Published in final edited form as:
Pediatr Transplant. 2012 March ; 16(2): 137–143. doi:10.1111/j.1399-3046.2011.01631.x.

Risk Factors for Chronic Anemia in Pediatric Orthotopic Liver Transplantation: Analysis of Data from the SPLIT Registry

RI Liem[1], **R Anand**[3], **W Yin**[3], and **EM Alonso**[2]

[1]Divisions of Hematology, Oncology & Stem Cell Transplant; Children's Memorial Hospital; Department of Pediatrics, Northwestern University Feinberg School of Medicine; Chicago, Illinois [2]Divisions of Gastroenterology, Hepatology & Nutrition; Children's Memorial Hospital; Department of Pediatrics, Northwestern University Feinberg School of Medicine; Chicago, Illinois [3]The EMMES Corporation; Rockville, Maryland

Abstract

Risk factors for chronic anemia in the post transplant period have not been clearly delineated in pediatric liver transplant recipients. We analyzed data from children transplanted from 2000 to 2008 with at least 2 consecutive hemoglobin values from follow-up between 6 months and 5 years post transplant. A multivariate model was derived to determine independent risk factors associated with chronic anemia. Of 1026 children in this analysis, 242 (23.6%) were found to have chronic anemia. On multivariate analysis, GI bleeding (OR 11.83 [2.08-67.49], $P = 0.0054$), presence of leukopenia (OR 9.55 [95% CI 3.71-24.62], $P < 0.0001$), use of cyclosporine (OR 3.69, [95% CI 1.56-8.76], $P = 0.0039$) and corticosteroids (OR 2.90 [95% CI 1.94-4.33], $P < 0.0001$), and calculated GFR < 90 mL/min/1.73m^2 (OR 4.62 [95% CI 2.47-8.67], $P < 0.0001$) represented the most significant risk factors for chronic anemia. Use of anti-hypertensive medications (OR 1.89 [95% CI 1.23-2.91], $P = 0.0039$) was also significantly associated with a higher risk. In summary, chronic anemia is common in children following liver transplant. Our findings underscore the need to define the mechanisms by which these risk factors, some of which are modifiable, result in chronic anemia in pediatric liver transplant recipients.

Keywords

Anemia; Liver Transplant; Cyclosporine; Tacrolimus; Renal Function

Introduction

Recent advances in the management of solid organ transplant recipients have improved overall survival rates. This has led to increasing recognition of previously underappreciated sequelae such as persistent hematological abnormalities in longterm survivors. In particular, chronic anemia is commonly observed in the late post transplant period in recipients of heart, lung and kidney transplants (1–3). In pediatric and adult survivors of kidney transplants, the prevalence of persistent low hemoglobin ranges from 20% to as high as 82%

Corresponding Author: Robert I. Liem, MD, MS, 2300 Children's Plaza, Box 30, Chicago, Illinois, Voice 773 880 3977, Fax 773 880 3053, rliem@childrensmemorial.org.

Author Contributions

RL, RA, WY and EA were involved in the concept and design of the study and data analysis/interpretation of results. RA and WY performed the statistical analysis. RL was involved in the drafting of the article. RL, RA, WY and EA were involved in the critical revision and final approval of the article.

in the late post transplant period (4–7). The etiology of chronic anemia in this population includes iron deficiency or immunosuppression related toxicity, but poor allograft function and reduced renal function remain the most commonly implicated reasons (8). Chronic anemia may impact growth and development, quality of life and physical functioning in those affected. Although its relationship to long term morbidity and mortality is not clear, chronic anemia may also be associated with a higher risk of eventual graft loss in renal transplant recipients (9).

