgia rheumatica activity score (PMR-AS) which is used in clinical practice to grade the severity of disease.
Results: Mean age of the study participants was 56.37±3.292 years. 94(39.2%) patients had mild activity disease, 112(46.7%) had moderate while 34(14.2%) had severe activity of illness. 132(55%) had serum fibrinogen levels within normal range while 108(45%) had raised levels of serum fibrinogen. It was revealed that long duration of illness and levels of fibrinogen had a statistically significant association with severity of illness among the patients suffering of polymyalgia rheumatica (p-value <0.05).
Conclusion: Polymyalgia rheumatica is a commonly diagnosed illness in severe forms in the rheumatology/medicine outpatient departments. Raised Serum fibrinogen levels and long duration of polymyalgia rheumatica emerged as strong predictors of presence of severe form of illness among the study participants.

Keywords: Fibrinogen, Polymyalgia Rheumatica, severity.

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INTRODUCTION

Polymyalgia rheumatic (PMR) has been a commonly diagnosed chronic rheumatological illness especially among the elderly around the globe.[1] Pakistan has been facing the burden of this disease equally and number of patients get diagnosed with this disease each year.[2] Routine blood investigations, inflammatory markers and specific immunological tests are the modalities which have been commonly adopted to support the clinical findings to make the diagnosis of PMR.[3] Some uncommon serum markers have been tested for long to establish the association with their derangement and severity of PMR.[4]

Serum Fibrinogen has a lot of direct and indirect clinical implications. There are some congenital diseases where affected patients are deficient of this factor and may even require transfusion of this agent. Trauma, liver diseases, various surgeries and immunological conditions may predispose the individuals to have altered levels of fibrinogen in their serum.[5,6] Though these alteration in levels is limited to research purposes at the moment but if longitudinal studies prove the correlation they might get incorporated in clinical practice.

PMR has slightly different age pattern as compared to other immunologic/rheumatological diseases and it usually occurs in the elderly. Predicting disease severity is gaining importance for chronic immunological conditions as most of these diseases cannot be cured so aim usually is to maintain them at least possible severity for the patient to make him achieve the best possible quality of life. McCarthy *et al.*, in 2013 did a study with the objective to establish whether plasma fibrinogen was a superior biomarker of disease activity in active PMR than the standard biomarkers, ESR and CRP. They came up with the conclusion that plasma fibrinogen is at least as useful as CRP and ESR for the diagnosis of active PMR and more specific for confirmation of response to treatment than either ESR or CRP.[7] Grau *et al.*, smelled this phenomenon very early and published a classic study back in 1994 in this regard. They studied 16

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PMR/ temporal arteritis (TA) patients and 10 control subjects using a sensitive radioimmunoassay for a specific type of FDP, namely, fibrin(ogen)-related D-antigen. Median serum D-antigen levels were increased five-fold in those 11 PMR/TA patients who were untreated compared with control subjects. In the five PMR/TA patients who were treated with prednisone the median D-antigen levels were not significantly different from those of the healthy controls. D-antigen concentration correlated significantly (r=0.83) with ESR in the seven untreated PMR patients. In PMR patients prednisone therapy was followed by a reduction of serum D-antigen levels.[8] In 2014 an interesting study was conducted in republic of Ireland and published in journal of rheumatology with a conclusion that Visual analog scale (VAS) disease activity and VAS quality of life are the most responsive patient rated outcome to changes in disease activity in PMR. In addition, plasma fibrinogen demonstrated greater responsiveness to changes in disease activity and superior correlation with the various patient reported outcome measures recorded than did the standard biomarkers ESR and CRP.[9]

Rheumatology has been a relatively newer specialty in Pakistan and limited work has been done and published regarding rheumatological diseases. PMR has been one of these under researched areas on which few small studies have been available which have been conducted on our own population.[10] Like all other populations, ageing has been a physiological phenomenon and with each passing day number of individuals with advancing age increase. We therefore need reliable and variable markers for these individuals suffering from PMR to predict the severity of illness, more so when other inflammatory markers are non-specifically raised due to co-existent other conditions. This study was designed with the objective to determine the role of serum fibrinogen as marker of disease severity in polymyalgia rheumatica.

