C-Reactive Protein Level can be a Better Indicator than Erythrocyte Sedimentation Rate in Assessing the Severity of Inflammation and Guiding Glucocorticoid Therapy in Subacute Thyroiditis

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Abstract

Background: Despite the widespread use of several diagnostic tests in subacute thyroiditis (SAT), their usage remains largely subjective. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are useful indicators of inflammation in patients with SAT. The purpose of this study was to compare the scope for utilising CRP and ESR objectively in deciding the requirement of glucocorticoid therapy. **Methods:** A total of 28 patients with SAT were included in this study. Serum CRP and ESR were measured in all the patients. The characteristics of these tests were assessed firstly by using previously accepted positivity criterion for the particular diagnostic test. The area under the receiver operating characteristics (ROC) curve was obtained to provide an index of the overall discriminative ability of both tests. **Results:** Fifteen out of 28 patients were found to have features of significant thyroid inflammation eventually requiring glucocorticoid based on the current recommendations. The mean CRP value was significantly higher in patients requiring glucocorticoids. The ROC curves indicated that the optimal positivity criterion was 19.3 mg/L for the CRP level and 46 mm at the 1st hour for ESR. CRP with a sensitivity of 0.67, a specificity of 0.92, a positive likelihood ratio of 8.67, and an accuracy of 0.64 appeared better than ESR, which showed a sensitivity of 0.93, a specificity of 0.53, a positive likelihood ratio of 2.02, and an accuracy of 0.60. **Conclusions:** The serum CRP level provided a clear advantage over ESR in the assessment of the severity of inflammation before initiation of glucocorticoid therapy in SAT. However, a well-powered study is needed to examine the clinical relevance of such a role for CRP in thyroidology.

Keywords: CRP, ESR, ROC, SAT, thyroiditis, thyrotoxicosis

INTRODUCTION

Subacute thyroiditis (SAT) is caused by the inflammation of the thyroid gland, which mostly is spontaneously remitting in nature.[1] SAT-affected patients show a pseudo-granulomatous pathological appearance in the thyroid gland. It becomes typically firm on palpation, enlarged, and tender. They may also have characteristic symptoms such as fever and malaise.[1] There is clinical and biochemical evidence of thyrotoxicosis, secondary to the release of pre-formed thyroid hormones from the destroyed thyrocytes.[1,2] Scientific evidence justifies the conclusion that neither this is an autoimmune disease, nor does it has any consistent serologic connection with any one group of

viruses.[3] Hence, thyroid-specific auto-antibodies do not have any role in the evaluation of SAT.

Amongst the other laboratory findings, an elevated erythrocyte sedimentation rate (ESR) is invariably present in the clinical

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records. The absence of elevated ESR may question a tenable diagnosis of SAT.[4] Usually, ESR is one of the most commonly used laboratory tools to detect an inflammatory syndrome.[4] However, acute-phase reactants have been becoming useful alternatives to ESR due to significantly lesser false positivity and false negativity.[5] The acute-phase response is usually a non-specific phenomenon, occurring early in the course of inflammation, in which the concentration of a number of plasma proteins is increased.[6,7] Alteration in acute-phase reactants can be a useful indicator of inflammatory response or infection when the clinical diagnosis is under doubt. Serum CRP is one such acute-phase reactant found to be characteristically elevated in inflammatory thyroid disorders.[8-10] However, CRP itself has major limitations in this regard [Box 1].[11] CRP and ESR are commonly used as markers for predicting and diagnosing infection and are frequently done together in practice. However, CRP and ESR are known to give discordance in the values. It is however still debatable whether the predictive value of one over the other is better or of one over two tests together.[12] A prospective study, looking at CRP and ESR as screening parameters, found CRP to have higher sensitivity and specificity and of more diagnostic relevance.[13] In a study with known discordance between the ESR and CRP, the latter was concluded as superior in detecting and predicting an inflammatory disease process. Doing both tests was found to be confounding.[14] Yet another study suggested the use of both the tests to avoid the implications of possible non-concordance between the results of ESR and CRP; however, the improvement in sensitivity was only slight when both the tests were performed together compared to when CRP was conducted alone.[15,16] A study on diagnosing periprosthetic infection before the revision of total hip arthroplasty suggested that both CRP as well as ESR have 'reasonable' accuracy and adequate predictive value, though the findings suggested higher specificity with CRP.[17]

