

Procalcitonin as an early diagnostic marker for septic complications in the immediate postoperative setting after Living Donor Liver Transplantation (LDLT)

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ABSTRACT

Background: Infection and rejection are the most common complications after liver transplantation. Both may develop during initial post-operative progress. Early differentiation is important for determination of the appropriate treatment. Objective: To investigate the ability of procalcitonin (PCT) in differentiation between infection and rejection in complicated cases in the immediate post-operative setting after LDLT.

Method: The study includes 40 cases post liver transplantation. All adult patients underwent post-operative clinical course analysis, APACHE II and MELD score. Lab investigations included Procalcitonin, C-Reactive protein and TLC every 48 hours starting from day 6 post-operative.

Results: Group 1: Patients without post-operative complication. Group 2: Patients with infection complication. Group 3: patients with early rejection pattern. Length of stay in ICU was longer in group 2 (16.40 ± 9.40 , p value: 0.02). PCT and TLC levels were significantly high in group 2 in day 6 (5.27 ± 6.67 , p value: 0.00) and (8.61 ± 6.94 , p value 0.02) respectively. PCT, TLC and CRP ROC curves for prediction of infection show highest results with PCT (sensitivity 60 %, specificity 97 % and cut-off value 0.75 ng/ml, the area under the curve is 0.883). In group 2, PCT levels showed significant percentage changes between day 8 to day 10 (15.86 ± 73.40 , p value 0.018), day 10 to day 12 (15.96 ± 56.69 p value: 0.018) and day 12 to day 14 (15.09 ± 71.74 p value 0.043). In group 2, there was strong direct correlation between the percentage changes of PCT, TLC in day 6 to day 8 (p value: 0.00, R + 0.998).

Conclusion: Based on these results, we recommend that PCT possesses important diagnostic and prognostic power in the post-transplant sepsis after liver transplantation.

Key words: Liver transplantation, Procalcitonin, sepsis, complication.

INTRODUCTION

Application and success of living donor liver transplantation (LDLT) has continued to grow, where liver transplantation has become accepted therapy for several causes of irreversible liver disease. With the increased number of transplants, increases the probability of post transplant problems as well.

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Among these problems is sepsis which is the most common cause of mortality, especially in patients undergoing an immune suppressive therapy and after a major surgical treatment. Despite the development and administration of new antimicrobial therapeutic modalities, the mortality rate of sepsis remains high. This is mainly due to high co morbidity and delayed establishment of the diagnosis and treatment. The currently used biochemical markers [C-reactive protein (CRP) or leukocyte count] aren't enough specific inflammation markers to establish a definite diagnosis in the early post-operative setting. (1-3)

Infection and rejection are the most common complications after liver transplantation. Both may develop during initial post-operative progress and are

presented with fever, an increase of liver enzymes and (or) bilirubin. At this clinical stage, early diagnosis is important for determination of the appropriate treatment. (4).

Procalcitonin (PCT) is a precursor protein of the hormone calcitonin. PCT is induced in the plasma of patients with severe bacterial or fungal infections or sepsis. Local bacterial infections, viral infections, autoimmune and allergic disorders do not induce PCT. (5)

Clinically significant infections (CSIs) are life-threatening but difficult to diagnose after liver transplantation. This study investigates the value of procalcitonin (PCT) in addition to C - reactive protein (CRP) and the leukocyte count (LC) as a diagnostic marker for CSIs in recipients. CSIs were defined as pulmonary, bloodstream, or intra-abdominal infections.

Aim of the work:

Investigate the ability of procalcitonin (PCT) in differentiating between infection and rejection in complicated cases in the immediate post-operative setting after living donor liver transplantation.

MATERIALS AND METHODS

We conducted an observational study on 42 patients; 20 retrospective cases from the 1st of September 2014 to 31st of March 2015 and 22 prospective cases from the 1st April 2015 to 30th September 2015. All patients who underwent liver transplantation as recipients were \geq 18 years old. Patients were admitted to the ICU (intensive care unit) post operatively in Wadi El-Neil hospital and El-Shiekh Zayed specialized hospital. The study is conducted after the approval of the Ethical committee by the ICU department, Kasr Al-Aini (Cairo University) and the approval of the medical and ethical committees in Wadi El-Neil and El-Shiekh Zayed specialized hospitals. Patients who received anti-thymocyte globulin (ATG) based immune-suppressive therapy were excluded as that therapy is a stimulus for synthesis and elevation of PCT. (6)

Our study Includes 3 groups.