METHODOLOGY

This cross-sectional study was conducted during the period of July 2019 to February 2020.

Inclusion Citeria: Patients presenting at Rheumatology Outpatient Department of Pak Emirates Military Hospital who fulfilled the 2012 PMR criteria by European League against Rheumatism/American College of Rheumatology with age between 50 and 80 years were included in this study.[11]

Exclusion Criteria: Patients who were in remission or with doubtful diagnosis or those with other comorbid autoimmune disease or those with any congenital disorder of fibrinogen were excluded from the study. Patients with comorbid malignant disease of any type were also excluded at the start of the study. Patients who suffered from any serious trauma or bleeding or Disseminated intravascular coagulation in past six months were also excluded from the study.

Sample size was calculated by using the WHO sample size calculator and keeping the population prevalence proportion of raised levels of fibrinogen in patients of PMR as 90%.[9] Non probability consecutive sampling technique was used to gather the required sample size for this study.

Permission from hospital ethics committee via letter number xxx was sought prior to commencement of study. All the patients signed the informed consent form before getting enrolled into the study. About 3 ml venous blood samples were taken in Sodium citrate tubes from the patients diagnosed as PMR. Fibrinogen levels were determined using Clauss Fibrinogen assay automated analyzer for each patient in the laboratory of our own hospital. The normal value for plasma fibrinogen levels was taken as normal <4 g/l.[12] More than this as regarded as increased levels of fibrinogen.

PMR activity score (PMR-AS) was used for measurement of disease activity in polymyalgia rheumatica. It is a valid and reliable tool for this purpose with Cronbach's α of 0.91 and 0.88. It predicts the activity and severity of underlying Polymyalgia rheumatica. PMR-AS values <7 indicated low disease activity, 7–17 medium disease activity, and >17 high disease activity.[13]

Statistical analysis was performed by using the SPSS 23.0. Frequency and percentage were calculated for the qualitative variables like gender, patients with mild, moderate or severe activity of disease or patients with and without the raised levels of fibrinogen. Mean and standard deviation was calculated for the age of the patients and duration of illness. Pearson chi-square test was used to see the association between the age, gender, presence of increased levels of fibrinogen and duration of PMR with the severity of illness. The *p*-value less than or equal to 0.05 was considered as significant for this study.

RESULTS

Two hundred and forty patients of polymyalgia rheumatica were recruited in the study after inclusion and exclusion criteria were applied. Mean age of the study participants was 56.37±3.292 years. Mean duration of rheumatoid arthritis among the study participants was 2.89±2.275 years. Table-I showed that 94(39.2%) patients had mild activity disease, 112(46.7%) had moderate while 34(14.2%) had severe activity of illness. 132(55%) had serum fibrinogen levels within normal range while 108(45%) had raised levels of serum fibrinogen.

Table-I: Characteristics of Patients with Polymyalgia Rheumatica (n=240)

Study parameters	n(%)
Age (years)	
Mean+SD	56.37±3.292 years
Range (min-max)	15 years - 57 years
Mean duration of illness (years)	2.89±2.275 years
Gender	
Male	107(44.6%)
Female	133(55.4%)
Serum Fibrinogen levels	
Within range	132(55%)
Increased	108(45%)
Disease activity	
Low	94(39.2%)
Moderate	112(46.7%)
Severe	34(14.2%)

Table-II: Relationship of Various Factors with the Severity of Polymyalgia Rheumatica among the Target Population (n=240)

Socio-demographic factors	Low activity	Moderate activity	Severe activity	*p*-value
Age				
≤65 years	57(66.7%)	59(44.4%)	14(41.7%)	0.135
>65 years	37(33.3%)	53(55.6%)	20(58.3%)	
Gender				
Female	49(73.7%)	62(73.9%)	22(80.5%)	0.445
Male	45(26.3%)	50(26.1%)	12(19.5%)	
Duration of illness				
≤2 years	51(56.6%)	39(35.6%)	16(47.2%)	0.018
>2 years	43(43.4%)	73(64.4%)	18(52.8%)	
Serum fibrinogen levels				
Within range	65(67.7%)	58(53.1%)	09(25%)	<0.001
Increased	29(32.3%)	54(46.9%)	25(75%)	

Pearson chi-square test revealed that long duration of illness and levels of fibrinogen had a statistically significant association with severity of illness among the patients suffering from polymyalgia rheumatica (*p*-value <0.001) while advancing age and gender of the patients had no such significant relationship found on chi-square (*p*-value>0.018) in our analysis.

