Journal of Hepatology and Gastrointestinal Disorders

Helfritz et al., J Hepatol Gastroint Dis 2015, 1:1
DOI: 10.4172/2475-3181.1000106

Research Article Open Access

Perioperative White Blood Cell Count as a Marker for Patient and Graft Survival after Orthotopic Liver Transplantation

Helfritz FA[1], **Lehner F**[1], **Manns MP**[2,3], **Klempnauer J**[1] **and Ciesek S**[2,3*]

[1]*Department of General, Visceral and Transplant Surgery, Hannover Medical School, Germany*

[2]*Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Germany*

[3]*Integrated Research and Treatment Centre – Transplantation (IFB-Tx), Germany*

[*]**Corresponding author:** Sandra Ciesek, Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Carl Neuberg Str. 1, 30625 Hannover, Germany, Tel: +49 511 532-4585; Fax: +49 511 532-4896; E-mail: Ciesek.sandra@mh-hannover.de

Received date: November 17, 2015, **Accepted date:** December 7, 2015, **Published date:** December 14, 2015

Copyright: © 2015 Helfritz FA, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Background: Orthotopic liver transplantation (OLT) is a standard procedure in end stage liver disease. However, recipients of OLT have a 10-15% risk to die within one year after transplantation. We evaluated whether different parameters of infection including inflammatory markers and white blood cells (WBC) predict post-OLT mortality, graft survival and rate of acute rejection.

Methods: We collected clinical and laboratory data of 102 patients undergoing liver transplantation between 2011 and 2012 at Hannover Medical School. Patients were stratified by i) patient survival, ii) graft survival and iii) episode of rejection(s) and were followed from OLT for one year. Laboratory data of peritransplant period (0-4 days after OLT) were analyzed.

Results: Inflammatory markers like CRP and procalcitonin had no significant effect on one-year patient or graft survival after OLT (p=0.3 or p=0.8 respectively). Interestingly, WBC early after OLT was a prognostic marker for patients (p=0.019) and graft survival (p=0.03). Importantly, white blood cell count early after OLT was independent from rate of acute rejection episodes. White blood cell count >20.000/µl within the first four days after OLT was associated with a higher patient and graft mortality. Patient mortality was 30% (WBC >20.000/µl) in comparison to 13% (WBC <20.000/µl). These results were independent from the underlying liver disease or type of immunosuppressive regimen.

Conclusions: These data demonstrate that white blood cell count >20.000/µl early after OLT is a cheap prognostic marker for patient and graft survival, while perioperative procalcitonin and CRP levels have no influence.

Keywords: Liver transplantation; Mortality; Inflammation; CRP; Leukocytes; White blood cell count; Survival

Introduction

Since the first human liver transplant in 1963 [1] orthotopic liver transplantation (OLT) is now established as the only definitive treatment for patients with end-stage liver disease (ESLD). In the US and Western Europe liver cirrhosis due to viral hepatitis B or C, alcohol abuse, hepatocellular carcinoma or genetic disorders like hemochromatosis are the main indications for OLT [2].

According to the United Network for Organ Sharing (UNOS), the 1-year and 5-year survival rates of patients undergoing OLT are 85% and 75%, respectively [3]. However, the 1-year survival rate after liver transplantation is only about 60% for those who are critically ill at the time of the surgery. A significant increase in survival rates after OLT could be achieved by the introduction of novel immunosuppressive drugs like calcineurin inhibitors, mycophenolate mofetile and mTOR inhibitors and the overall more experience with the procedure [4].

The highest mortality rate is observed within the first year after OLT due to early graft failure due to preexisting disease of the donated organ or technical complications during surgery such as revascularization [5]. Another major clinical problem after OLT is infection: infections are one of the leading causes of morbidity and mortality in liver transplant recipients [6]. More than two-thirds of liver transplant recipients have infections in the first year after transplantation, and in up to one-third of organ transplant recipients infections are the leading cause of death [6,7]. In addition, release of cytokines during the infection may have other indirect and negative effects, including allograft injury, opportunistic superinfection, and malignancy [7].

C-reactive protein (CRP) is a protein, which is synthesized by the liver in response to cytokines released by macrophages and adipocytes [8]. Procalcitonin is a peptide precursor of calcitonin. It is produced by parafollicular cells also called C cells of the thyroid gland and by neuroendocrine cells of the lung and the intestine. In contrast to CRP, PCT is produced independently from the liver function. PCT is a marker for severe bacterial sepsis [9].

