ORIGINAL ARTICLE

ERYTHROCYTE SEDIMENTATION RATE AND C-REACTIVE PROTEIN AS MARKER OF ACUTE VERSUS CHRONIC MEDICAL CONDITIONS

Azmat Ali, Awais Saeed Abbasi, Tehrim Amjad, Fyza Saleem
Medicine Department, KRL Hospital Islamabad-Pakistan

Background: The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are frequently requested investigations that aid health professionals in precisely diagnosing and following a number of complicated disease conditions. The aim of this study is to ascertain whether a rise in any of these acute phase reactants has predilection for an acute illness versus chronic disease. **Methods:** Current study includes 144 patients admitted to Medical ward and Intensive care unit of Khan Research Laboratory (KRL) Hospital Islamabad from January to April 2017. ESR was measured using conventional Westergren method. CRP level (mg/L) was measured from venous or capillary blood using a point of care testing (POCT) device. SPSS version 20 was used for data analysis. **Results:** Out of 144 patients who participated in this study 60.5% (n=87) were males while 39.6% (n=57) were females. Mean age was 53.4±18.9 years. Among acute medical conditions, Pneumonia and Enteric fever were common 13.2% (n=12) each. Diabetes Mellitus (DM) with complications was the commonest chronic medical condition 22.6% (n=12). Thirty-two patients had ESR <15 mm/Hour; out of them 71.8% (n=23) had acute while 28.2% (n=9) had chronic medical conditions. Thirty-four patients had ESR ≥15 & <30 mm/Hour; out of them 52.9% (n=18) had acute while 47.1% (n=16) had chronic medical conditions. Seventy-eight patients had ESR ≥30 mm/Hour; out of them 64.1% (n=50) had acute while 35.9% (n=28) had chronic medical conditions. All results were statistically significant with *p*-value ≤0.05. 75 patients had CRP <10 mg/L; out of them 66.7% (n=50) had acute while 33.3% (n=25) had chronic medical conditions. Sixty-nine patients had CRP ≥10 & <100 mg/L; out of them 59.4% (n=41) had acute while 40.6% (n=28) had chronic medical conditions. All results were statistically significant with *p*-value ≤0.05. In acute medical conditions mean CRP was 16.8±17.7 mg/L and average ESR was 35.9±25.6 mm/Hour. In chronic medical conditions mean CRP was 16.3±17.2 mg/L and mean ESR was 40.8±32.5 mm/Hour. **Conclusion:** No difference was found between CRP and ESR as markers of acute versus chronic medical conditions. Both CRP and ESR have positive association with acute as well as chronic medical conditions. Elevated ESR was seen more frequently in acute medical conditions as compared to CRP.

Keywords: Erythrocyte sedimentation rate; ESR; C-reactive protein; CRP; Acute medical conditions; Chronic medical conditions; Pneumonia; Typhoid; Diabetes Mellitus; Pakistan

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INTRODUCTION

A systemic response which follows a physiological condition that takes place in the beginning of an inflammatory process is called acute phase reaction. It is a physiological change which lasts for 1 to 2 days, though the systemic acute phase response usually lasts longer. Restoration of homeostasis is the aim of this systemic response.[1] The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are frequently requested investigations that aid health professionals in precisely diagnosing and following a number of complicated disease conditions. While these investigations are influenced by numerous factors and have a low index of specificity, they may provide clinicians with valuable data when used in conjunction with other clinical and diagnostic tests. CRP and ESR are vital in rapid yet complex decision making; in the setting of patients admitted to intensive care units (ICUs) having multiple co-morbid conditions.[2] CRP was first discovered in the serum of patients during acute phase of pneumococcal pneumonia and this whole phenomenon was labelled as acute phase response. This discovery was made by Tillet and Francis in 1930. This interacts with C-polysaccharide of streptococcus pneumonia cells and so the name C-reactive protein.[3,4] Acute phase response is a misnomer as this response accompanies both acute and chronic inflammatory conditions associated with a wide variety of disorders, including trauma, infection, inflammatory arthritis, infarction, systemic autoimmune diseases and neoplasms.[1] In acute inflammatory conditions, CRP rises by 50 to 100 mg/L in 4–6 hours of a mild to moderate toxic

