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The accuracy of procalcitonin in detecting non-viral infections in liver transplant recipients following orthotopic liver transplantation: A single center experience

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Abstract

Background: Infections are a leading cause of complications and mortality following orthotopic liver transplantation. Although microbiological cultures are the gold standard for diagnosis, their delayed results can hinder timely intervention. Procalcitonin has been widely studied as a diagnostic marker for bacterial infections. This study evaluates the diagnostic value of procalcitonin in detecting non-viral infections in liver transplant recipients.

Material and Methods: In this single-center observational study, 29 adult patients who underwent first-time orthotopic liver transplantation between March 2023 and March 2024 were prospectively evaluated. Participants were assessed before orthotopic liver transplantation and on the second postoperative day and were followed until hospital discharge. Logistic regression and receiver operating characteristic (ROC) analysis were used to assess predictors of infection.

Results: Seven patients (24.1%) developed post-transplantation infections. Six (20.6%) patients died during hospitalization, three of whom (50%) due to sepsis. Multiorgan failure, cardiac arrest, and thrombotic events were other death causes. Postoperative procalcitonin levels were significantly associated with infection risk (OR: 1.119, 95% CI: 1.013–1.237). Procalcitonin at a cutoff value of 0.85 ng/mL yielded 85.7% sensitivity, 54.5% specificity, and 37.5% and 92.3% positive and negative predictive values, respectively. Postoperative infections were not associated with demographic factors, comorbidities, model for end-stage liver disease score, surgery duration, or transfusion requirements.

Conclusion: Early postoperative procalcitonin levels demonstrated good diagnostic accuracy in detecting non-viral infections following orthotopic liver transplantation. Despite limitations including small sample size and lack of serial measurements, the findings support the clinical utility of procalcitonin in infection detection of liver transplant recipients.

Introduction

Orthotopic liver transplantation is the treatment of choice in cases of end-stage liver disease and acute liver failure [1,2]. Among post-transplantation complications, graft rejection and infections account for the most common and serious adverse outcomes [3,4]. Infections remain the leading cause of morbidity and mortality following orthotopic liver transplantation [5–7], with bacterial infections predominating at a rate of 30–70% within the first month post-transplantation often presenting as septicemia, surgical site, respiratory and urinary tract infections [1,5,7]. The timely diagnosis of infection is challenging in liver transplant recipients due to the immunosuppression attenuating the clinical symptoms of infection [8,9]. Although microbiological cultures stand as the gold standard for infection diagnosis, their time-consuming nature is considered a significant limitation [9,10]. Nonetheless, early diagnosis of infection in liver transplant recipients is crucial in preventing severe complications and improving the outcomes [6].

Procalcitonin (PCT) is the calcitonin precursor and an acute phase reactant with minimal serum concentrations (< 0.5 mg/dl) In healthy individuals [8,11]. PCT rises in response to a systemic challenge of the organism with bacterial endotoxin and often remains at low concentrations in viral and fungal infections and non-specific systemic inflammatory conditions [6,11,12]. Unlike systemic inflammatory biomarkers like C-reactive protein (CRP) and leukocyte count, PCT remains less affected by impaired liver function and immunosuppression which are common in liver transplant recipients [6,8]. Furthermore, PCT demonstrates superior kinetics with rapid elevation and decline compared to other biomarkers, indicating favorable diagnostic properties for bacterial infections [9,13].

However, increased PCT has been observed in some non-infectious medical conditions as well. Wanner et al. observed in 405 injured patients, that higher PCT levels within three days after mechanical trauma is associated with increased risk of sepsis and multiple organ dysfunction syndrome [14]. In a study on 110 patients after orthotopic liver transplantation, patients with early allograft dysfunction (EAD) had significantly higher PCT levels on the second day post-transplantation, even though the rate of infection was not different between EAD and non-EAD groups [15]. On the other hand, in a prospective study of 40 liver transplant recipients, patients with graft rejection showed no increase in PCT levels, while those with infection demonstrated significantly higher PCT concentrations [16]. Nonetheless, data regarding the diagnostic performance and optimal cut-off levels of post-transplantation PCT in liver transplant recipients remains limited. In this study, the diagnostic values of PCT in detecting early post-transplant non-viral infections in liver transplant recipients are assessed.