DISCUSSION

Rheumatology is a relatively nascent and also a growing specialty in our country with limited number of trained doctors available for huge amount of patients who are mostly relying on general physicians for diagnosis, treatment and follow up. Thorough knowledge about all the aspects of rheumatological diseases can only enable the doctors to manage patients effectively, to diagnose patients at earliest cases for appropriate and aggressive management plan. Various immune based tests or blood indices have been used in the diagnosis and prediction of severity of illness in PMR.[3-5] We planned this study with the rationale to determine the role of serum fibrinogen as marker of disease severity in polymyalgia rheumatica presenting to our teaching hospital from all parts of the country.

Manzo *et al.,* in 2018 came up with interesting finding regarding diagnosis and prognosis of PMR. Usual markers considered for this disease like CRP and ESR may be normal in a lot of cases and still the clinician could make up the diagnosis of PMR.[14] Their findings become useful in a way that still a lot of research required to find the biomarkers associated with presence and severity of PMR and fibrinogen levels ma be one of these missing links.

Salvarani *et al.,* in 1999 analyzed the association of HLA-DRB1 alleles with polymyalgia rheumatica (PMR) in a Mediterranean country and to elaborate the role of HLA-DRB1 genes in determining disease severity. They came up with the conclusion that the data showed no association of rheumatoid epitope with PMR in northern Italian patients. A high ESR at diagnosis and the presence of rheumatoid epitope encoded by a non-DR4 allele are independent valuable markers of disease severity.[15] In the same search for ideal biomarkers we chose fibrinogen levels and they were found strongly related to severity of PMR in our sample population. Study of Mackie *et al.,* published in 2010 in also worth mentioning in this perspective. They studied various factors which could predict severity and prognosis of PMR and revealed that a higher plasma viscosity in PMR increases the risk of prolonged steroid therapy and late Giant cell arteritis (GCA). Female sex and particular HLA alleles may increase the risk of late GCA.[16] Positive relationship with plasma viscosity rang the bell in the ears of researchers and ten years later significant relationship

of serum fibrinogen levels with severity of illness in our analysis demands more work in this regard.

McCarthy and colleagues in 2013 and 2014 published series of studies on relationship of serum fibrinogen levels and activity of PMR.[7,9] Findings of their studies and our study strengthen each other and fibrinogen levels in both emerged as predictors of severity of PMR. More research required to ascertain these findings in order to incorporate the fibrinogen levels in routine investigations once a patient has been diagnosed with PMR.

Other than fibrinogen levels, long duration of illness was also significantly related to presence of severe disease in our sample population. Though we did not categorize that disease was severe in treated or untreated cases of long standing illness but still it was a notable finding as existing literature also highlights that long standing PMR may turn into GCA or late onset rheumatoid arthritis.[17,18]

Ours has been a preliminary study with a small sample size from one rheumatology unit of the country. Incorporation of other public and private sector patients and longitudinal follow up of patients after the diagnosis of PMR can address the limitations of our study and may help the researchers and clinicians in generating results which could be true representative of local population and may be incorporated in making local guidelines for diagnosis and management of PMR.

CONCLUSION

Polymyalgia rheumatica is a commonly diagnosed illness in severe forms in the rheumatology/medicine outpatient departments. Raised Serum fibrinogen levels and long duration of polymyalgia rheumatica emerged as strong predictors of presence of severe form of illness among the study participants.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SR & AF: Data acquisition, data analysis, critical review, approval of the final version to be published.

AK & AB: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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