There exist fewer studies that describe the prevalence of chronic anemia and its associated risk factors in recipients of liver transplants. In a recent adult cohort, the prevalence of anemia, defined by World Health Organization criteria of hemoglobin less than 13 g/dL for men and less than 12 g/dL for women, reached 50% and 53% at 6 and 12 months post liver transplant, respectively (10). Data regarding chronic anemia in pediatric recipients of liver transplants are limited as well, although the reported prevalence ranges from 20% to 28% in recent small, retrospective studies (11, 12). The risk factors associated with persistent anemia post liver transplant are not well established, but poor renal function, iron restricted erythropoiesis as well as marrow suppression from chronic infection or medications are believed to play a role, as in renal transplant recipients (13).

The objectives of this analysis were to 1) calculate the prevalence of chronic anemia in pediatric liver transplant recipients included in the Studies in Pediatric Liver Transplantation (SPLIT) cohort during the first 5 years post transplant, and 2) evaluate the relationship between renal function and chronic anemia in the study population. We hypothesized that chronic anemia is a frequent finding in the first 5 years post liver transplant and is most commonly related to reduced renal function.

Patients and Methods

SPLIT cohort

The SPLIT registry, established in 1995, represents a prospective, longitudinal effort by more than 40 participating centers to systematically assess outcomes associated with pediatric orthotopic liver transplantation. The SPLIT data repository offers a unique opportunity to evaluate chronic anemia in a large cohort of pediatric liver transplant recipients. All centers obtained local institutional review board approval for participation as well as informed consent from patients prior to data submission. For this analysis, we defined our cohort as all children between 6 months and 18 years of age who received their first liver transplant between January 2000 and May 2008. Hemoglobin data were formally collected from 38 of the participating institutions in the registry beginning July 2005. Including only patients transplanted in or after 2000 guaranteed that at least 1 hemoglobin value collected during follow-up visits between 6 months and 5 years after transplant would be available for inclusion in our analysis.

Study population and definition of anemia and risk factors

Patients were eligible for inclusion in our primary analysis if they had at least 2 consecutive hemoglobin values collected during scheduled follow-up visits between 6 months and 5 years post transplant. The interval between scheduled follow-up visits during which hemoglobin was collected was 6 months in the first 2 years post transplant and 1 year thereafter. We used this approach to exclude patients with temporary decreases in hemoglobin attributable to interval infections or other transient risk factors. The following lower limits of normal for hemoglobin were applied to subjects by age for determination of anemia: 11.0 g/dL for 0.5 to 4 years old; 11.5 g/dL for 5 to 7 years old; 12.0 g/dL for 8 to 11 years old; 12.0 g/dL (females) and 12.5 g/dL (males) for 12 to 14 years old; and 12.0 g/dL

(females) and 13.0 g/dL (males) for 15 to 18 years old (14). Patients whose hemoglobin values on 2 consecutive occasions fell below the lower limit of normal for age and gender met criteria for chronic anemia and were designated the anemia group. The control group comprised all others with 2 consecutive hemoglobin values that did not both fall under the lower limit of normal.

We considered clinical characteristics as well as several post transplant risk factors in our assessment of differences between the anemia and control groups. Clinical characteristics consisted of patient demographics, including age, gender and race; recipient and donor ABO status; primary diagnosis; disease severity, including ICU status, weight and height deficits, and pediatric end-stage liver disease (PELD) score; renal function measured by calculated glomerular filtration rate (GFR); immunosuppression; and corticosteroid use at time of transplant. Post transplant risk factors included documented infections such as cytomegalovirus (CMV) or Epstein Barr virus (EBV); leukopenia; post transplant lymphoproliferative disease (PTLD) and aplastic anemia; GI bleeding; antihypertensive medication use; immunosuppressive therapy; corticosteroid use; and calculated GFR. Patients in the anemia group were determined to have these risk factors if they were present at the time of the first follow-up visit meeting criteria for anemia. For the control group, the presence or absence of complications or medications was assessed at the time of the last follow-up hemoglobin value documented. GFR was calculated using the following Schwartz equation: GFR (mL/min/1.73m^2) = ($\kappa \times$ height (cm))/creatinine (mg/dL). In this equation, the constant $\kappa = 0.45$ for infants less than 1 year, 0.55 for children 1 to 12 years, 0.55 for females 13 to 18 years, and 0.7 for males 13 to 18 years.