Materials and methods

Design and sampling

This single-center observational study was conducted at Firoozgar Hospital in Tehran, Iran, between March 2023 and March 2024. The study protocol was conformed to the ethical guidelines of the 1975 Helsinki Declaration, and approved by the Ethics Committee of Iran University of Medical Sciences (IUMS) (Number: IR.IUMS.FMD.REC.1401.685). Eligible participants were adult patients (≥ 16 years old) with end-stage liver disease who underwent orthotopic liver transplantation for the first time. Patients were excluded if they were diagnosed with an active infection prior to the surgery, at the discretion of an infectious disease specialist. Informed consent was obtained from all participants. Infections were diagnosed according to criteria established by the Centers for Disease Control and Prevention (CDC), which include pulmonary, bloodstream, or intra-abdominal infections characterized by clinical symptoms and confirmed by microbiological, radiological, or surgical findings, and responsive to appropriate therapy. Patients were evaluated both before transplantation and on the second postoperative day. All participants were followed until hospital discharge. All liver transplant donors included in this study were deceased donors. No transplantation from living donors was included in this study.

Measurements and endpoints

Demographic characteristics, existing comorbidities, underlying causes of liver failure, laboratory findings, including serum PCT, Model for End-Stage Liver Disease (MELD) and MELD-Na scores, the length of surgery, and hospitalization length were measured and calculated. Patients underwent a complete physical examination before and after the surgery, and blood and urine cultures were obtained. Additional infection screening, including chest or abdominal imaging and stool, sputum, and surgery site cultures, if necessary. All patients received antibacterial prophylaxis and immunosuppressive regimens, mostly consisting of calcineurin inhibitors (tacrolimus or cyclosporine) and low-dose corticosteroids. PCT levels were measured based on quantitative immunoassay using LUMI test PCT kits (BRAHMS Diagnostica, Berlin, Germany). The endpoint of this study was to assess the diagnostic values of serum PCT in detecting post-surgical non-viral infections in liver transplant recipients. Preoperative and postoperative length of hospital stays, the need for dialysis (yes/no), blood transfusion (packed red blood cell units) preoperative, intraoperative, and postoperative, and the length of the surgery were recorded and evaluated in association with the risk of post-transplantation infections. Demographics and laboratory data across patients with and without infections were also evaluated.

Data analysis

Categorical variables were expressed as frequencies, and continuous variables were presented as mean ± standard deviation (SD). The normality of the data was assessed using the Shapiro-Wilk test and Q-Q plots. Depending on the distribution, continuous variables were compared using either the independent samples t-test or the Mann-Whitney U test. The Chi-square test was performed to compare categorical variables. Binary logistic regression analyses were performed to examine the association between study variables and the odds of post-transplantation infections. The area under the receiver operating characteristic (ROC) curve (AUC) was calculated to evaluate the predictive performance of postoperative PCT levels for post-transplantation infections, and the optimal cutoff value was determined. All analyses were conducted at a significance level of 0.05. Statistical analyses were performed using SPSS software, version 18.

Results

General description

In total, 29 patients were eligible for the study of whom 20 (69%) and 9 (31%) were male and female, respectively. Participants' age ranged from 17 to 69 with an average of 42.6 ± 15.36. The frequency of diabetes, hypertension, ulcerative colitis, ischemic heart disease, and hypothyroidism was 6 (20.7%), 3 (10.3%), 4 (13.8), 1 (3.4%), and 1 (3.4%), respectively. As for the underlying causes of orthotopic liver transplantation in the patients, 6 (20.7%) had autoimmune hepatitis, 5 (17.2%) had primary sclerosing cholangitis (PSC), 2 (6.9%) had cholangiocarcinoma, 4 had hepatitis B virus (HBV), 3 (10.3%) had non-alcoholic steatohepatitis (NASH), 2 (6.9%) had Wilson's disease, 2 (6.9%) had alcoholic steatohepatitis

(ASH), 2 (6.9%) had cryptogenic hepatitis, and 3 (10.3%) had other rooting causes of liver failure. None of the patients presented with an organ failure other than liver failure before the surgery. Baseline characteristics and laboratory findings (except for INR), Model for End-Stage Liver Disease (MELD), and MELD-Na, were not significantly different between patients with and without infection (Table 1).