Classical nuclear imaging of the thyroid using either radioactive iodine or technetium pertechnetate shows low uptake and helps differentiate SAT from Graves' disease, which is another important cause of thyrotoxicosis. Recently ultrasonography documenting typical hypoechoic areas with low vascularity has been found to be equally useful.[18]

SAT is a prototype of inflammatory thyroid disease leading to significant comorbidity. In patients failing to respond to conventional Non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoid is the drug of choice. The main objective of

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Box 1: Limitation of CRP as a diagnostic tool.[11] CRP, C-reactive protein

Limitation of CRP as a diagnostic tool

Poor positive predictive value prevents usage of CRP as a single tool for evaluating inflammation in depth

Various studies and recommendation have suggested different cut-offs, which makes it difficult to adopt a universal cut-off

More extensive evidence favouring CRP across different geographies is required

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starting glucocorticoid therapy is to relieve persistent pain despite NSAIDs.[19] Glucocorticoid also imparts significant well-being to the patient, so much so that the very diagnosis of SAT is questioned if such improvements are not seen within days of glucocorticoid use.[2,4] In an epidemiological study from Rochester, USA, 55% were treated with glucocorticoid alone or along with NSAID. Though glucocorticoid caused significant pain relief, it did not seem to prevent early- and late-onset thyroid dysfunction.[20]

As of now, there is no 'gold standard' objective criterion to guide clinicians as to when and where glucocorticoid has to be prescribed leading to its injudicious use. We tried to examine whether commonly used inflammatory markers, by discriminating between 'glucocorticoid requiring' and 'non requiring inflammation', can help clinicians to come to a decision point or not. To be clinically useful, a 'decision point' biomarker has to provide definitive information additional to what is already available from established clinical assessments.

METHODS

Patient Selection Criteria: All subjects were selected from the endocrine outpatient service of a multispecialty clinic. A local human research ethics committee approved the study protocol. Informed consent was obtained from each of the subjects before inclusion in the study. The study group consisted of patients with SAT who were diagnosed on the basis of clinical presentation (high ESR, neck pain, and biochemical evidence of thyrotoxicosis), supported either by typical ultrasound findings and/or isotope thyroid scan performed by using isotope 99 m Tc-pertechnetate as described previously.[9] Subjects, who had undergone radiological studies using intravenous contrast during the previous three months or were taking thyroid hormone, amiodarone, lithium or had been previously exposed to radioactive iodine in the past were excluded from the study. Subjects having possible and probable inflammation of any organ system other than the thyroid were also excluded from this study.

CRP and ESR level estimation: The serum CRP level was measured turbidimetrically at 340 nm by a standardized immune-turbidimetric assay using commercial kits (Roche Diagnostics, Germany) with an assay range of 0.3–160 mg/L in samples collected at the initial presentation as discussed previously.[9] Any value of CRP <5 mg/L was considered as normal. ESR was measured in an automated counter (Beckman Coulter). These assays were performed independently by one of the authors (BB) who was unaware of the modality of treatment (glucocorticoid, NSAID or anti-thyroid drugs) offered to the index patient.

Glucocorticoid therapy: The decision regarding the use of glucocorticoid was based upon internationally accepted standards for the treatment of patients with SAT.[1,2,4] Patients with persistent neck pain of moderate to severe intensity after a week of optimal NSAID therapy were started on a standard dose of prednisolone 40 mg per day for 2 weeks, which was

tapered over the next 4 weeks depending on the resolution of symptoms. One of the authors (MPB) was exclusively responsible for the initiation of such therapy and follow-up thereafter. The treating physician was unaware of the serum CRP or ESR level of the index patient.