Statistical considerations

Demographics and clinical characteristics of patients assigned to anemia and control groups were categorically summarized and reported using proportions. We performed univariate analysis using logistic regression to identify risk factors for anemia and to calculate odds ratios and 95% confidence intervals (CI) associated with risk factors. The initial multivariate model included risk factors significant at the $P = 0.10$ level in the univariate analysis. The final multivariate model was derived using stepwise backward elimination procedure. Factors remaining significant at $P \leq 0.05$ were considered to be statistically significant and kept in the final model. All statistical analyses were performed using SAS for Windows, version 9.2 (SAS Institute Inc., Cary, NC).

Results

Demographics and characteristics of study population

Since 2000, a total of 1537 children between 6 months and 18 years old received their first liver transplant (Table 1). Of these children, 1026/1537 (66.8%) had at least 2 consecutive hemoglobin values measured during follow-up visits and thus, were eligible for inclusion in this analysis. In these 1026 children, the follow-up period post transplant was at least 24 months in 65.7% and 60 months in 18.7%. The largest age group represented in this study population was between 1 and 5 years of age (40%). Just over half were white (56.6%) and female (53.2%). As expected for a pediatric population, biliary atresia (39.6%) represented the most common indication for transplantation. A significant proportion of children demonstrated height (27.3%) and weight (23.3%) deficits greater than 2 standard deviations below the mean at the time of transplant. At the time of transplant, PELD scores were 20 or greater in 25.1% of recipients, 20.5% of whom were hospitalized in the ICU (data not shown). ABO incompatibility between recipient and donor was present in 1.6% of the transplants. The most common primary immunosuppressant used at the time of transplant was Tacrolimus (80.5%), with concomitant corticosteroid (90%) use in the majority of

children. A calculated GFR < 90 mL/min/1.73m^2 was documented in 10% of recipients at the time of transplant.

Prevalence of chronic anemia and risk factors

In total, 242/1026 (23.6%) children met criteria for chronic anemia based upon consecutive hemoglobin values obtained on average 7.8 months apart. These children were designated the anemia group in our analysis. Their mean hemoglobin, averaged between the 2 consecutive values analyzed, was 10.24 g/dL (IQR 9.7-10.75). Mean hemoglobin was 12.98 g/dL (IQR 12.2-13.8) in the non-anemia group. Several variables were significantly associated with a greater risk of chronic anemia on univariate analysis, including patient age, race, primary diagnosis as well as presence of certain co-morbid conditions, immunosuppression regimen, anti-hypertensive therapy and renal function at the time of data collection (Table 2). Children who were greater than 13 years old (OR 2.29 [95% CI 1.43-3.67], $P = 0.0006$) and Black (OR 1.75 [95% CI 1.19-2.59], $P = 0.0049$) had the greatest risk of developing chronic anemia over time. We found that when compared to biliary atresia, almost every other primary diagnosis was associated with a higher risk of developing chronic anemia. The odds of having a concomitant history of aplastic anemia (OR 6.56 [95% CI 1.19-36.01], $P = 0.0305$) and leukopenia (OR 7.74 [95% CI 3.61-16.60], $P < 0.0001$) were significantly higher in children with chronic anemia post transplant. A diagnosis of GI bleeding (OR 4.45 [95% CI 1.53-12.95], $P = 0.0062$) was also significantly associated with chronic anemia post transplant.

In our analysis, children found to be anemic were significantly more likely to have remained on cyclosporine (CSA)-based immunosuppression (OR 3.37 [95% CI 1.81-6.29], $P = 0.0001$), when compared to Tacrolimus-based therapy. Corticosteroid use (OR 3.32 [95% CI 2.45-4.50], $P < 0.0001$) was also significantly associated with chronic anemia in this population. Children with chronic anemia post transplant were more likely to have had a calculated GFR < 90 mL/min/1.73m^2 (OR 4.73 [95% CI 2.81-7.87], $P < 0.0001$) and to be on antihypertensive therapy (OR 2.71 [95% CI 1.96-3.75], $P < 0.0001$) at the time they were first found to be anemic.