Group 1: Normal patients (no early rejection pattern or infection; normal PCT, TLC and CRP; and liver function tests regress to normal values).

Group 2: Patients with infection complication (fever with increased PCT, TLC, CRP and liver function tests impaired) and

Group 3: patients with early rejection pattern (Fever may be elevated, normal PCT, increased TLC & CRP with impaired liver function tests).

Graft dysfunction: was defined as the occurrence of at least one of the following criteria: the need for re-transplantation (primary non function, PNF), a rise in aminotransferases of above 2,000 UI/L, impairment of factor V (<30%) with synchronous increase of bilirubin without a retrospective need for re-transplantation,

serum bilirubin greater than 10 mg/ml; PT of at least 17 sec; hepatic encephalopathy (7).

Certain hepatic biochemical test abnormalities can indicate early acute cellular rejection within 90 days of the liver transplantation. Such abnormalities may include elevations of some or all of the following: serum aminotransferases, alkaline phosphatase, gamma-glutamyl transpeptidase and bilirubin levels. These abnormalities are useful in distinguishing acute cellular rejection from other causes of hepatic allograft dysfunctions. Among these dysfunctions are hepatic artery thromboses, biliary anastomosis leak and biliary stenosis by Doppler ultrasound. However, liver histology remains the gold standard for the diagnosis and grading according to BANFF criteria (8, 9).

Postoperative complications were defined as hepatic dysfunction, infection, pulmonary, renal, surgical complications or biliary complications. Surgical complications include bleeding, hepatic artery thrombosis (HAT), and thrombosis of the portal or cava vein; while biliary complications include insufficiency, stenosis, and ischemic type biliary lesion (ITBL).

The definition of clinically significant infections (CSIs) included pulmonary, bloodstream, or intra-abdominal infections accompanied by clinical symptoms proven by microbiological, radiological, or surgical findings and reacting to instituted therapy.

Infection was diagnosed if clinical; biochemical or radiologic signs of infection were evident. Chest X-rays and ultrasound examinations were performed on daily basis during the ICU stay and computed tomography (CT) scans when a clinical infection was suspected, and on the basis of these examinations, prompt therapy was initiated. In cases where samples from the suspected site of infection were positive, a proven infection could be defined With signs and symptoms of Systemic Inflammatory Response Syndrome (SIRS), Sepsis, Severe Sepsis and/or Septic shock (according to 2012 revised ACCP/SCCM sepsis definitions) (10).

Immunosuppression protocol and antibiotic prophylaxis:

All patients were initially treated with tacrolimus, starting 24-36 hours after transplantation at 0.1 mg/kg twice daily and 500 mg methylprednisolone in the an-hepatic phase. Some patients (who were expected to have any delay in introduction of immunosuppressive therapy i.e. elevated serum creatinine preoperatively) received basiliximab (Simulect, 20 mg) in the an-hepatic phase followed by a second administration (20mg), 4 days after transplantation and these patients were excluded. Mycophenolatemofetil (500 mg twice daily, intravenous or per oral) was administered starting on the 5th postoperative day. Acute rejection was diagnosed clinically and if not resolved diagnosis was based on the histo-pathological examination after liver biopsy according to BANFF criteria (8, 9).

All recipients received broad spectrum antimicrobial prophylaxis, consisting of antibacterial and antimycotic agents: with piperacilline-tazobactam for 3 days.

Selective digestive decontamination consisted of 200mg of oral amphotericin B 3 times daily until the 21st postoperative day.

Clinical assessment and investigations:

Applied Scoring systems: APACHE II score (The acute physiology and chronic health evaluation) was used to determine the initial severity of illness at the time of admission. APACHI SCORE: Approximate Mortality Interpretation score from 0 to 71 is computed based on several measurements - higher scores correspond to more severe disease and a higher risk of death. MELD SCORE (Model for End-Stage Liver Disease) is a scoring system for assessing the severity of chronic liver disease; The range is from 6 (less ill) to 40 (badly ill). (11, 12)

Laboratory tests requested:

Routine labs included CBC, CRP, liver function tests, renal function tests and blood levels of immunosuppressive drugs were determined daily. Specific labs included Procalcitonin, C-Reactive protein every 48 hours for all patients starting from day 6 post-operatively in the early ICU period.

Statistical methodology:

Data is statistically described in terms of range, mean, standard deviation (\pm SD), median and percentages. Normal distributed parametric data in the present study is analysis using ANOVA test with post hoc tests for the determination of the source of variation. For comparing non parametric data, Chi square (χ^2) test was performed. A probability value (P value) less than 0.05 is considered significant.