We here investigated whether different parameters of infection including the inflammatory markers CRP, PCT and WBC predict post-OLT mortality, graft loss and rate of acute rejection.

Methods

In this single-center analysis we retrospectively reviewed 102 adult patients who underwent OLT between January 2011 and December 2012 at the Hannover Medical School, Germany. All patients under 18 were excluded. All adult patients were stratified by i) patient survival, ii) graft survival and iii) episode of rejection(s) and were followed from OLT for one year. Laboratory data including CRP, PCT and WBC of the peri transplant period (0-4 days after OLT) were analysed.

Patient demographics were collected from the electronic medical records of the Hannover Medical School. LabMELD was calculated as previously described directly before OLT.

Patient and graft survival as well as episodes of rejection and other severe adverse events as well as primary graft non-function were recorded. Other recorded clinical outcomes included the need for re-transplantation, the duration of time spent on intensive care unit (ICU) and in hospital.

The primary clinical outcomes included graft and patient survival one year after OLT and duration of stay on ICU and in hospital.

Ethical aspects

This study was based on hospital databases and patient medical histories and was performed in accordance with the principles stated in the Declaration of Helsinki. The study had been approved by the ethics committee of Hannover Medical School, Germany.

Software and statistical analyses

Data were analyzed using Excel (MS Office 2010, Microsoft Corp., Redmond, WA, USA). Unpaired two-sided student's t-test was performed accordingly to determine significance. A p-value of less than 0.05 was considered to indicate statistical significance.

Results

Clinical characteristics

Between January 2011 and December 2012, a total of 102 adult patients underwent OLT. The clinical characteristics of these patients are shown in Table 1. Mean age at the time of OLT was 49 years (range 20-73 years). 45 out of 102 patients were female (44%) and 94 patients were Caucasian (92%). The main indication for liver transplantation was cirrhosis due to viral hepatitis B or C (21.6%) followed by primary sclerosing cholangitis (19.6%). Overall, 22 patients had hepatocellular carcinoma (HCC). Median labMELD score at time of OLT was 20 (range 6-40).

Baseline characteristics		
Patients, n	102	
Gender	n	%
Male	57	56
Female	45	44
Age		Range
Mean	49	20-73 Years
Origin	n	%
Caucasian	94	92.2
Asian	3	2.9
African	2	2
Arabic	3	2.9
Underlying Ld	n	%
Viral Hepatitis	22	21.6
PSC	20	19.6
AIH	7	6.8
ALF	11	10.8
Alcohol	14	13.7
Budd Chiari Syndrome	2	2
Hemochromatosis	2	2
Morbus Wilson	2	2
SSC	4	3.9
Polycystic Liver Disease	8	7.8
Others	10	9.8
Additional HCC	22	21.6
Initial Is	n	%
CsA	72	71
Tac	30	29
MMF	98	96.1
Steroids	79	77.4
Basiliximab	96	94.1
Others	4	

PSC = primary sclerosing cholangitis; AIH = autoimmune hepatititis; ALF = acute liver failure; SSC = secundary sclerosing cholangitis;

CsA= cyclosporine A; Tac= Tacrolimus; MMF = Mycophenolate mofetil

Table 1: Baseline characteristics of the study cohort

Initial immunosuppression was based on a calcineurin inhibitor: 72 patients received cyclosporine A (71%) and 30 received tacrolimus (29%). In addition, 98 patients were treated with mycophenolate mofetil (MMF, 96.1%) and 77.45% were treated with steroids. The majority of our patients received an induction therapy with an IL-2 receptor antibody (94.1%)

Clinical outcome

54 out of 102 patients showed no signs of an acute rejection episode within one year after OLT (52.94%) (Table 2). 48 had at least a mild rejection and were treated with steroid bolus therapy or a change in the immunosuppressive regimen. There was no significant difference in age (51.1 versus 49.6 years), sex (44.4% versus 43.75% female) and labMELD (20 versus 19.3) at time of OLT the group of patients with an acute rejection episode in comparison to patients without any rejection

(Table 3). Patients with a CsA-based immunosuppression had at least a slightly higher rate of acute rejection than patients with a tacrolimus-based immunosuppression: 75% of all patients who developed an acute rejection were treated with CsA while only 66% of patients who did not develop an acute rejection were treated with CsA. Interestingly, addition of steroids to the immunosuppressive regimen had no influence on the rate of rejection: 18.75% of patients with at least one episode of an acute rejection were not treated with steroids, while 25.6% in the group of patients without rejection had a steroid-free immunosuppressive regimen (Table 3).