Statistical analysis

The results were expressed as mean ± SEM (standard error of mean). Continuous variables were compared by Student's *t*-test. Comparison of the categorical variables of age, body mass index (BMI), and CRP in patients with SAT using the Mann–Whitney U test. Differences and statistical comparisons between groups of patients were considered significant when *P* values were < 0.05 using Fisher's exact test and Chi-square test on MedCalc software. Comparisons of sensitivity and specificity were made using McNemar's test. Pearson's correlation coefficient assessed the importance of the different variables. Differences were considered significant if *P* < 0.05. The determination of the predictive value was done by MedCalc software beta version 16.2.1 (Belgium).[21]

For the construction of receiver operating characteristics (ROC) curves, relations between sensitivity (ordinate) and specificity (abscissa) for various cut-off points were plotted. The area under the ROC curve (AUC) was obtained to provide an index of the overall discriminative ability of the test.[22] Another practical method for choosing an appropriate cut-off value was adopted, wherein the maximal summative value of sensitivity and specificity, which is indicative of a point in the ROC curve with the highest vertical distance from the 45° diagonal line, which in turn indicates the maximum difference between the true positive rate and false-positive rate for the test (1-Sp).[23] AUCs derived from both of the diagnostic tests performed on the same set of patients were to be compared. Correlated *U* statistical comparison along with Pearson correlation coefficients was used to estimate the correlation of the 2 AUCs.

RESULTS

A total of 28 patients with SAT were included in the study. Characteristics of the patients including age, gender ratio, and basic anthropometry are described in Table 1. Serum CRP and ESR were measured in all patients. Glucocorticoid had to be initiated in 15 (54%) of the patients. The mean ± SD of serum CRP levels amongst patients requiring glucocorticoid was 41.73 ± 33.6 mg/L (median value = 46.3 mg/L) compared to 11.2 ± 15.4 mg/L amongst those not requiring glucocorticoid (p = 0.0058). The distribution of patients according to various cut-offs for CRP and ESR are given in Table 1. Considering CRP as the predictor for glucocorticoid requirement, the two-tailed *P* value was found to be 0.021, which is significant, whereas the same was 0.128 for ESR as a predictor, which is not significant. The Chi-square value for CRP was 6.785 with a *P* value of 0.0092 with 1 degree of freedom, whereas the same for ESR was 0.179 with a *P* value of 0.6726 with 1 degree of freedom.

The details of criterion values and coordinates of the ROC curves with the respective sensitivity and specificity along with a 95% confidence interval, summative values of sensitivity and specificity, and positive and negative likelihood ratio for the mean for serum CRP and ESR are given in Table 2. The respective ROC curves of cut-off levels for each of the parameters in SAT patients eventually requiring glucocorticoids are shown in Figure 1. ROC analysis revealed higher AUC for the CRP levels at 0.774 (*P* = 0.0038) as compared to the corresponding AUC for ESR levels at 0.751 (*P* = 0.0110) [Table 3, Figure 1]. The Youden index for CRP (criterion of >19.3 mg/L) was 0.5897 and 0.4718 for ESR (criterion of >46 at the end of the 1st hour) [Table 2].

DISCUSSION

In the present study, a total of 28 patients clinically diagnosed with SAT were closely monitored by measurements of

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Table 1: Baseline characteristics of patients with SAT

Parameters	Patient groups (*n*)		
	SAT (28)	Patients on glucocorticoids (15)	Patients not on glucocorticoids (13)
Age in years : range, (mean±S.E.)	20-55, 37.96±8.53	27-55, 39.6±9.17	20-48, 36.08±8.02
Gender ratio (female: male)	16:12	12:03	04:09
BMI (kg/m²) (mean±S.D.)	22.56±2.92	23.3±2.75	21.72±3.1
*CRP levels (mg/L) (mean±S.D.)	27.55±29.96	41.73±33.59	11.2±15.41
Numbers of patients with CRP <5 mg/L, *n* (%)	11 (39%)	4 (27%)	7 (54%)
Numbers of patients with CRP >5 mg/L, *n* (%)	17 (61%)	11 (73%)	6 (46%)
Number of patients with CRP >15 mg/L, *n* (%)	12 (43%)	10 (67%)	2 (15%)
Numbers of patients with CRP >25 mg/L, *n* (%)	9 (32%)	8 (53%)	1 (8%)
#ESR levels mm/AEFH (mean±S.D.)	66.00±32.68	78.13±29.53	52.0±32.84
Numbers of patients with ESR <20 mm AEFH, *n* (%)	1 (3.6%)	0 (0%)	1 (7.6%)
Numbers of patients with ESR >20 mm AEFH, *n* (%)	27 (96.4%)	15 (100%)	12 (92.3%)
Numbers of patients with ESR >60 mm AEFH, *n* (%)	15 (53.5%)	10 (66.6%)	5 (38.4%)
Numbers of patients with ESR >100 mm AEFH, *n* (%)	5 (17.6%)	4 (26.6%)	1 (7.6%)