Cutoff points were determined to maximize the accuracy (percentage of correctly predicted patients) of classification via PCT. **ROC curve** (Receiver Operator Characteristic) was used to find out the best cut off value of certain predictor and its validity.

All statistical calculations were done using computer program Microsoft Excel version 2010 and SPSS (Statistical Package for the Social Science) statistical program version 12.

RESULTS

This research included a total of 42 patients (37 males and 5 females ranging from 19 to 66 years old (with mean age of 52.95 ± 8.18). The patients were

divided into three groups: **Group 1**: Normal without early mild rejection or infection (23 cases), **Group 2**: Infection infected patients (10 cases) and **Group 3**: Early mild rejection (9 cases). The mean age and gender of the 3 groups is shown in [table 1](#) and the indications of liver transplantation are shown in [table 2](#).

Table-1. Patients' gender and mean age according to study groups

Age /Group	Group 1	Group 2	Group 3	P value
Age	51.35 \pm 8.74	55.60 \pm 6.08	54.11 \pm 8.62	0.461
Male: 37	N: 20 (87%)	N: 8 (80%)	N: 9 (100%)	0.393
Female: 5	N: 3 (13%)	N: 2 (20%)	N: 0 (0%)	

Table-3. Comorbidities potentially affecting the outcome

Co morbidities	Group 1	Group 2	Group 3
Non N : 16	N: 11 (47.8%)	N: 1 (10%)	N: 4 (44.4%)
DM N: 25	N: 12 (52.2%)	N: 9 (90%)	N: 4 (44.4%)
HTN N: 1	N: 0	N: 0	N: 1 (11.1%)
P value = 0.074			

Comorbidities as hypertension does not affect the outcome, however DM was risk factor in group 2 the infection group as shown in [tables 3 and 4](#).

The sources of infection in group 2 were mainly pulmonary (60%), blood born (30%) and abdominal drains (10%). Culture results were +ve only in group 2 (infection group) in which *Klebsiella* (40%), *E.coli* (30%) & *Pseudomonas* (20%) were the main causative organisms. However culture results in groups 1 and 3 were no growth. MELD score & APACHI 2 score among the study groups were not significant as shown in [table-5](#).

Table-4. DM & incidence of infection

Table-2. Indications of liver transplantation among the study groups.

Indications/ group	Group 1 n:35	Group 2 n:10	Group 3 n:9
HCV + ve N: 35	N: 18 (78.3%)	N: 10 (100%)	N: 7 (77.8%)
HBV + ve N: 2	N: 2 (8.7%)	N: 0 (0%)	N: 0 (0%)
Cryptogenic liver cirrhosis N: 3	N: 2 (8.7%)	N: 0 (0%)	N: 1 (11.1%)
Alcoholic liver cirrhosis N: 1	N: 0 (0%)	N: 0 (0%)	N: 1 (11.1%)
Auto-immune liver cirrhosis N: 1	N: 1 (4.3%)	N: 0 (0%)	N: 0 (0%)
P value = 0.476			

		Non-infection groups (1 & 3)	Infection group(2)	Total	P value
DM	No DM	N: 16 (50%)	N: 1 (10%)	17	0.024
	DM	N: 16 (50%)	N: 9 (90%)	25	
Total		N: 32	N: 10	42	

Table-5. MELD score & APACHI 2 score among the study groups

	Group 1	Group 2	Group 3	P value
MELD score (Mean \pm SD)	18.34 \pm 4.41	20.10 \pm 2.88	16.89 \pm 3.76	0.255
APACHI 2 score (Mean \pm SD)	6.82 \pm 1.43	8.70 \pm 2.90	6.66 \pm 2.50	

There is no relation between incidence of complications and the patient groups, but infection is the most common complication in all patients (23%), followed by post-operative bleeding (11.9%). There was only 1 patient suffering from acute graft rejection (2.3%), and only 1 patient suffering from hepatic artery thrombosis (2.3%). Length of stay in ICU post liver transplantation was significantly different among the groups of patients, where the longest stay was among group 2 (table 6).

Laboratory tests and markers variables:

Groups 1, 2 and 3:

PCT levels were significantly different among the 3 groups of patients in day 6 as PCT level was only elevated in group 2. Also TLC levels show significant difference among the 3 study groups in day 6 as it was elevated in group 2 & 3 but not in group 1 (table 7). ROC curves for predicting infections:

PCT has sensitivity of 60%, high specificity of 97%, area under the curve (0.883) and a cut off value of 0.75 ng/ml, p value 0.000 and a cutoff value 0.75ng/ml; with +ve predictive value is 85.7% and -ve predictive value is 88.6%. **N.B:** in day 6 to day 14, 9 cases out of 10 (group 2) had PCT value \geq 0.75. All group 3 (early acute mild rejection) patients had PCT values <0.75ng/ml (figure 1).