Clinical Outcomes		
Patients, n	102	
Acute Rejection	n	%
Yes	48	47.1
No	54	52.9
Patient Survival	n	%
Yes	86	84.4
No	16	15.6
Graft Survival	n	%
Yes	82	80.4
No	20	19.6

Table 2: Clinical outcome of patients

Rejection		
Patients, n	102	
	Yes	No
Age (years)	51.1	49.6
Sex		
Male (%)	55.6	56.25
Female (%)	44.4	43.75
LabMELD	20	19.3
Immunosuppression		
Csa (n)	36	36
Tacrolimus (n)	12	18
Steroid free treatment (%)	18.75	25.6
Underlying liver disease		
Viral hepatitis (n)	12	10
Psc (n)	14	6
Aih (n)	3	4
Alf (n)	7	4
Alcohol (n)	3	11
Budd chiari syndrome (n)	0	2
Hemochromatosis (n)	1	1
Morbus wilson (n)	0	2
Ssc (n)	1	3
Polycystic liver disease (n)	2	6
Others (n)	5	5

Table 3: Comparison of patients with and without acute rejection

At least in our cohort, patients with an acute liver failure seems to have a slightly higher risk to develop an acute rejection within the first year after OLT (64% develop an acute rejection), while other underlying liver diseases such as viral hepatitis and autoimmune hepatitis or primary sclerosing cholangitis do not have any influence on the rejection rate. Only 25% of patients with polycystic liver disease had an acute rejection.

16 out of 102 patients die within one year after OLT (15.6%) (Table 2). The main reason for death was severe infection leading to sepsis and multiorgan failure (87.5%): while 3 patients suffered from cholangiosepis, one patient died due to CMV encephalitis. Two patients developed aspergillosis of the lung (Table 4). Eight patients died due to bacterial sepsis. Two patients died due to severe intracerebral bleeding. As expected, patients who did not survive the first year after OLT were significant older than patients, who survived (53.9 years versus 48.2 years, $p<0.05$). Interestingly, labMELD at time of OLT was no risk factor for one-year patients survival in our cohort (22.1 versus 19.3 points, $p=0.34$). In addition, we were not able to detect any correlation between the underlying liver disease and rate of one-year survival of the patients as well as type of immunosuppressive regimen (Table 4). However, there was a trend that patients with alcoholic liver cirrhosis have a lower survival rate after one year since 31.3% of the deceased patients were former alcohol addicted. Six patients needed a re-transplantation within one year (5.88%) and out of these patients four died afterwards.

Survival			
Patients, N	102		
	Yes	**No**	
Age (Years)	48.16	53.9	P=0.045
Sex			
Male (%)	54.7	62.5	
Female (%)	45.3	37.5	
Labmeld	19.31	22.1	P=0.34
Immunosuppression			
CsA (N)	60	12	
Tacrolimus (N)	26	4	
Steroid Free Treatment (%)	26	25	
Underlying Liver Disease			
Viral Hepatitis (N)	20	2	

PSC (N)	19	1	
AIH (N)	6	1	
ALF (N)	9	2	
Alcohol (N)	9	5	
Budd Chiari Syndrome (N)	2	0	
Hemochromatosis (N)	2	0	
Morbus Wilson (N)	2	0	
SSC (N)	3	1	
Polycystic Liver Disease (N)	7	1	
Others (N)	7	3	
Reason For Death			
Cholangiosepsis	n.a.	3	
Viral Enzephalitis	n.a.	1	
Aspergillosis	n.a.	2	
Sepsis	n.a.	8	
Intracerebral Bleeding	n.a.	2	

Table 4: Comparison of patients with and without survival after OLT

Next, we evaluated the overall one-year graft survival in our cohort. 20 out of 106 patients lost their graft within one year after OLT (18.86%) (Table 2). Six patients had to undergo re-OLT due to initial non-function of the graft (5.9%). Out of these patients, only four survived for more than one year.

Overall, the median stay at the hospital was 45.77 days and median stay on the intensive care unit (ICU) was 30.6 days. The median stay at hospital and ICU was significantly longer in the group of patients who died within one year after OLT ($p< 0.001$ for both terms).