Patients are categorized into two subgroups, i.e., requiring and not requiring glucocorticoid. The number of patients in different categories of CRP and ESR are also shown. *P*=0.021 between the two groups, #*P*=0.128 between the two groups. SAT, subacute thyroiditis; CRP, C-reactive protein (serum); ESR, erythrocyte sedimentation rate; AEFH, at the end of the 1st hour
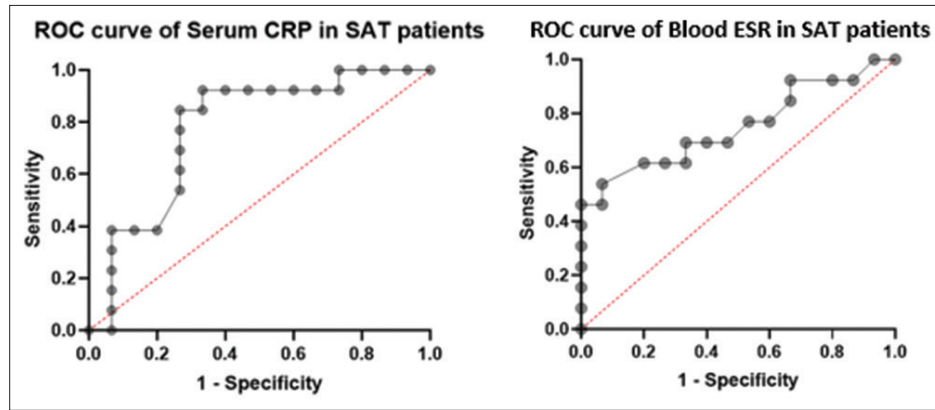
Figure 1: Diagnostic performance of the serum CRP and ESR measurements in the samples of SAT patients plotted as a ROC curve. The dotted lines express the 95% confidence limits. A larger AUC for CRP compared to that of ESR is notable. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ROC, receiver operating characteristics; AUC, area under the curve; SAT, subacute thyroiditis

Table 2: ROC curve details for CRP and ESR levels in SAT patients (*n*=28) requiring glucocorticoid (*n*=15, 53%)

Classification variable	CRP (>19.3 mg/L)	ESR (>46 AEFH)
AUC	0.774	0.751
Standard Error	0.0947	0.0988
95% Confidence interval	0.578 to 0.910	0.553 to 0.894
z statistic	2.896	2.544
Significance level *P* (Area=0.5)	0.0038	0.0110
Youden index (J)	0.5897	0.4718
Sensitivity	0.67	0.93
Specificity	0.92	0.54

The Youden index (J)[28] indicates the performance at a given cut-off. The larger the value, the better, as seen in the case of the diagnostic cut-off of CRP 19.3 mg/L compared to optimal ESR level of 46 AEFH which can discriminate glucocorticoid requiring SAT patients from those who would not require them. SAT, subacute thyroiditis; CRP, C-reactive protein (serum); ESR, erythrocyte sedimentation rate; AEFH, at the end of the 1st hour; ROC, receiver operating characteristic

acute-phase inflammation markers, viz., CRP and ESR. Patients were treated according to the current standard of practice (1, 2, 4). Patients not responding to NSAIDs were given glucocorticoids for alleviation of pain. As expected, both CRP and ESR values were significantly elevated beyond the reference range in almost all of the patients.

