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# Use of C-Reactive Protein as a Diagnostic Tool for Early Detection of Bacterial Infection After Liver Transplantation

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## *Dear Editor,*

Bacterial infection is one of the major causes of mortality in the first two weeks after liver transplantation (LT) (1). Even in the presence of the gravest bacterial infections, fever can be absent and other symptoms and signs of infection may only be trivial (2). There are other important causes of fever 3 - 10 days after LT, including viral infection and rejection (3, 4).

C-reactive protein (CRP) has been proposed as an early marker of inflammation. Quantitative measures of this protein have been used to diagnose a variety of inflammatory diseases, including bacterial infections (5, 6).

In a prospective study at the organ transplantation center (OTC) in Nemazi hospital, Shiraz, all adult liver recipients from May to September 2015 were evaluated for possible infections 3 - 10 days after LT. All patients with fever, new-onset abdominal pain, cough, deterioration of oxygenation, deterioration of mental status, or new-onset laboratory abnormalities (increased liver enzymes, increased BUN, leukocytosis) were evaluated for possible bacterial infections with chest X ray and cultures from blood, urine, sputum, and abdominal taps, with Gram staining of the latter two when appropriate. Patients were also evaluated for other causes of symptoms, including hepatic artery thrombosis, cytomegalovirus (CMV), herpes simplex (HSV) infection, and organ rejection.

The exclusion criteria were known infections (bacterial, fungal, or viral) before transplantation, hemodialysis before or after transplantation, hepatocellular carcinoma or cholangiocarcinoma, indications for liver transplantation other than cirrhosis, and therapy with antithymocyte globulin (ATG) as an induction immunosuppressive drug.

For all patients, the white blood cell count (WBC) and CRP level (Biorex Diagnostic Ltd., Antrim Technology Park, Muckamore, Antrim, United Kingdom) were checked at the time of the first clinical suspicion of a bacterial infection.

Written consent was obtained from all participants, and the data were anonymized before the analysis.

During the study period, 188 patients received LT, of whom 152 were older than 18 years. In 51 patients, there was clinical suspicion of a bacterial infection, which was later confirmed in 25 patients. In 36 others, the final diagnosis was rejection in five, CMV infection in three, HSV in five, and no specific cause in 13. Using a CRP cutoff value of 52 mg/L, there was sensitivity of 68.0% (95% CI 46.5 - 85.1) and specificity of 80.77% (95% CI 60.6 - 93.4), with a positive predictive value of 72.4% and a negative predictive value of 77.3% for bacterial infection. The area under the ROC curve (AUC) was 0.704 (95% CI 0.560 - 0.823) (Figure 1). This AUC for leukocytosis (WBC $>$ 10,000/$\mu$L) in the diagnosis of a bacterial infection was 0.624 (95% CI 0.477 - 0.756).

There have been reports on post-LT elevated CRP levels due to surgery, hepatocellular carcinoma, rejection, and viral infections, but the highest levels have been reported with bacterial infections (7, 8). This makes CRP an attractive biomarker for the early detection of sepsis in these patients (7, 9, 10).

In this study, we attempted to determine a cutoff level to aid in decision-making for the initiation of antibiotics in the early post-LT period. At a cutoff value of 52 mg/L, the AUC was 0.743, which was far better than that of leukocytosis for the diagnosis of bacterial infections. This could save the patient's life while reducing the cost of the hospital stay due to delayed diagnosis of a bacterial infection.

There have been reports on the use of other biomarkers for the early detection of sepsis in the post-LT period, including procalcitonin and interleukin-6 (IL-6) (10). The former showed a poor correlation with sepsis, and the lat-