Multivariate analysis

We performed multivariate analysis to identify independent predictors among the risk factors determined to be significantly associated with chronic anemia in univariate analysis. Following adjustment for each risk factor, primary diagnosis and presence of aplastic anemia were no longer significantly associated with chronic anemia in our study population. Of those variables that remained significant risk factors, a history of GI bleeding (OR 11.83 [2.08-67.49], $P = 0.0054$), the presence of leukopenia (OR 9.55 [95% CI 3.71-24.62], $P < 0.0001$), the use of CSA-based therapy (OR 3.69, [95% CI 1.56-8.76], $P = 0.0039$), and calculated GFR < 90 mL/min/1.73m^2 (OR 4.62 [95% CI 2.47-8.67], $P < 0.0001$) at the time anemia was first found were associated with the highest odds ratios (Table 3). The use of anti-hypertensive medication and corticosteroids also remained significant as risk factors for chronic anemia. Of the different age groups, we found that the risk of chronic anemia was significantly lower in transplant recipients between 1 and 4 years old. In this multivariate model, Black children remained at highest risk for developing chronic anemia, although overall race was not an independent risk factor.

Discussion

The present analysis represents the largest study to date to determine the prevalence of chronic anemia in pediatric recipients of orthotopic liver transplantation. It is also the largest pediatric study to report the risk factors, some of which have not been previously described,

associated with chronic anemia in this population. We found that chronic anemia is common among children during the first 5 years post transplant, with a prevalence of 24% in our analysis similar to that reported in other pediatric studies (11, 12). We relied on stringent criteria dependent on 2 consecutive hemoglobin values at least 6 months apart on follow-up to define chronic anemia and to establish cases in our analysis, thereby minimizing the effect of interval illnesses or temporary circumstances that might result in transient decreases in hemoglobin. Although we found several risk factors on univariate analysis associated with chronic anemia, only a history of GI bleeding, leukopenia, CSA-based immunosuppressive therapy, corticosteroid use, anti-hypertensive medication use, and reduced renal function at the time of data collection were independently associated with chronic anemia on multivariate analysis. Children transplanted between 1 and 4 years of age were least likely to develop chronic anemia, while Black children were most likely to develop chronic anemia.

Some of these risk factors for chronic anemia, such as poor renal function and medication toxicity, are well described in the general pediatric and adult transplant literature (3–7, 10, 11, 15). Others, such as leukopenia and age, represent novel risk factors not previously identified. As risk factors, leukopenia and age are non-specific and are likely surrogate indicators for other pathophysiologic processes that may cause anemia. Leukopenia may reflect underlying residual marrow dysfunction due to chronic viral infection, history of aplastic anemia or toxicity from chronic immunosuppression, all of which might also contribute to the development and persistence of anemia. It is unknown, however, why children transplanted between 1 and 4 years old were least likely to develop chronic anemia in our analysis. We found that young age at transplantation was protective for chronic anemia even after adjusting in our model for co-variates that might explain this finding, such as primary diagnosis. It is also unclear why Black children followed in this registry were more likely to have chronic anemia. The presence of thalassemia trait, a common cause of mild anemia among individuals of African descent, could not be excluded as a confounding variable since that data were not collected in this registry.