Postoperative outcomes and infection risk assessment

The orthotopic liver transplantation was performed without any serious adverse outcome in 18 (62%) patients. However, adverse outcomes in this study included portal vein and hepatic artery thrombosis in 4 (13.7%), multiorgan failure in 2 (6.9%), intraabdominal hemorrhage in 2 (6.9%), and abdominal free fluid, intestinal mesenteric oozing, and biliary stenosis in 3 (10.3%) patients. Out of 29 patients, 7 (24.1%) developed post-transplantation infections. Microbiological studies identified *Klebsiella pneumoniae* in five (17.24%) patients (three positive hepatic collection cultures, one positive blood culture and one positive sputum culture), *Pseudomonas aeruginosa* in two (6.88%) patients (one positive hepatic collection culture and one positive blood culture), *Staphylococcus aureus* in two (6.88%) patients (two positive sputum cultures), and *Entamoeba histolytica* in one (3.44%) patient (positive stool smear). Six (20.6%) patients sadly died during the post-transplantation hospitalization among which 3 (50%) were sepsis related. Multiorgan failure, cardiac arrest, and thrombotic events were other causes of death in the patients.

Age (OR:1.04, 95%CI:0.97–1.10), male gender (OR:3.42, 95%CI:0.34–33.79), BMI (OR:1.25, 95%CI:0.92–1.69), MELD and MELD-Na scores (OR:0.94, 95%CI:0.85–1.03, and OR:0.94, 95%CI:0.85–1.03, respectively), Preoperative hospitalization length (OR:1.00, 95%CI:0.90–1.10), blood transfusion (preoperative OR:1.00, 95%CI:0.90–1.10, intraoperative OR:1.05, 95%CI:0.48–2.28, and postoperative OR:0.83, 95%CI:0.51–1.36), postoperative dialysis (OR:1.06, 95%CI:0.16–7.05), and the length of transplant surgery (OR:1.64, 95%CI:0.70–3.85) were not associated with risk of postoperative infections (Fig. 1).

Patients with post-transplantation infections had significantly higher levels of white blood cells ($p < 0.001$), and slightly elevated levels of laboratory findings, such as renal and liver function tests, compared to the non-infected group. Although the length of transplant surgery was longer in the group with infection, it was not statistically significant (6.14 ± 0.8 versus 5.61 ± 1.1 hours, $p = 0.255$). (Table 2)

The role of PCT

In a binary logistic regression model, post-operative PCT levels were a significant predictor of post-operative infection (OR:1.119, B = 0.113, 95%CI:1.013–1.237).

The area under the Receiver Operating Characteristic (ROC) curve (AUC) was 0.81 for diagnosing infection after liver transplantation, with post-operative PCT levels as the predictor. PCT at the optimal cutoff of 0.85 ng/mL yielded 85.7% sensitivity, 54.5% specificity, 37.5% positive predictive value (PPV), and 92.3% negative predictive value (NPV). (Fig. 2)

Discussion

Liver transplant recipients are more susceptible to postsurgical bacterial infections compared to other solid organ recipients, primarily due to the complexity of the surgical procedure [7]. In a single-center study on 463 liver transplant recipients, 190 (41%) developed at least one infection in a two-year follow-up [17]. Similarly, Kim et al. reported a 39.9% incidence of infections within the first month after transplantation in a nine-year retrospective study [18]. A meta-analysis of 23 studies identified MELD score (OR: 2.09, 95% CI: 1.10–3.97), intraoperative blood transfusion (OR: 2.14, 95% CI: 1.04–4.38), and hospital length of stay (OR: 1.03, 95% CI: 3.06–7.61) as significant risk factors for post-transplant bacterial infections; however, these factors were not statistically significant in this study. Preoperative antibiotic use was also reported as a strong predictor of post-transplant bacterial infections, particularly drug-resistant gram-negative infections (OR: 3.62, 95% CI: 1.83–7.17) [1]. These findings emphasize the importance of early infection diagnosis and appropriate antibiotic management to reduce complications and improve outcomes following liver transplantation.

PCT has been proposed as a useful biomarker for the early detection of bacterial infections [4,13,19,20]. In one study of 55 suspected catheter-related bloodstream infections after orthotopic liver transplantation, a PCT threshold of ≥ 3.1 ng/mL achieved 72% sensitivity and 87% specificity [21]. Another study involving 90 patients undergoing major abdominal surgery showed that PCT levels ≥ 1 ng/mL yielded 50% sensitivity and 80% specificity on the first postoperative day, and 57% sensitivity and 81% specificity on the second day in diagnosing infections. Consistent with the current study's findings, patient age, sex, BMI, and comorbidities were not associated with the risk of postoperative infections [22]. Kaido T. et al. conducted a prospective study on 104 adults undergoing liver transplantation which demonstrated that serum PCT was significantly elevated in patients with bacteremia compared to those without, including cases of graft rejection or viral infection. They reported positive and negative predictive values of 83.3% and 97.4% for PCT in detecting bacteremia at cutoff values of 2.0 and 0.5 ng/ml, respectively [23]. In this study, a PCT cutoff of ≥ 0.85 ng/mL demonstrated 85.7% sensitivity, 54.5% specificity, 37.5% PPV, and 92.3% NPV for detecting non-viral infections on the second postoperative day (Fig. 2).