Risk Factors Associated with Graft and Patient Survival

Most of the patients in our cohort died due to severe viral, fungal or bacterial infections and its complications within one year after OLT. We therefore wanted to investigate the role of inflammatory markers like CRP, PCT and elevated WBC of more than 20.000/µl early after OLT that are associated with infection (Table 5). We were not able to detect any significant differences in CRP or PCT levels in the early phase after OLT in the group of patients that died or lost the graft within one year after OLT ($p=0.3$ or $p=0.8$ respectively). Interestingly, WBC early after OLT was significant higher in patients that died within the first year after OLT ($p=0.019$) and also in patients who lost their graft within one year after OLT ($p=0.03$). There was no correlation between the amount of WBC and the rate of rejections episodes. White blood cell count > 20.000/µl within the first four days after OLT was associated with a higher patient mortality and rate of graft loss. Patient mortality was 30% (WBC >20.000/µl) in comparison to 13% (WBC <20.000/µl). No correlation of WBC with the underlying liver disease or type of immunosuppressive regimen was determined (Table 5).

Inflammatory Parameters							
Patients, N		102					
		Rejection		**Patient Survival**		**Graft Survival**	
	Overall	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
CRP (mean in mg/dl)	112	113	111	111	120	108	111
PCT (mean in mg/dl)	26	28	24	25	33	25	30
WBC (mean in/µl)	13.93	13.71	14.16	13.24	17.72	13.13	17.13

Table 5: factors associated with graft and patient survival.

Discussion

In this retrospective single-center study we reported the one-year graft and patient survival after OLT. Overall, 84.4% of the patients survived for more than one year. The main reason for death within the first year after OLT was bacterial, viral or fungal infection leading to sepsis and multiorgan failure. Interestingly, an increase of WBC factors of more than 20.000/µl within the first four days after OLT was a significant risk factor for patient and graft loss, while an increase of CRP and PCT was no marker of survival.

WBC are important components in protecting us against infections. They are produced from hematopoetic stem cells in the bone marrow. Leukocytosis is a typical finding in patients with acute or chronic infection, but also after stress, convulsions or after anesthesia or epinephrine administration [10]. In contrast, immunosuppressive therapy based on calcineurin inhibition and/or mycophenolate mofetil often result in the decline of WBC [11]. Here we observed that an increase of WBC of more than 20.000/µl early after OLT was associated with patient and graft loss. One possible explanation for this observation might be that these patients develop signs of infection already in the very early phase after OLT, which is leading to their worse prognosis. Another possible explanation might be that elevated WBC can also be detected after stress. However, in our study all patients underwent the same procedure and duration of OLT was not significantly different within both patient groups. Importantly, in our cohort survival did not correlate with labMELD score at time of OLT. Last but not least also steroid administration can elevate WBC, however, we could not observe any correlation between use of steroids as part of immunosuppressive regimen and rate of survival. Therefore we do not believe that leucocytosis is here in these cases mainly

associated with stress or trauma. Also such a high increase of WBC due to anesthesia administration seems to be an unlikely explanation. We therefore believe that the early increase of WBC is an early and cheap marker for an early onset of severe infections after OLT. If an early antibiotic therapy or the escalation of antibiotic therapy in patients with more than 20.000 leukocytes/µl within the first four days after OLT might have a positive influence on patient and graft survival should be part of a prospective controlled study.

Interestingly, CRP and PCT elevation within the first four days after OLT did not correlate with patient survival and/or graft loss. One possible explanation might be that CRP is in general produced in the liver and that CRP production can be delayed in the graft, especially when the graft shows delayed or primary non-function. In contrast, PCT is produced in C cells of the thyroid gland and by neuroendocrine cells of the lung and the intestine [12,13]. However, PCT is more a marker for bacterial than for viral infections [14-16]. Furthermore, it is possible that we here did not detect any statistical significance because the maximal increase of PCT might be at a later than fours days after OLT.

We also observed several cases of death due to cholangiosepsis. A possible explanation might be that in our center PSC was one of the leading indications for OLT. Patients with PSC have in general more frequently problems with bacterial infection of the bile ducts than patients with other underlying liver diseases [17,18]. If it might be useful to take samples of the bile duct for microbiological tests during OLT should be investigated in further studies.

Interestingly, it has been shown by several other studies that lymphopenia is a prognostic marker for survival after trauma [19] or in patients with advanced carcinomas; sarcomas [20], differential blood counts were not available from our patients since it does not belong to a routine testing on our transplant intensive care unit. In addition, Fernandez-Ruiz et al. found out that pre transplant lymphocyte count can predict the incidence of infection during the first two years after OLT. Unfortunately, perioperatively differential blood counts were not available from our patients since it does not belong to a routine testing on our transplant intensive care unit. However, in our cohort absolute leukocyte count was associated with overall patient mortality.