TLC has low sensitivity 40%, high specificity 97% and area under the curve (0.463) but p value 0.723. With levels >12000, +ve predictive value is 75 % and levels < 12000, -ve predictive value is 81.6 % (Figure 2).

Figure-1. PCT day 6 ROC curve

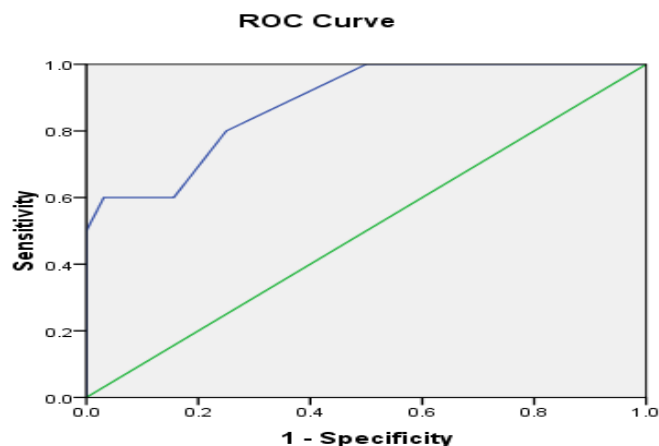


Figure-2. TLC day 6 ROC curve

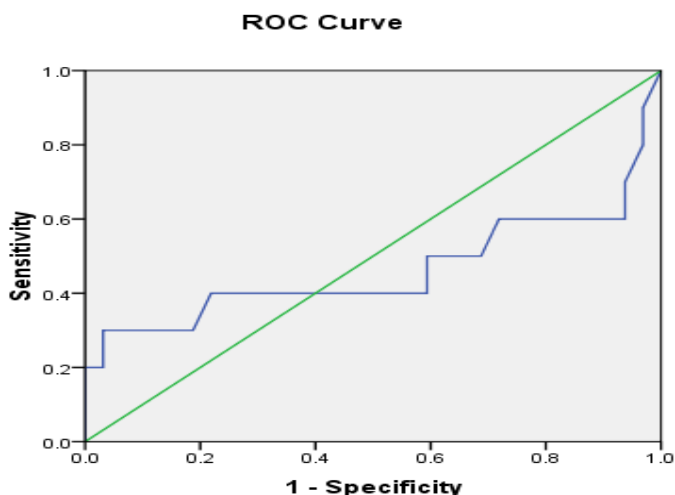
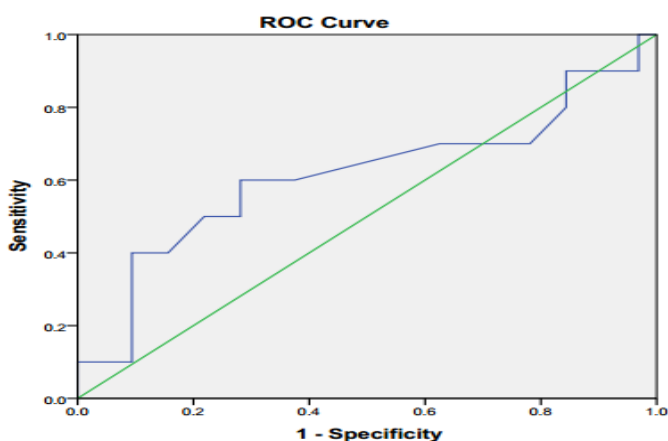


Figure-3. CRP day 6 ROC curve



CRP has low sensitivity 50%, specificity 79%, and area under the curve (0.613) but p value 0.288. with levels >17.5 mg/ml +ve predictive value is 41.7% and levels < 17.5 mg/ml -ve predictive value is 83.3 % (figure 3).

Group 2 (infection group):

PCT levels were elevated in this group of patients - with the highest level in day 8. Procalcitonin levels showed significant change between day 8 to day 10, day 10 to day 12 and day 12 to day 14. Also TLC and CRP levels were elevated but nonspecifically as they were also elevated in group 3 (Table 8 & 9). No significant differences were detected between percentage changes of TLC, PCT or CRP levels. (Figure-4).