stimulus. CRP peaks 36–50 hours after onset of inflammation.[5] Marked elevation of CRP (>100–500 mg/L) are strongly seen in bacterial infections.[6] ESR measures the rate at which erythrocyte fall in plasma after centrifugation in a tube. Current techniques of centrifugation can generate results in 5 minutes.[7,8] Anaemia will decrease while polycythemia will increase ESR. Patients with sickle cell disease have a low ESR during sickle crisis that rises with infections.[9,10] ESR is a reflection of severity of systemic inflammation. Infections, autoimmune diseases and malignancies are associated with elevation in ESR.[11–13] ESR and CRP are ordered together in patients with suspected inflammation or infection but the tests results can disagree in approximately 33 % of patients. Three explanation were given to define these disagreements; (I) development of an intercurrent illness; (II) slight fluctuations in ESR and CRP around the upper limit of normal for these tests; and (III) different time courses of ESR and CRP elevations, in which the CPR rose and fell faster than the ESR.[14]

Infections, malignancies, abnormally sized and shaped red blood cells or serum protein concentrations all have been shown to influence ESR.[15] ESR is generally higher in females than in males for any age.[16,17] It also rises with body mass index (BMI).[18] Studies favour CRP over ESR in rheumatoid arthritis,[19] with a belief that it reflects more current disease activity[20,15]. CRP has benefit over ESR being less influenced by factors like age and sex.[20] The aim of this study is to ascertain whether a rise in any of these acute phase reactants has predilection for an acute illness versus chronic disease.

MATERIAL AND METHODS

Current study includes 144 patients admitted to Medical ward and Intensive care unit of Khan Research Laboratory (KRL) Hospital Islamabad from February to April 2017. This study was done with approval from ethical review board of hospital.

ESR measures the rate at which erythrocyte fall in plasma after centrifugation in a tube over a specific time which is mostly 60 minutes. Current techniques of centrifugation can generate results in 5 minutes.[8] ESR was measured using conventional method, in which at the time of sampling, 1.6 cc pf patient's whole blood was gently mixed with 0.4 cc of 3.8 % sodium citrate. Then this anticoagulated blood was sucked into a glass Westergren pipette, placed onto a stand, and fixed in vertical position for 60 minutes. The sedimentation rate was estimated by measuring the column of serum at the top of tube, based on millimetre per hour. CRP level in milligram/Litre (mg/L) was measured from venous or capillary blood using point of care testing (POCT) device ranging from less than 6 mg/L and above.

SPSS-20 was used for data analysis. The clinical data of the study patients were stated as percentages. The difference between two groups were examined by t-test or ANOVA for continuous variables and by chi-square test for categorical variables. p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Out of 144 patients who participated in this study 60.5% (n=87) were males while 39.6% (n=57) were females. Mean age was 53.4±18.9 years. Average age of males was 53.6±20.1 and average age of females was 53.2±17.5.

Out of 144 patients 91 suffered from acute medical conditions while 53 had chronic medical illnesses. Among acute medical conditions, Pneumonia and Enteric fever were common 13.2% (n=12) each followed by acute gastroenteritis (AGE) 12.1% (n=11), urinary tract infection (UTI) 9.9% (n=9), upper respiratory tract infection (URTI) and Infective exacerbation of Asthma 5.5% (n=5) each, upper gastrointestinal (UGI) bleed and acute kidney injury (AKI) 4.4% (n=4) each, Ischemic Stroke 3.3% (n=3), Viral Encephalitis, deep venous thrombosis (DVT) and Acute exacerbation of chronic obstructive pulmonary disease (COPD) 2.2% (n=2) each. Details are illustrated in table-1.

Table-2 demonstrates details of chronic medical conditions. Diabetes Mellitus (DM) with complications was the commonest 22.6% (n=12) followed by Pulmonary Tuberculosis and Iron deficiency anaemia 7.5% (n=4) each, Rheumatoid Arthritis, Lung carcinoma, Crohn's disease and Beta thalassemia major 3.8% (n=2) each. Vascular dementia and Tuberculous lymphadenitis 1.9% (n=1) each.

Patients were further divided into 6 main groups on the basis of ESR and CRP. ESR less than 15 mm/Hour included 32 patients, 34 patients had ESR equal to or more than 15 but less than 30 mm/Hour and 78 patients had ESR equal to or more than 30 mm/Hour. Seventy-five patients had CRP less than 10 mg/L, 69 patients had CRP value equal to or more than 10 mg/L but less than 100 mg/L. No patients had CRP equal to or above 100 mg/L.

There was a total of 32 patients having ESR <15 mm/Hour. Out of those 68.7% (n=22) were males while 31.3% (n=10) were females.