The null hypothesis (H$_o$) for either parameter (ESR or CRP) is 'there is no association of an elevated parameter with the eventual requirement of glucocorticoids for the SAT patients'. Hence, the alternative hypothesis (H$_1$) is that there is an association of an elevated parameter (ESR or CRP) with the eventual requirement of glucocorticoids for the SAT patients. As the calculated Chi-square value for CRP (6.785 with a *P* value of 0.0092 with 1 degree of freedom) was not in the acceptance region; our null hypothesis with respect to serum CRP gets rejected, enabling us to conclude that there is a significant association of its elevation and eventual requirement of glucocorticoids for the SAT patients. However, the Chi-square value for ESR was 0.179 with a *P* value of 0.6726 with 1 degree of freedom, which is in the acceptance region, proving our null hypothesis with respect to ESR right and hence enabling us to conclude that there is an insignificant association of elevated ESR with eventual requirement of glucocorticoids for the SAT patients.

Our ROC analysis showed the best diagnostic accuracy for a higher grade of inflammation in SAT that merits treatment with glucocorticoid would be at a peak serum CRP cut-off of 19.3 mg/L (sensitivity, 66.67%; specificity, 92.31%; AUC = 0.774) and at a peak ESR cut-off of 46 mm AEFH (sensitivity, 93.33%; specificity, 53.85%; AUC = 0.751). With significantly higher specificity, such a cut-off level of CRP would be much more reliable for the diagnostic discrimination and clinical decision of starting glucocorticoids. This same analysis however makes such a cut-off of ESR as a much better screening tool with a lesser chance of leaving out the true positive cases. However, a higher probability of picking up too many false-positive cases would make such an ESR cut-off an unreliable guide to the clinical decision-making process. Bingham *et al.* documented that an ESR cut-off of 30 mm/AEFH and a CRP cut-off of 10 mg/L give unacceptably low sensitivity for detecting periprosthetic joint infection, which, however, could be increased to >95% if the cut-offs are lowered to 10 mm/AEFH and 5 mg/L, respectively.[24,25] Wolfe *et al.* have documented that a median value of CRP 5.9 mg/L but no value of ESR was significantly associated with functional disability, joint tenderness, pain, fatigue, global severity, and depression, along with notable correlations with the BMI and sex.[25] Quite contrastingly, elevated ESR >47 mm/AEFH, and no other parameters including CRP, was the only variable associated significantly with re-operation to tackle prosthetic joint infection.[26] A recent meta-analysis found CRP to be of superior diagnostic accuracy for various inflammatory conditions except for orthopaedic infections. Diagnostic accuracy was enhanced if both CRP and ESR were combined.[27] However, we did not

Table 3: Criterion values and coordinates of the ROC curve of CRP and ESR of SAT patients

Criterion	Sensitivity% (95% CI)	Specificity% (95% CI)	Sensitivity + Specificity	+LR	−LR
CRP (mg/L)					
≥2.9	100.00 (78.2-100.0)	0.00 (0.0-24.7)	100.00	1.00	
>4.4	93.33 (68.1-99.8)	38.46 (13.9-68.4)	131.79	1.52	0.17
>4.7	80.00 (51.9-95.7)	38.46 (13.9-68.4)	118.46	1.30	0.52
>10.2	73.33 (44.9-92.2)	84.62 (54.6-98.1)	157.95	4.77	0.32
>19.3	**66.67 (38.4-88.2)**	**92.31 (64.0-99.8)**	**158.98**	**8.67**	**0.36**
>60	26.67 (7.8-55.1)	92.31 (64.0-99.8)	118.98	3.47	0.79
>95	0.00 (0.0-21.8)	100.00 (75.3-100.0)	100.00		1.00
ESR (AEFH)					
≥18	100.00 (78.2-100.0)	0.00 (0.0-24.7)	100.00	1.00	
>46	**93.33 (68.1-99.8)**	**53.85 (25.1-80.8)**	**147.18**	**2.02**	**0.12**
>50	80.00 (51.9-95.7)	61.54 (31.6-86.1)	141.54	2.08	0.33
>60	66.67 (38.4-88.2)	69.23 (38.6-90.9)	135.90	2.17	0.48
>82	33.33 (11.8-61.6)	84.62 (54.6-98.1)	117.95	2.17	0.79
>108	13.33 (1.7-40.5)	92.31 (64.0-99.8)	105.64	1.73	0.94
>138	0.00 (0.0-21.8)	100.00 (75.3-100.0)	100.00		1.00