Table-6. Shows ICU length of stay

Group	Group 1	Group 2	Group 3	P value
Days of ICU Stay	7.65 ± 1.07	16.40 ± 9.40	7.56 ± 1.02	0.02

Correlations:

There is no strong relation between the percentage changes of PCT, TLC and CRP except for PCT and TLC in day 6 to day 8 with p value 0.000 and r value 0.998 (strong direct correlation). Also the percentage change of PCT in day 10 to day 12 is correlated with T.BIL percentage change with p value 0.035 and r value 0.788 (figure 5).

Group 3: early rejection pattern

There was a significant difference in procalcitonin levels between day 6 to day 8 in group 3, PCT values were in normal range (not elevated) and declined from day 6 to day 8. There is a significant difference in TLC levels between days 6 to day 8 in group 3; TLC values showed declining from day 6 to day 8. There is no significant difference in CRP levels between days 6 to

There is significant difference in ALT levels between day 6 to day 8 in group 3. There is significant difference in T.BIL levels between day 6 to day 8 in group 3. There is significant difference in GGT levels between day 6 to day 8 in group 3 (table 10).

Comparison between Group 2 and Group 3:

Only PCT level in day 6 and day 8 showed significant difference between group 2 and 3, as TLC, CRP and other variables were rising abnormally in group 2 and 3 (table-11).

Table-9. Comparing blood levels of PCT, TLC & CRP every 48 hours among group 2 (starting from day 6)

	Day 6- day 8	Day 8- day 10	Day 10 – day 12	Day 12- day 14
PCT p value	0.735	0.018	0.018	0.043
TLC p value	0.646	0.683	0.528	0.138
CRP p value	0.249	0.176	0.344	0.414

Table-10. blood levels of PCT, TLC, CRP, liver enzymes and bilirubin

	Day 6	Day 8	P value
PCT	0.32 ± 0.18	0.11 ± 0.07	0.017
TLC	13.54 ± 2.46	8.22 ± 3.20	0.015
CRP	15.11 ± 8.40	11.37 ± 7.82	0.110
ALT	173.0 ± 174.6	109.5 ± 112.6	0.008
T.BIL	3.4 ± 1.6	2.6 ± 1.3	0.008
GGT	128 ± 33.4	147.0 ± 25.3	0.021

Table-7. Value of laboratory variables in day 6 among the 3 groups

Chi-square test	PCT day6	TLC day6	CRP day6	ALT day6	T.BIL day6	GGT day6
Group 1	0.20 ± 0.19	2.40 ± 5.86	13.3 ± 6.93	151.4 ± 78.5	11.5 ± 3.8	142.2 ± 71.5
Group 2	5.27 ± 6.67	6.94 ± 8.61	20.7 ± 21.8	286.6 ± 4.0	5.4 ± 3.4	142.0 ± 57.8
Group 3	0.32 ± 0.18	13.5 ± 2.4	15.1 ± 8.4	173.0 ± 1.74	3.4 ± 1.6	128.1 ± 33.4
P value	0.00	0.01	0.369	0.527	0.281	0.965

Table-8. Blood levels of PCT, TLC & CRP every 48 hours among group 2 (starting from day 6)

	Day 6	Day 8	Day 10	Day 12	Day 14
PCT (n < 0.5 ng/ml)	5.27 ± 6.67	9 ± 7.898	6.61 ± 10.40	3.76 ± 4.16	1.91 ± 2.03
TLC (4-11 ^{10*3c.c})	8.61 ± 6.94	9.49 ± 4.54	10.20 ± 5.06	10.27 ± 6.66	7.88 ± 5.72
CRP (6-12mg/ml)	21.8 ± 20.7	16.1 ± 9.4	18.5 ± 10.5	21.8 ± 23.2	27.0 ± 30.5

day 8 in group 3 (table 10).

Table-11. comparison of values of PCT, CRP, TLC, ALT, T.BIL & GGT in day 6 and day 8 between group 2 & 3

	PCT day6	TLC day6	CRP day6	ALT day6	T.bil day6	GGT day6
Group2	5.27 ± 6.67	8.6 ± 6.9	13.3 ± 6.9	286.6 ± 4.0	5.4 ± 3.4	142.0 ± 57.8
Group3	0.32 ± 0.18	13.5 ± 2.4	21.8 ± 20.7	173.0 ± 1.74	3.4 ± 1.6	128.1 ± 33.4
P value	0.024	0.178	0.743	0.288	0.165	0.902
	PCT day8	TLC day8	CRP day8	ALT day8	T.bil day8	GGT day8
Group2	8.99 ± 7.89	9.4 ± 4.5	16.1 ± 9.4	181.4 ± 212.9	5.2 ± 4.0	180.4 ± 68.4
Group3	0.11 ± 0.07	8.2 ± 3.2	11.3 ± 7.8	109.5 ± 112.6	2.6 ± 1.3	147.0 ± 25.3
P value	0.001	0.462	0.314	0.413	0.094	0.414