71.8% (n=23) were suffering from acute medical conditions while 28.2% (n=9) were suffering from chronic medical conditions. All results were statistically significant as *p*-value ≤0.05. This is shown in table-3.

There was a total of 34 patients having ESR ≥ 15 & < 30 mm/Hour. Out of those 67.6 % (n=23) were males while 32.4% (n=11) were females. 52.9% (n=18) were suffering from acute medical conditions while 47.1% (n=16) were suffering from chronic medical conditions. All results were statistically significant as *p*-value ≤0.05. This is shown in table-4.

There were a total of78 patients having ESR ≥30 mm/Hour. Out of those 53.8% (n=42) were males while 46.2% (n=36) were females. 64.1% (n=50) were suffering from acute medical conditions while 35.9% (n=28) were suffering from chronic medical conditions. All results were statistically significant as *p*-value ≤0.05. This is shown in table-5.

There was a total of 75 patients having CRP <10 mg/L. Out of those 54.7% (n=41) were males while 45.3% (n=34) were females. 66.7% (n=50) were suffering from acute medical conditions while 33.3 % (n=25) were suffering from chronic medical conditions. All results were statistically significant as *p*-value ≤0.05. This is shown in table-6.

There were a total of69 patients having CRP ≥10 & <100 mg/L. Out of those 66.7% (n=46) were males while 39.1% (n=27) were females. 59.4% (n=41) were suffering from acute medical conditions while 40.6% (n=28) were suffering from chronic medical conditions. All results were statistically significant as *p*-value ≤0.05. This is shown in table-7.

In acute medical conditions mean CRP was 16.8±17.7 mg/L, minimum value was 1 mg/L while maximum value was 60.3 mg/L. Mean ESR was 35.9±25.6 mm/Hour, minimum value was 10 mm/Hour while maximum value was 120 mm/Hour. Mean Total Leucocyte Count (TLC) was 9.1±4.6 × 10^9/L. Minimum value was 3.2 × 10^9/L while maximum value was 28.3 × 10^9/L. This is shown in table-8. In chronic medical conditions mean CRP was 16.3±17.2 mg/L, minimum value was 1 mg/L while maximum value was 57.6 mg/L. Mean ESR was 40.8±32.5 mm/Hour, minimum value was 4 mm/Hour while maximum value was 187 mm/Hour. Mean Total Leucocyte Count (TLC) was 10.5±21.7×10^9/L. Minimum value was 1.7×10^9/L while maximum value was 158×10^9/L. This is shown in table-9.

Table-1: Acute medical conditions (n=91)

Medical Condition	Number of patients	Percentage
Pneumonia	12	13.2
Enteric Fever	12	13.2
Acute Gastro-Enteritis (AGE)	11	12.1
Urinary Tract Infection (UTI)	9	9.9
Upper Respiratory Tract Infection (URTI)	5	5.5
Acute Infective Exacerbation of Asthma	5	5.5
Upper Gastro-Intestinal Bleed (UGI Bleed)	4	4.4
Acute Kidney Injury (AKI)	4	4.4
Ischemic Stroke	3	3.3
Viral Encephalitis	2	2.2
Deep Venous Thrombosis (DVT)	2	2.2
Acute Infective Exacerbation of COPD	2	2.2
Warfarin Toxicity	1	1.1
Vestibular Neuronitis	1	1.1
Uremic Encephalopathy	1	1.1
Transient Ischemic Attack	1	1.1
Thigh Abscess	1	1.1
Pyogenic Meningitis	1	1.1
Porto Systemic Encephalopathy	1	1.1
Pulmonary Embolism	1	1.1
Lumbar Disc Prolapse	1	1.1
Guillain Barre Syndrome	1	1.1
Cervical Radiculopathy and Tendonitis	1	1.1
Cellulitis	1	1.1
Boils on face	1	1.1
Bells palsy	1	1.1
Bronchial Asthma	1	1.1
Acute Viral Hepatitis	1	1.1
Acute Infective Exacerbation of Diffuse Parenchymal Lung Disease (DPLD)	1	1.1
Acute Gastritis	1	1.1
Left Ventricular Failure (LVF)	1	1.1
Acute Cholecystitis	1	1.1

Table-2: Chronic medical conditions (n=53)