We found an independent association between concomitant corticosteroid use and higher risk of chronic anemia in our cohort, yet the mechanism of action to explain this finding is unclear. This is in contrast to data from Guitard et al.'s study (10), which demonstrated that higher doses of corticosteroids post liver transplant were protective against anemia, presumably due to the stimulatory effect of corticosteroids on red blood cell production. Although data related to iron deficiency were not collected in the SPLIT data registry, the association between chronic corticosteroid use and anemia in our study population may be explained by the increased risk of gastritis conferred by chronic corticosteroid use. This explanation is plausible and supported by our finding that the presence of GI bleeding in the post transplant period represented the most significant risk factor for chronic anemia. That CSA-based therapy, when compared to Tacrolimus-based therapy, represented a bigger risk factor for development of chronic anemia in our analysis was also surprising since the association between anemia and Tacrolimus has been more frequently demonstrated in adult recipients of solid organ transplants (16, 17). Both calcineurin inhibitors, however, may cause anemia through several mechanisms. Anemia caused by Tacrolimus may be mediated through direct effects on the bone marrow (i.e. pure red cell aplasia) (18, 19), nephrotoxicity or alternatively, development of microangiopathy-related hemolysis (20). Like Tacrolimus, CSA may result in anemia by causing microangiopathy-related hemolysis and nephrotoxicity (21). Biologic evidence suggests, however, that CSA may also directly inhibit erythropoietin production both *in vitro* and *in vivo* (22, 23). Further work to delineate the differential effects of CSA versus Tacrolimus on marrow erythropoietic activity is therefore warranted.

Although persistent renal dysfunction is a well-established risk factor for chronic anemia in renal transplant recipients, the relationship is less clear for adult liver transplant recipients and has not previously been evaluated in pediatric liver transplant recipients. Our finding that a calculated GFR < 90 mL/min/1.73m^2, which indicates at least stage II chronic kidney disease, was associated with chronic anemia was not unexpected given the kidney's role in maintaining erythropoiesis and adequate red blood cell production. Severe renal dysfunction, including end stage renal failure, is a frequent complication in adult recipients of orthotopic liver transplant, with prevalence rates reported between 4% and 48% on longterm follow-up, depending on the specific definition used (24–27). In the pediatric liver transplant population, persistent renal dysfunction may be present in 25 to 32% of recipients at last follow-up (28, 29). The etiology of longterm renal dysfunction following liver transplantation in children and adults is likely multi-factorial but may include renal disease associated with the primary diagnosis, co-existing conditions such as diabetes or hypertension or hepatorenal syndrome in end stage liver disease. Calcineurin inhibitor-induced nephrotoxicity may also occur in the post-transplant period, suggesting the relationship between renal dysfunction and chronic anemia may be mediated through medication toxicity. However, we found that immunosuppression and reduced renal function at the time of data collection were independent risk factors for anemia in our multivariate model. In this analysis, underlying renal dysfunction may in part explain why the use of anti-hypertensive therapy was associated with chronic anemia in this cohort. Alternatively, certain antihypertensive medications such as angiotensin-converting enzyme inhibitors may independently be associated with anemia, although the specific type of antihypertensive used post transplant was not available from the registry.

Several limitations related to our results warrant discussion. First, our present study relied on the analysis of historical data collected from participating centers in the US and Canada. As is often the case with multicenter registries, laboratory studies were obtained prospectively for clinical purposes, yet collection of some data may have been missed. The SPLIT registry did not begin to systematically collect hemoglobin data until 2005, so our analysis included only that subset of patients transplanted in or after 2000 to ensure we would have at least 1 hemoglobin value reported between 6 months and 5 years post transplant. Limiting our analysis to this era of transplant may have contributed to the low number of patients on CSA-based immunosuppression since a major shift to Tacrolimus-based therapy was evident around this time period. The cross-sectional nature of this analysis also limited our ability to determine the onset of chronic anemia in those children transplanted prior to 2005. Second, we relied on an estimated GFR calculated using the Schwartz formula to define renal dysfunction even though GFR measured directly by nuclear labeling would have been more accurate. Calculating GFR using the Schwartz equation, however, is considered a well accepted, validated method for estimating renal function in the pediatric population (30). In contrast to that used in other studies, we adopted a more liberal definition of renal dysfunction in the present study and found that even mild reductions in renal function were associated with chronic anemia. Third, although the collection of data related to complications such as aplastic anemia, PTLD, persistent viral disease (CMV or EBV), GI bleeding and leukopenia was standardized, participating institutions only reported the presence or absence of each complication. Thus, the use of definitions that did not differentiate among degrees of severity may have prevented a deeper understanding of the relationship between these co-existing conditions and development of chronic anemia in our analysis. Similarly, we did not assess risk factors by severity of anemia since there is lack of consensus regarding the definition of severe anemia and transfusion history in the post transplant period was not available. Finally, lack of available details related to post transplant corticosteroid, immunosuppression and anti-hypertensive medication use made it challenging to determine if these medications may have represented surrogate markers for other pathophysiologic causes of anemia. Our multivariate analysis, however, allowed for

some exploration of the interactions, or lack thereof, between medications use and other factors, including renal dysfunction.