Figure-4. Comparing percentage changes of PCT, TLC & CRP every 48 hours

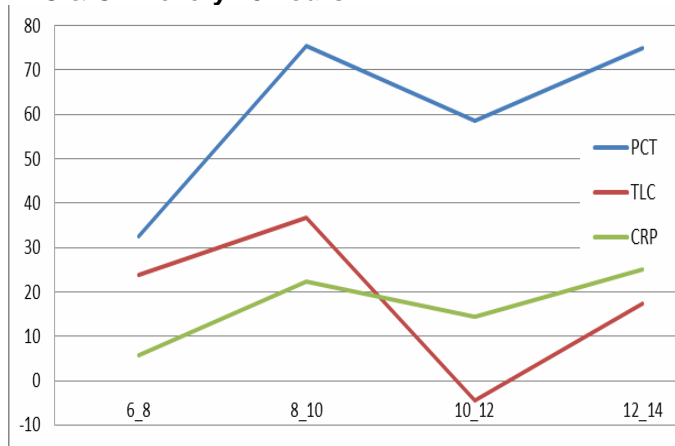
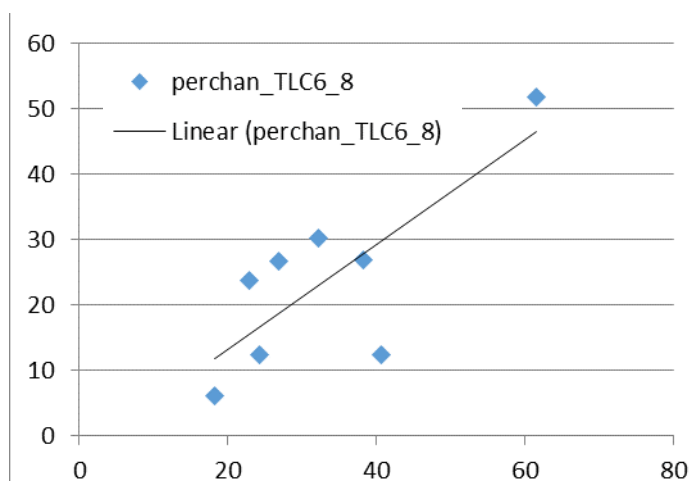


Figure-5. Correlation between Percentage changes of PCT day 6-8 and, TLC day 6-8



DISCUSSION

Aim of this study was to evaluate PCT as an early diagnostic marker of septic complication in the Immediate Post-operative ICU period after living donor liver transplantation. Forty-two patients were enrolled in this study, 37 males and only 5 females. The mean age of the study group is 52.95 ± 8.18 ranging from 19 to 66 years old. The study concludes that age and gender of patients had no influence on the incidence of infections or other complications. However Kim SI. et al reported that age > 45 yrs. and female gender are risk factors for bacterial infection in liver transplantation recipients. (13)

The mean MELD score was 16.88 ± 6 ranging from 10 to 22 and the mean APACHI II score was 6.66 ± 5 ranging from 2 to 14. Neither the APACHI II score nor the MELD score affected the incidence of septic complications in our study. However Maria Del Pilar et al. reported that MELD score > 30 increases the risk of infections after OLT. Also Narayanan et al (2004) reported that MELD score >21 is a risk factor for death within 30 days of OLT. Boin Ide F et al also reported that MELD over 25 was associated with poor survival. (14, 15, 16).

(As for the length of ICU stay (mean 9.71 ± 5.87) it is found to be significant in patients who developed septic complications or acute graft rejection requiring re-transplantation. In other studies length of stay in ICU was both a risk factor and a result due to complications. Kim et al reported that stay in ICU more than 9 days is considered a risk factor for bacterial infections post OLT. (13).

This study concludes that the majority of patients with septic complications are diabetics (p value = 0.03) as a result, DM is considered a risk factor for developing septic complications. This result is consistent with DARE

AJ et al. which reported DM as the strongest predictor of post-operative event rate ($P < 0.001$) and longer hospital stays (5.81 days, $P < 0.01$). Also Monica et al. discussed the effect of diabetes on deranging the immunological system and hence leaving the patient more vulnerable to infections. As a result they declared diabetes as the strongest risk factor in their analysis. Souza et al (2007) also reported that diabetes was a significant risk factor for infection developed after OLT. On the other hand, Ling Q et al and Li C et al. reported that Pre-operative diabetes mellitus didn't increase the risk of postoperative infection. (17, 18, 19, 20).