	Number of patients	Percentage
Diabetes Mellitus (DM) with complications	12	22.6
Pulmonary Tuberculosis (TB)	04	7.5
Iron Deficiency Anaemia	04	7.5
Rheumatoid Arthritis (RA)	02	3.8
Lung carcinoma	02	3.8
Chron's Disease	02	3.8
Beta Thalassemia Major	02	3.8
Vascular Dementia	01	1.9
Tuberculous lymphadenitis	01	1.9
Spinal stenosis	01	1.9
Recurrent Stroke	01	1.9
Polycythemia	01	1.9
Osteoarthritis	01	1.9
Multiple Sclerosis	01	1.9
Megaloblastic Anaemia	01	1.9
Lymphoma	01	1.9
Ischemic Stroke	01	1.9
Ischemic Cardiomyopathy	01	1.9
Generalized Anxiety Disorder	01	1.9
Fibrous dysplasia	01	1.9
Epilepsy	01	1.9
Disseminated Koch's	01	1.9
Decompensated Chronic Liver Disease	01	1.9
Chronic Myeloid Leukaemia	01	1.9
Chronic Lymphocytic Leukaemia	01	1.9
Chronic Kidney Disease	01	1.9
Chronic Gastritis	01	1.9
Cardiac Syndrome X	01	1.9
Carcinoid Syndrome	01	1.9
Carcinoma breast	01	1.9
Chronic Moderate Persistent Asthma	01	1.9
Abdominal Tuberculosis	01	1.9

Table-3: Characteristics of patients with ESR values less than 15 mm/Hour

ESR less than 15 mm/Hour (n=32)		
	No. of patients	*p*-value
Male	22	0.001
Female	10	0.001
Acute medical conditions	23	0.001
Chronic medical conditions	09	0.001

Table-4: Characteristics of patients with ESR values equal to or more than 15 and less than 30 mm/Hour

ESR ≥ 15 &< 30 mm/Hour (n=34)		
	No. of patients	*p*-value
Male	23	0.001
Female	11	0.001
Acute medical conditions	18	0.001
Chronic medical conditions	16	0.001

Table-5: Gender distribution and acute versus chronic medical conditions with ESR more than 30 mm/Hour

ESR ≥ 30 mm/Hour (n=78)		
	No. of patients	*p*-value
Male	42	0.001
Female	36	0.001
Acute medical conditions	50	0.001
Chronic medical conditions	28	0.001

Table-6: Characteristics of patients with CRP values greater less than 10 mg/L

CRP less than 10 mg/L (n=75)		
	No. of patients	*p*-value
Male	41	0.001
Female	34	0.001
Acute medical conditions	50	0.001
Chronic medical conditions	25	0.002

Table-7: Characteristics of patients with CRP values equal to or more than 10 and less than 100 mg/L

CRP ≥ 10 &< 100 mg/L (n=69)		
	No. of patients	***p*-value**
Male	46	0.001
Female	27	0.001
Acute medical conditions	41	0.001
Chronic medical conditions	28	0.001

Table-8: CRP, ESR and TLC values in acute medical conditions

	CRP (mg/L)	**ESR (mm/Hour)**	**TLC (10^9/L)**
Mean	16.8	35.9	9.1
Standard Deviation	17.7	25.6	4.6
Mode	01	10	11.9
Minimum	01	03	3.2
Maximum	60.3	120	28.3

Table-9: CRP, ESR and TLC values in chronic medical conditions

	CRP (mg/L)	**ESR (mm/Hour)**	**TLC (10^9/L)**
Mean	16.3	40.8	10.5
Standard Deviation	17.2	32.5	21.7
Mode	01	25	06
Minimum	01	04	1.7
Maximum	57.6	187	158

DISCUSSION

In the past, it was thought that CRP is a more sensitive and reliable marker of acute inflammatory events compared to ESR.[21] CRP and ESR are often employed in aiding diagnosis of acute inflammatory conditions such as osteomyelitis, septic arthritis, and acute rheumatic fever. Some publications have indicated that CRP is a superior test in diagnostic evaluation of these conditions,[22] because it rises earlier than ESR[8]. Our study focused on examining this assumption in our population and for this purpose we divided our study population into two main groups on the basis of acute and chronic medical conditions and measured these two serum markers in both conditions.