Ghiasvand and colleagues reported similar findings in a prospective study of 28 liver transplant recipients, suggesting that serial PCT measurement could serve as a valuable diagnostic tool in early post-transplant days, with 77.8% sensitivity and 79% specificity at a cutoff of 0.5 ng/mL within 2 days after liver transplantation [6]. Conversely, a larger prospective study of 135 liver transplant recipients showed only marginal abilities of peak PCT in discriminating patients with and without clinically significant infections (CSI) in a multivariable analysis (hazard ratio:1.0 per unit (ng/mL) increase, $p = 0.368$), even though the median PCT was significantly higher in patients with CSI ($p = 0.014$) [10]. Interestingly, Perrakis et al. observed that while the initial PCT peak was not associated with postoperative infections, a second peak correlated with both infectious and non-infectious complications as well as mortality. They also identified surgery duration as a significant risk factor for postoperative infections [8]. Univariate analysis showed a significant association between PCT levels on

the second postoperative day and an increased risk of infections (OR: 1.119, 95% CI: 1.013–1.237). This study had some limitations, including a lack of data on other inflammatory biomarkers such as CRP, a limited sample size that restricted the ability to perform multivariable analyses to adjust for potential confounders, and the absence of serial PCT measurements to evaluate its dynamic association with study outcomes.

Collectively, the findings suggest that early postoperative PCT levels may serve as a promising diagnostic tool for non-viral infections following orthotopic liver transplantation. Regarding the current study's limitations, further studies on this subject are required.

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Tables

Tables 1 and 2 are available in the supplementary files section.