The present study has some limitations: the size of the study cohort, the inhomogenous distribution and the retrospective design. However, this is the first single center study investigating WBC early after OLT in a real world setting. Indeed, the influence of WBC count on survival early after OLT should be restudied by multicenter studies. Future investigations should also include differential blood counts early after OLT. This might help to further characterize our finding an to confirm that bacterial, viral and/or fungal infection are responsible for the increased mortality after OLT.

In summary, these data demonstrate that white blood cell counts >20.000/µl early after OLT might be a cheap and simple prognostic marker for patient and graft survival, while elevated PCT and CRP early after OLT showed no significant correlation.

References

1. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, et al. (1963) Homotransplantation of the liver in humans. Surg Gynecol Obstet 117: 659-676.
2. Udompap P, Kim D, Kim WR (2015) Current and Future Burden of Chronic Nonmalignant Liver Disease. Clin Gastroenterol Hepatol 13: 2031-2041.
3. Roberts MS, Angus DC, Bryce CL, Valenta Z, Weissfeld L (2004) Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. Liver Transpl 10: 886-897.
4. Adams DH, Sanchez-Fueyo A, Samuel D (2015) From immunosuppression to tolerance. J Hepatol 62: S170-185.
5. Itri JN, Heller MT, Tublin ME (2013) Hepatic transplantation: postoperative complications. Abdom Imaging 38:1300-1333.
6. Pedersen M, Seetharam A (2014) Infections after orthotopic liver transplantation. J Clin Exp Hepatol 4: 347-360.
7. Blair JE, Kusne S (2005) Bacterial, mycobacterial, and protozoal infections after liver transplantation--part I. Liver Transpl 11: 1452-1459.
8. Pepys MB, Hirschfield GM (2003) C-reactive protein: a critical update. J Clin Invest 111: 1805-1812.
9. Meisner M, Tschaikowsky K, Palmaers T, Schmidt J (1999) Comparison of procalcitonin (PCT) and C-reactive protein (CRP) plasma concentrations at different SOFA scores during the course of sepsis and MODS. Crit Care 3:45-50.
10. Abramson N, Melton B (2000) Leukocytosis: basics of clinical assessment. Am Fam Physician 62: 2053-2060.
11. Danesi R, Del Tacca M (2004) Hematologic toxicity of immunosuppressive treatment. Transplant Proc 36: 703-704.
12. Morris-Stiff G, Gomez D, Prasad KR (2008) C-reactive protein in liver cancer surgery. Eur J Surg Oncol 34: 727-729.
13. Yu XY, Wang Y, Zhong H, Dou QL, Song YL, et al. (2014) Diagnostic value of serum procalcitonin in solid organ transplant recipients: a systematic review and meta-analysis. Transplant Proc 46: 26-32.
14. Pfister R, Kochanek M, Leygeber T, Brun-Buisson C, Cuquemelle E, et al. (2014) Procalcitonin for diagnosis of bacterial pneumonia in critically ill patients during 2009 H1N1 influenza pandemic: a prospective cohort study, systematic review and individual patient data meta-analysis. Crit Care 18:R44.
15. Sridharan P, Chamberlain RS (2013) The efficacy of procalcitonin as a biomarker in the management of sepsis: slaying dragons or tilting at windmills? Surg Infect (Larchmt) 14: 489-511.
16. Sammons C, Doligalski CT (2014) Utility of procalcitonin as a biomarker for rejection and differentiation of infectious complications in lung transplant recipients. Ann Pharmacother 48: 116-122.
17. Aberg F, Mäkisalo H, Höckerstedt K, Isoniemi H (2011) Infectious complications more than 1 year after liver transplantation: a 3-decade nationwide experience. Am J Transplant 11: 287-295.
18. Rizvi S, Eaton JE, Gores GJ (2015) Primary Sclerosing Cholangitis as a Premalignant Biliary Tract Disease: Surveillance and Management. Clin Gastroenterol Hepatol 13: 2152-2165.
19. Heffernan DS, Monaghan SF, Thakkar RK, Machan JT, Cioffi WG, et al. (2012) Failure to normalize lymphopenia following trauma is associated with increased mortality, independent of the leukocytosis pattern. Crit Care 16:R12.
20. Ray-Coquard I, Cropet C, Van Glabbeke M, Sebban C, Le Cesne A, et al. (2009) Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. Cancer Res 69: 5383-5391.