We found out that Pneumonia and Enteric fever were the commonest acute medical conditions in our study; 13.2% each. Community acquired pneumonia (CAP) is a serious health problem worldwide and its incidence varies from 5 to 11 per 1000, with higher rates in elderly.[23] Typhoid fever is one of the many diseases burdening the third world countries. In 2000, over 2.16 million episodes of typhoid were recorder worldwide. In 2004, typhoid fever caused 216,000 deaths, of which more than 90% occurred in Asia.[24]

As far as chronic medical conditions are concerned Diabetes Mellitus (DM) with complications was the commonest; 22.6% followed by Pulmonary Tuberculosis 7.5%. In 2011, the estimated prevalence of diabetes in Pakistan was approximately over 35 million and it is expected to be over 55 million by year 2030.[25]

In terms of absolute number of TB cases, in 2011, Pakistan ranked 5th among 22 high burden countries. The estimated incidence and prevalence rates of all forms of TB were 231 (95% confidence interval (CI), 189–277) and 364 (95%CI, 154–611) per 100,000 populations, respectively.[26]

For the sake of thorough understanding of any association of CRP and ESR with acute or chronic medical conditions we made 6 sub-groups. Three sub-groups studied association of ESR with gender, acute and chronic medical conditions while the other 3 sub-groups studied association of CRP with gender, acute and chronic medical conditions. These sub-groups were made on the basis of cut-off values of ESR and CRP respectively.

We found that average CRP was 16.8±17.7 mg/L in acute medical conditions as compared to 16.3±17.2 mg/L in chronic medical conditions. 52.1% of patients had CRP less than 10 mg/L; of these, 66.7% had acute medical conditions. 47.9% patients had CRP equal to or more than 10 and less than 100 mg/L and 59.4% of these had acute medical conditions. No patient had CRP equal to or more than 100 mg/L. It is reported that raised levels of CRP occurs in infections, often bacterial. It was found that levels up to 500 mg/L may occur.[27] According to our observations, there exist significant association of CRP with both acute and chronic medical conditions but our study do not support this assumption that raised CRP levels are associated with infections. This can also be judged by this fact that CRP can influence multiple stages of inflammation, and CRP has both pro-inflammatory and anti-inflammatory actions.[28]

We also found that average ESR was 35.9±25.6 mm/Hour in acute medical conditions as compared to 40.8±32.5 mm/Hour in chronic medical

conditions. 22.2% of patients had ESR less than 15 mm/Hour; 71.8% of these had acute medical conditions. 23.6% patients had ESR equal to or more than 15 and less than 30 mm/Hour and 52.9% of these had acute medical conditions. 54.1% of patients had ESR equal to or more than 30 mm/Hour, 64.1% patients had acute medical conditions and 35.9% had chronic medical conditions. Previously it was thought that ESR is a marker of chronic conditions which is again not observed in our present study as more patients with acute medical condition had ESR values more than 30 mm/Hour. In a study it was reported that marked elevations in the ESR are more often due to infection than other causes, but non-infectious disorders are also a common aetiology. In a retrospective study of 1006 consecutive outpatients, ESR values of over 100 mm/hour were reported in infections, malignancies and inflammatory disorders, from 33 to 14%.[29] In our study, significant association of ESR was observed with both acute and chronic medical conditions and marked elevations of ESR was observed with acute medical conditions.

Discrepancies between ESR and CRP are found with some frequency. Systemic lupus erythematosus (SLE) represents an exception to the generalization that CRP concentrations correlate with the extent and severity of inflammation in patients with rheumatic disorders; the ESR may be elevated, sometimes markedly, in patients with active SLE, while the CRP response is muted.[30] In patients with active rheumatoid arthritis, the ESR and CRP generally tend to both be elevated or not in the same patients. Though, one study found that results for the two tests were discordant (ESR >28 mm/Hr with CRP ≤0.8 mg/dL or ESR ≤28 mm/Hr with CRP >0.8 mg/dL) in about one quarters of patients with active rheumatoid arthritis.[31]Several studies have suggested that elevations of the acute phase protein, procalcitonin, are highly specific for infection.[32] A 2012 meta-analysis of 9 observational studies that evaluated procalcitonin as a marker of infection in autoimmune disease found that procalcitonin and CRP exhibited similar sensitivity for infection (75 versus 77 %), but that procalcitonin had significantly higher specificity (96 versus 56 %).[33]

CONCLUSION

No difference was found between CRP and ESR as markers of acute versus chronic medical conditions. Both CRP and ESR have positive association with acute as well as chronic medical conditions. Elevated ESR was seen more frequently in acute medical conditions as compared to CRP. Other markers like pro-calcitonin shall be studied for better sensitivity and specificity in terms of diagnosing acute or chronic medical conditions.

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Address for Correspondence:
Dr. Azmat Ali HOD, Medicine, KRL Hospital Islamabad-Pakistan
Email: ali99azmat@gmail.com)