In our study we found that 10 patients (23 %) in group 2 suffered from septic complications. Clinically significant infections (CSIs) occurred during their ICU stay, with the main sources of infection were chest and blood stream infections; CSIs Included 6 pulmonary infections (60 % of group 2, 14.2 % of all patients), 3 blood stream infections (30 % of group 2, 7 % of all patients), and 1 intra-abdominal Infection (10 % of group 2, 2.3 % of all patients). The isolated causative organism were *klebsiella* (40 %), *E-coli* (30 %), *Pseudomonas* (20 %) and *Candida* (10 %).

Monica et al argued that despite the advances in immune suppression and surgical techniques, the incidence of infections remain high - with great variation between the different centers (range 10 % - 80 %). Nevertheless, the mortality rate has fallen, though infections are still one of the most important causes of death. Monica et al also indicated that the most frequent types of infection included bacteremia, abdominal infections (especially cholangitis) and pneumonias. In these patients previous metabolic derangements from their long-term liver disease, exposure to the nosocomial flora of the ICU, and high doses of immunosuppressive drugs during the early post-transplantation period may be risk factors for infection. (17).

Losada et al. reported that incidence of infection was higher the first 30 days after transplantation, with bacterial infection predominating. Gram +ve organisms were the most frequently isolated bacteria. (21).

Kim et al (2009) reported infection rate of 30.2% during the first month. The important infection sites are the abdomen (including the biliary tract), surgical wound, respiratory tract, and blood stream with or without catheter-related infections. Enteric gram-negative bacteria (GNB) and gram-positive bacteria (GPB) comprise a major portion of the causative organisms, although the predominant pathogens differ between the centers and between geographical areas. (13).

Souza et al (2007) argued that Infections after liver transplantations were mostly during the first month after transplantation. The most common were bacteremia, intra-abdominal infections and pneumonia, predominantly with bacteria, especially *Staphylococcus sp* (and particularly *S. aureus*) and *E.coli*. Saner et al (2008) also reported that blood stream infections in adult living donor liver transplantation (LDLT) predominated and occurred in 33% out of 55 LDLT patients, in

comparison to pulmonary infections that were experienced by 18% of LDLT. (22,23).

In our study starting from day 6, CRP did not show any significant difference between the studied groups of patients. CRP with sensitivity 10% and specificity 97%, and Area Under Curve (AUC 0.61) with (p value: 0.288). In 2010 Aristotelis Perrakis et al concluded the same result as CRP did not show any significant difference between the complication and non-complication groups. (5).

Contrary to our results, Song GW et al (2008) suggested that Serum CRP is quite sensitive but non-specific marker for diagnosis of infection and acute cellular rejection-ACR. Serum CRP was a more sensitive marker for infection and ACR than fever or leukocytosis. The serum CRP level showed significant increase in infectious complications, the median peak value was 12.6 mg/dL and the range was 0.5-40.7 mg/dL. And recipients accompanying septic feature showed higher level of peak CRP. The recipients with acute rejection also showed elevated CRP but modest elevation (1.5-8.7 mg/dL). (24).

Van den Broek et al (2010) in a large study with 135 patients also underlined the importance of CRP, as it was found to be an independent risk factor for a critical systemic infection. However they recommended that peak PCT was found not to be an independent factor for occurrence of serious infections and septic episodes. (25)

In our study TLC is insignificantly different among the study groups with sensitivity 30%, specificity 97%, and Area Under Curve (AUC 0.46), (p value=0.723) for diagnosis of infection. On the other hand it has significant difference between group 1 (no infection or rejection=TLC was normal) and group 3 (early rejection group, TLC was elevated. Helfritz FA et al (2015) indicated that white blood cell count $> 20,000/\mu\text{l}$ early after OLT is a cheap prognostic marker for patient and graft survival, while perioperative PCT and CRP levels have no influence (26).

In our study starting from the day 6 post liver transplantation, we observed that; the PCT was considered better positive than negative and more valid compared to CRP. The best cut-off level for the PCT to predict significant infection was 0.7ng/ml with sensitivity 60% and specificity 80%, and Area Under Curve 0.88, so that patients with PCT level of ≥ 0.70 ng/ml may have significant infection. PCT mainly showed significant difference among the groups of patients, especially in group 2 (infection), PCT was only elevated in this group with mean level (5.27 ± 6.67) in comparison to early mild rejection (group 3), PCT levels was in normal range (0.32 ± 0.18).