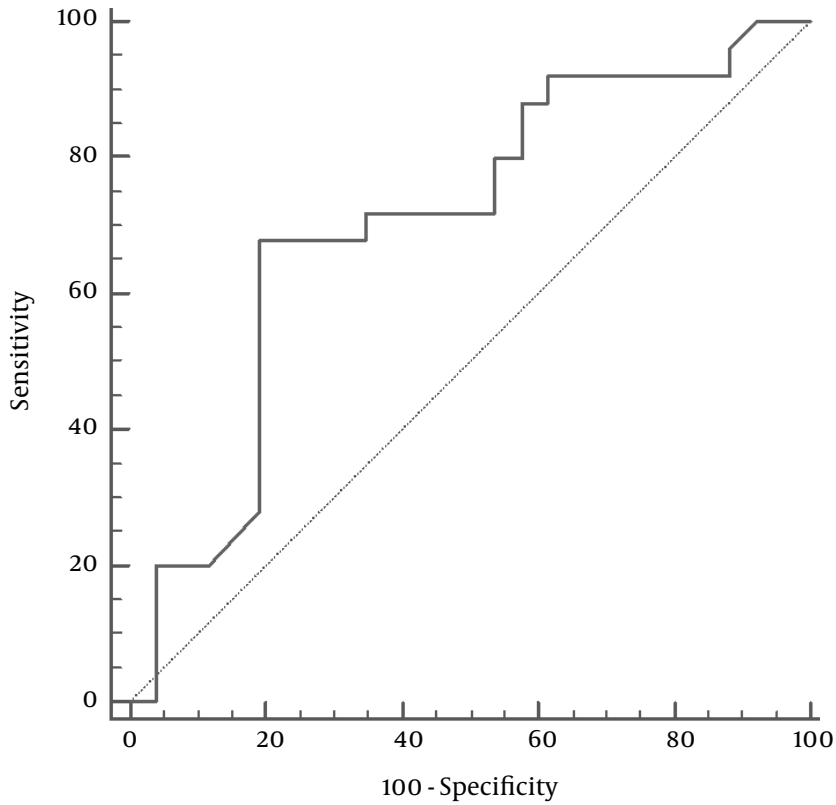


**Figure 1.** Receiver Operating Characteristic (ROC) Curve for CRP and Bacterial Infections in the Early Post-Liver Transplantation Period

ter is not widely available.

We propose that CRP levels 72 hours after liver transplantation could help physicians diagnose bacterial infections more rapidly. The dynamics of such increases might be of interest, as an increasing level within hours might be more alarming. This needs to be evaluated in further studies.

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## References

1. Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med.* 2007;**357**(25):2601–14. doi: 10.1056/NEJMra064928. [PubMed: 18094380].
2. O'Shea DT, Humar A. Life-threatening infection in transplant recipients. *Crit Care Clin.* 2013;**29**(4):953–73. doi: 10.1016/j.ccc.2013.06.012. [PubMed: 24094386].
3. De Gasperi A, Feltracco P, Ceravola E, Mazza E. Pulmonary complications in patients receiving a solid-organ transplant. *Curr Opin Crit Care.* 2014;**20**(4):411–9. doi: 10.1097/MCC.0000000000000120. [PubMed: 24979712].
4. Arslan H. Infections in liver transplant recipients. Experimental and clinical transplantation. *J Middle East Society Organ Transplant.* 2014;**12**:24–7.
5. Albrich WC, Harbarth S. Pros and cons of using biomarkers versus clinical decisions in start and stop decisions for antibiotics in the critical care setting. *Intensive Care Med.* 2015;**41**(10):1739–51. doi: 10.1007/s00134-015-3978-8. [PubMed: 26194026].
6. Stubljar D, Skvarc M. Effective Strategies for Diagnosis of Systemic Inflammatory Response Syndrome (SIRS) due to Bacterial Infection in Surgical Patients. *Infect Disord Drug Targets.* 2015;**15**(1):53–6. [PubMed: 25809624].
7. Their M, Ronnholm K, Sairanen H, Holmberg C, Jalanko H. Serum C-reactive protein in pediatric kidney and liver transplant patients. *Pediatr Transplant.* 2002;**6**(2):153–60. [PubMed: 12000473].
8. Kornberg A, Witt U, Kornberg J, Muller K, Friess H, Thrum K. Postoperative peak serum C-reactive protein is a predictor of outcome following liver transplantation for hepatocellular carcinoma. *Biomarkers.* 2016;**21**(2):152–9. doi: 10.3109/1354750X.2015.1118548. [PubMed: 26643974].
9. Ashkenazi-Hoffnung L, Mozer-Glassberg Y, Bilavsky E, Yassin R, Shamir R, Amir J. Children post liver transplantation hospitalized with fever are at a high risk for bacterial infections. *Transpl Infect Dis.* 2016;**18**(3):333–40. doi: 10.1111/tid.12528. [PubMed: 26989885].
10. Zant R, Melter M, Knoppke B, Ameres M, Kunkel J. Kinetics of interleukin-6, procalcitonin, and C-reactive protein after pediatric liver transplantation. *Transplant Proc.* 2014;**46**(10):3507–10. doi: 10.1016/j.transproceed.2014.08.048. [PubMed: 25498081].