**Sp3: Are biochemical investigations like ESR, CRP and tests of immune response important in the diagnosis of spinal tuberculosis (STB)?**

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**Response/Recommendation:** Several serum biomarkers including elevated levels of fibrinogen, hs-CRP, LBP, IFN Gamma, S100 A8, moderate increases in ESR and CRP, and low levels of WBC and Neutrophils, could indicate the presence of STB. However, these values are predominantly supportive and do not serve as confirmatory tests to diagnose STB.

**Level of Evidence**: Limited

**Delegate Vote:**

**Rationale**: Conventionally, the diagnosis of Spinal tuberculosis (STB) is made by a combination of clinical examination and MRI radiological features, while the final conclusive evidence is derived from tissue studies for culture and histopathological assessment[1,2]. But, for initial assessment, several serological investigations including inflammatory markers like erythrocyte sedimentation rate (ESR), C - reactive protein (CRP), tubercular immune response tests and other serum biomarkers are performed as corroborative tests. Despite their ubiquity, the value of these investigations in diagnosing STB in a patient with back pain and in differentiating pyogenic spondylitis from tubercular spondylitis is unclear.

We performed a systemic review of articles (n=228), and after screening the abstracts and full texts, nine articles were included for the final analysis. To differentiate back pain from STB, a few studies have studied the role of several serum biomarkers. Mann et al compared 26 patients of proven STB with 17 patients of back pain and noted that out of 17 serum biomarkers, Fibrinogen, CRP, Interferon Gamma (IFN-g) and Neural Cell Adhesive Molecule were the individual markers with the highest discrimination utility[3]. Lou et al studied 100 patients with STB and noted that serum liposaccharide binding protein, which is an acute phase inflammatory protein, had a significant correlation with STB when compared to normal volunteers[4]. To increase the diagnostic usefulness of normal CRP, serum high sensitivity CRP was assessed by Rao and Murthy in a study of 56 patients[5]. The authors noted that hs-CRP was raised in 70.96% of patients with STB and also correlated with a worse visual analogue scale score and neurological status. Similarly, serum neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR)[6] and expression levels of S100-A8 protein[7], a major member of the leukocyte protein S100 family have also shown to be potential biomarkers. Disease specific immune response tests (Interferon gamma release assays) including T-SPOT TB test, the QuantiFERON-TB Gold In-Tube (QFT-GIT) test, and the QuantiFERON-TB Gold Plus assay have been studied, and among these, the QFT-GIT test has a high sensitivity (92.16%) but a low specificity (67.14%) to diagnose STB[8].

Since pyogenic spondylitis is also associated with elevated serum inflammatory markers, specific biomarkers to differentiate pyogenic and STB infections would be beneficial. Lertudomphonwanit et al compared 73 patients of STB and 68 patients with pyogenic infections and noted that based on ROC curve, WBC $\leq$ 9,700/mm$^3$, neutrophil fraction $\leq$ 78% and ESR $\leq$ 92 mm/hr with an area under the curve of 0.921, was highly predictive of STB[9]. Similarly two other studies comparing STB and pyogenic infections have shown that significantly lower levels of WBC, neutrophils, lymphocytes, ESR, CRP, serum albumin and sodium in STB cases[10,11].

**Conclusion**:

The current evidence indicates that lowered WBC and neutrophil counts, as well as mildly increased ESR and CRP values are present in STB cases as compared to pyogenic infections. In patients who present with back pain suspicious of spinal infection, elevation of biomarkers including hs-CRP, fibrinogen, S-100 A8 protein, and positive Quantiferon Gold test would indicate the presence of STB infection. Since these studies do not have a robust methodology (Level 4 studies) and lack validation, the strength of recommendation to rely on these tests for confirmatory diagnosis of STB remains low.

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