In summary, chronic anemia is commonly observed in children during the first 5 years following orthotopic liver transplantation and is most highly associated with presence of GI bleeding, persistent leukopenia, corticosteroid use, CSA-based immunosuppressive therapy and reduced renal function at the time anemia was first found. Our findings underscore the need for prospective studies that specifically address the evaluation and management of anemia in the post liver transplant period. Comprehensive data collection should be aimed at further delineating the pathophysiologic mechanisms responsible for development of chronic anemia that may be attributable to potential risk factors and contributors, some of which may be modifiable, identified in this study. The detrimental effects of chronic anemia in this population, such as impact on growth and development, overall graft health, as well as important outcome measures such as quality of life and physical functioning, represent additional areas that should be investigated in future studies.

Acknowledgments

We are indebted to Dr. Alexis Thompson for her in-depth, critical review of this manuscript. This study was funded in part by the National Institute of Diabetes and Digestive and Kidney Diseases (U01 DK061693).

References

1. Hunt BJ, Amin S, Halil O, Yacoub M. The prevalence, course, and characteristics of chronic anemia after heart and lung transplantation. Transplantation. 1992; 53:1251–1256. [PubMed: 1604480]
2. Muller HM, Horina JH, Kniepeiss D, et al. Characteristics and clinical relevance of chronic anemia in adult heart transplant recipients. Clin Transplant. 2001; 15:343–348. [PubMed: 11678961]
3. Sezer S, Ozdemir FN, Tutal E, Bilgic A, Haberal M. Prevalence and etiology of anemia in renal transplant recipients. Transplant Proc. 2006; 38:537–540. [PubMed: 16549168]
4. Kausman JY, Powell HR, Jones CL. Anemia in pediatric renal transplant recipients. Pediatr Nephrol. 2004; 19:526–530. [PubMed: 15007719]
5. Shah N, Al-Khoury S, Afzali B, et al. Posttransplantation anemia in adult renal allograft recipients: prevalence and predictors. Transplantation. 2006; 81:1112–1118. [PubMed: 16641595]
6. Shibagaki Y, Shetty A. Anaemia is common after kidney transplantation, especially among African Americans. Nephrol Dial Transplant. 2004; 19:2368–2373. [PubMed: 15213318]
7. Yorgin PD, Belson A, Sanchez J, et al. Unexpectedly high prevalence of posttransplant anemia in pediatric and young adult renal transplant recipients. Am J Kidney Dis. 2002; 40:1306–1318. [PubMed: 12460052]
8. Afzali B, Al-Khoury S, Shah N, Mikhail A, Covic A, Goldsmith D. Anemia after renal transplantation. Am J Kidney Dis. 2006; 48:519–536. [PubMed: 16997048]
9. Winkelmayer WC, Chandraker A, Alan Brookhart M, Kramar R, Sunder-Plassmann G. A prospective study of anaemia and long-term outcomes in kidney transplant recipients. Nephrol Dial Transplant. 2006; 21:3559–3566. [PubMed: 17040993]
10. Guitard J, Ribes D, Kamar N, et al. Predictive factors for anemia six and twelve months after orthotopic liver transplantation. Transplantation. 2006; 81:1525–1531. [PubMed: 16770241]
11. Iglesias-Berengue J, Lopez-Espinosa JA, Ortega-Lopez J, et al. Hematologic abnormalities in liver-transplanted children during medium- to long-term follow-up. Transplant Proc. 2003; 35:1904–1906. [PubMed: 12962842]
12. Misra S, Moore TB, Ament ME, Vargas JH, Busutill RW, McDiarmid SV. Profile of anemia in children after liver transplantation. Transplantation. 2000; 70:1459–1463. [PubMed: 11118090]
13. Maheshwari A, Mishra R, Thuluvath PJ. Post-liver-transplant anemia: etiology and management. Liver Transpl. 2004; 10:165–173. [PubMed: 14762852]
14. Hermiston ML, Mentzer WC. A practical approach to the evaluation of the anemic child. Pediatr Clin North Am. 2002; 49:877–891. [PubMed: 12430617]