Sensitivity and specificity of the CRP and ESR measurements in the samples of SAT patients at various cut-off levels are shown. The maximal summative value of sensitivity and specificity which invariably corresponds to a point in the ROC curve with the highest vertical distance from the 45° diagonal linear is shown in bold. CRP, C-reactive protein (serum); ESR, erythrocyte sedimentation rate; AEFH, at the end of the 1st hour; ROC, receiver operating characteristics; SAT, subacute thyroiditis; CI, confidence interval; +LR, positive likelihood ratio; −LR, negative likelihood ratio

examine the predictability of CRP and ESR in combination for glucocorticoid requirement in comparison to either of them alone, as narrated above.

In our clinical practice, continuous measures are frequently converted to dichotomous tests. Here, we have used ROC analysis [Table 2] to select the optimal threshold under a variety of clinical circumstances, balancing the inherent trade-offs that exist between sensitivity and specificity. The AUC for the CRP levels was higher as compared to the AUC for ESR levels [Table 2 and Figure 1]. The AUC is used to quantify the overall ability of a test to discriminate between 2 outcomes. Curves that approach closest to the coordinate (x = 0, y = 1) are more highly predictive, whereas ROC curves that lie close to the line of equality indicate that the result is no better than that obtained by chance. The optimum sensitivity and specificity have been determined from the ROC analysis as the point where the minimum distance line crosses the ROC curve. This point corresponds to the the Youden index (J)[28] which measures the effectiveness of diagnostic markers (larger the better) and enables the selection of an optimal threshold value (cut-off point). The Youden index method defines the optimal cut-point as the point maximizing the Youden function which is the difference between the true positive rate and false-positive rate over all possible cut-point values.[23] The larger Youden index in our study is indicative of the suitability of CRP over ESR as a discriminatory test for selecting SAT patients for glucocorticoid treatment. [Table 2].

We have also attempted to combine the conventional diagnostic test indexes, that is, sensitivity and specificity into a single index, that is, the likelihood ratio (LR+). Putting glucocorticoid requirement in SAT as the precondition, the positive LR was found to be the highest (8.67) at the optimal threshold of

19.3 mg/L for the CRP test [Table 2]. The largest value of LR+ occurs when the specificity tends to be close to 1 and sensitivity also to be close to 1. Thus, the higher value of LR+ for CRP revealed greater discriminatory power as a diagnostic test. The summative value of sensitivity and specificity at this CRP cut-off (158.98) was also the highest. At an optimal ESR cut-off of 46 mm AEFH, the corresponding LR+ is 2.08 and the summative value of sensitivity and specificity is 147.18, showing a weaker discriminatory power. [Table 3].

The low number of patients has been a limitation of the study. In that regard, our findings can be hypothesis-generating at best. We also acknowledge the fact that in the absence of any 'gold standard', the decision to initiate glucocorticoid treatment in our patients was based only on subjective assessment of patients' clinical condition. Not using any standard pain scoring protocol was another limitation of the study.

Conclusion

The serum CRP level provided a clear advantage over ESR as a diagnostic or predictive test with respect to the assessment of inflammation before the initiation of glucocorticoid therapy in SAT. However, a well-powered study is needed to examine the clinical relevance of such a role for CRP in thyroidology. While most diagnostic tests are not precise enough or otherwise not practicable in the limited golden time for the predicting the course of SAT , decisive serum levels of CRP can provide helpful information easily and rapidly to assess the infection severity along with initialization of appropriate glucocorticoid therapy. Our findings revealed that with high specificity, a CRP level of 19.3 mg/L can be considered to be the justified cut-off level for the treating SAT with glucocorticoids. We suggest that serum CRP be measured and monitored before

making a decision on choosing glucocorticoid therapy, which is considered to be an important agent in the current armamentarium of treatment.

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Conflicts of interest
There are no conflicts of interest.

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