Figures

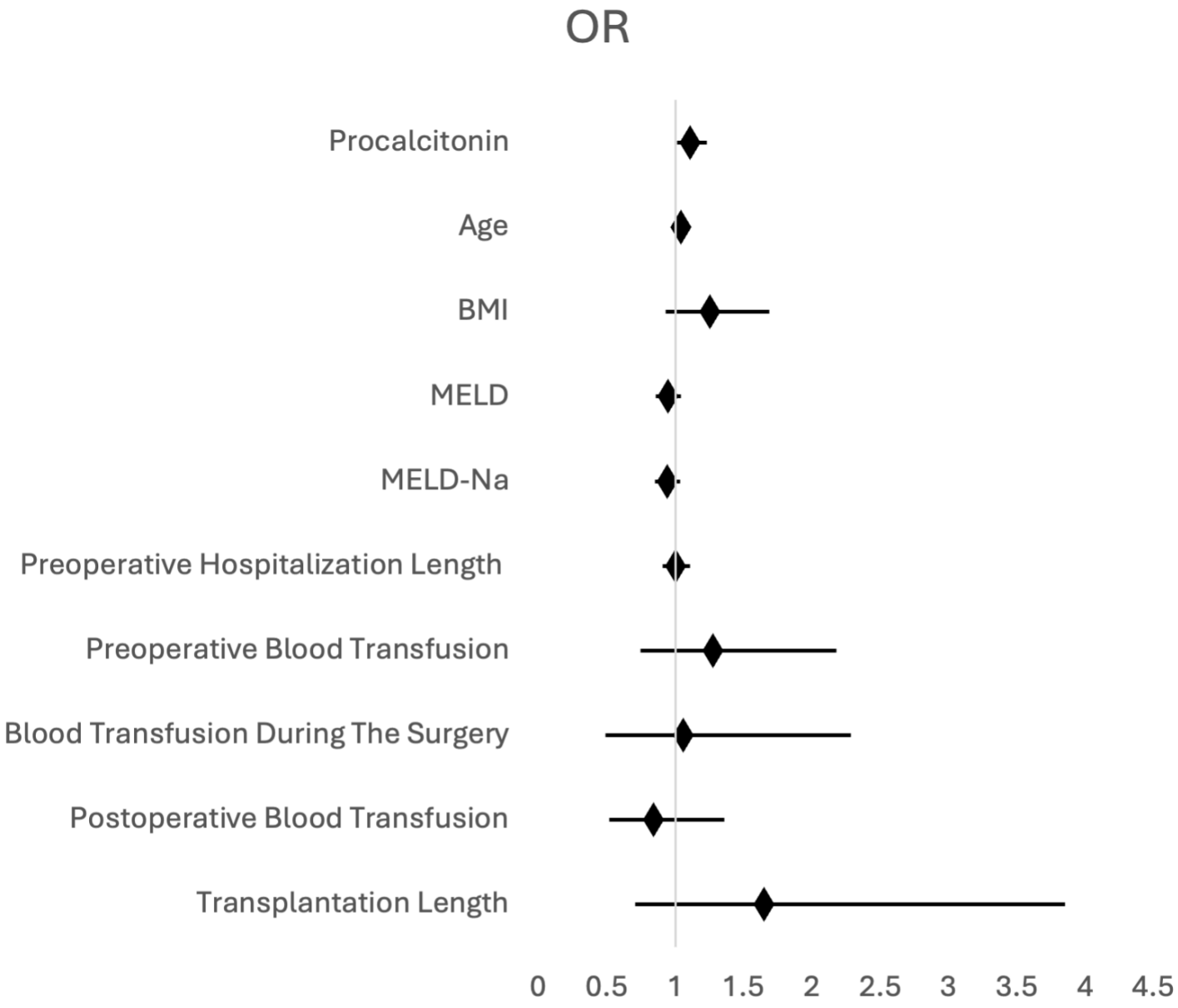


Figure 1

Forest plot of univariate analyses of study variables in detecting non-viral infections on the second day post orthotopic liver transplantation (OLT)

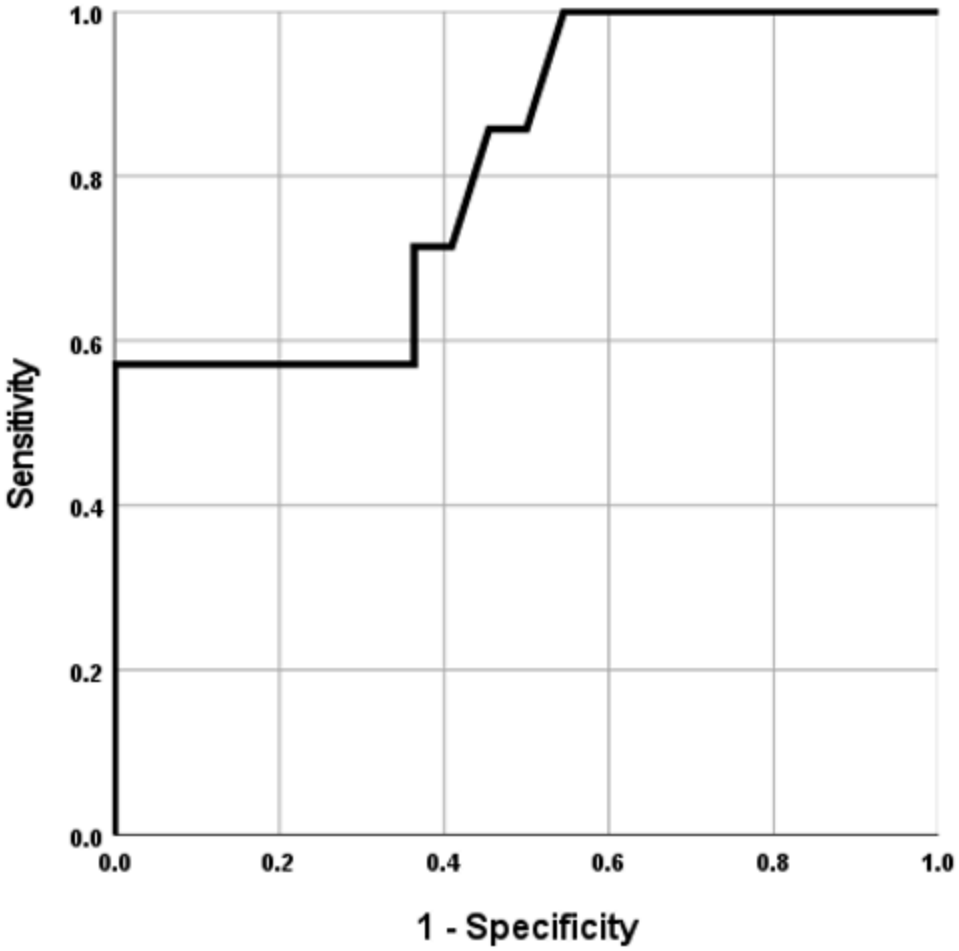


Figure 2

The Receiver Operating Characteristic (ROC) curve for PCT levels in detecting non-viral infections on the second day post orthotopic liver transplantation (OLT)

Supplementary Files

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- Table1.docx
- Table2.docx