Hammer et al (1999) reported that after liver transplantation, the mean PCT value in patients showing neither infection nor rejection was (0.2 ± 0.1 ng/ml). Also in patients showing acute rejection the mean PCT value was (0.5 ± 0.4 ng/ml), comparing with patients with systemic infections was significantly higher (11.9 ± 11.2 nm/ml). the same study concluded that PCT was found

to be a reliable parameter to distinguish clearly infection from acute rejection, but shouldn't be regarded as the only reliable parameter for infection in intensive care unit, and should be used in combination with TLC and CRP to improve and accelerate the appropriate Clinical management for longer survival. (27).

Kuse ER et al (2000) in a study that included 40 patients after liver transplantation reported that PCT allows for differentiation between rejection and infection in patients with fever of unknown origin. The result was that eleven patients experienced an infectious complication resulting in an increase in PCT concentrations (2.2-41.7 ng/mL). Eleven patients had a rejection episode; none of these patients showed a rise in PCT concentrations. The statistical difference between PCT concentrations in rejection and infection was significant ($p < .05$) on the day of diagnosis. They concluded that elevation of PCT plasma concentrations develop early post operatively from operation trauma, and in the case of fever of unknown origin, with no rise in PCT, a rejection may be suspected. (28).

Coelho et al (2009) illustrated in a study with pediatric liver transplant recipients that it was possible to differentiate between bacterial infection and rejection by PCT measurement. In all patients with bacterial infection, an increase in PCT was registered. On the other hand patients suffering from acute graft rejection and having an uneventful post-transplant course did not show an increase of PCT. (29).

Another study by Perrakis et al (2009) in a research included a retrospective study in a cohort liver transplant recipients underwent 32 liver transplantations and a prospective part including patients underwent 75 OLT reported that the peak value of PCT, usually occurring 2nd or 3rd postoperative day, was not an independent factor for a fatal outcome according to the present series. An initially high PCT has been described to not indicate a poor prognosis when followed by an adequate decline. A rapidly rising PCT without a decline after the postoperative day is associated with a fatal outcome correlating with a bacterial or fungal infection. (30).

An updated study by Perrakis et al (2014) based on their results, confirmed that PCT course and the occurrence of a 2nd peak seem to possess important diagnostic and prognostic power in the post-transplant setting after liver transplantation. Between January 2007 and April 2011, 65 patients with end-stage liver disease underwent 75 LT in the Surgical Department of the University of Erlangen - Nuremberg. The study also reported that there was no association between the level of the 1st peak PCT and the further postoperative course or the occurrence of complications. Patients in whom a 2nd PCT peak occurred had a significantly higher risk for a complicated course, for a complicated sepsis course and for mortality ($p < 0.0001$). This research also indicates the significance of the role of PCT as independent factor as far as its course and the 2nd peak are concerned. The authors also admitted that PCT must not be regarded to be the only reliable diagnostic parameter. (31).

On the Contrary to the above conclusions Van den Broek et al (2010) reported that peak PCT was found not to be an independent factor for occurrence of serious infections and septic episodes. But the authors underlined the importance of CRP, as it was found to be an independent risk factor for a critical systemic infection. (25).

In our study 9 patients (group3) developed transient elevation in liver function tests, but PCT levels were low (in normal range), graft U/S imaging was normal; early mild rejection suspected. These patients showed improvement of liver functions by increasing the immune-suppressive drugs; in these patients culture results were negative.

In our study the most common complication in the immediate postoperative setting after OLT was infection, 10 out of 42 patients developed infection (23 %). One patient (from group 2; as a result of having an episode of CSIs) developed acute graft rejection (1 patient = 2 %). Other surgical complications; post-operative abdominal bleeding (5 patients = 11 %) and hepatic artery thrombosis (1 patient = 2 %).

We also observed that, starting from day 6 post liver transplantation, the PCT was considered better positive than negative and more valid compared to CRP. The best cut-off level for the PCT to predict significant infection was 0.7ng/ml with sensitivity 60 % and specificity 80 %, and Area Under Curve (AUC 0.88), Hence patients with PCT level of ≥ 0.70 ng/ml may have significant infection. Compared to PCT, TLC with sensitivity 40 % and specificity 97 %, and Area Under Curve (AUC 0.46). Also CRP with sensitivity 50 % and specificity 79 %, and Area Under Curve (AUC 0.61).

Conflict of Interests

Authors declare that there is no conflict of interests regarding the publication of this paper.

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