15. Al-Uzri A, Yorgin PD, Kling PJ. Anemia in children after transplantation: etiology and the effect of immunosuppressive therapy on erythropoiesis. Pediatr Transplant. 2003; 7:253–264. [PubMed: 12890002]
16. Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. European FK506 Multicentre Liver Study Group. Lancet. 1994; 344:423–428. [PubMed: 7520105]
17. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. The U.S. Multicenter FK506 Liver Study Group. N Engl J Med. 1994; 331:1110–1115. [PubMed: 7523946]
18. Misra S, Moore TB, Ament ME, Busuttil RW, McDiarmid SV. Red cell aplasia in children on tacrolimus after liver transplantation. Transplantation. 1998; 65:575–577. [PubMed: 9500636]
19. Nosari A, Marbello L, De Carlis LG, et al. Bone marrow hypoplasia complicating tacrolimus (FK506) therapy. Int J Hematol. 2004; 79:130–132. [PubMed: 15005339]
20. Trimarchi HM, Truong LD, Brennan S, Gonzalez JM, Suki WN. FK506-associated thrombotic microangiopathy: report of two cases and review of the literature. Transplantation. 1999; 67:539–544. [PubMed: 10071024]
21. Young BA, Marsh CL, Alpers CE, Davis CL. Cyclosporine-associated thrombotic microangiopathy/hemolytic uremic syndrome following kidney and kidney-pancreas transplantation. Am J Kidney Dis. 1996; 28:561–571. [PubMed: 8840947]
22. Vannucchi AM, Grossi A, Bosi A, et al. Effects of cyclosporin A on erythropoietin production by the human Hep3B hepatoma cell line. Blood. 1993; 82:978–984. [PubMed: 8393357]
23. Bardet V, Junior AP, Coste J, et al. Impaired erythropoietin production in liver transplant recipients: the role of calcineurin inhibitors. Liver Transpl. 2006; 12:1649–1654. [PubMed: 17058250]
24. Fisher NC, Nightingale PG, Gunson BK, Lipkin GW, Neuberger JM. Chronic renal failure following liver transplantation: a retrospective analysis. Transplantation. 1998; 66:59–66. [PubMed: 9679823]
25. Gonwa TA, Mai ML, Melton LB, et al. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy: risk of development and treatment. Transplantation. 2001; 72:1934–1939. [PubMed: 11773892]
26. Moreno JM, Cuervas-Mons V, Rubio E, et al. Chronic renal dysfunction after liver transplantation in adult patients: prevalence, risk factors, and impact on mortality. Transplant Proc. 2003; 35:1907–1908. [PubMed: 12962843]
27. Schmitz V, Laudi S, Moeckel F, et al. Chronic renal dysfunction following liver transplantation. Clin Transplant. 2008; 22:333–340. [PubMed: 18341597]
28. Campbell KM, Yazigi N, Ryckman FC, et al. High prevalence of renal dysfunction in long-term survivors after pediatric liver transplantation. J Pediatr. 2006; 148:475–480. [PubMed: 16647407]
29. Harambat J, Ranchin B, Dubourg L, et al. Renal function in pediatric liver transplantation: a long-term follow-up study. Transplantation. 2008; 86:1028–1034. [PubMed: 18946339]
30. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009; 20:629–637. [PubMed: 19158356]

Table 1

Patient Demographics and Clinical Characteristics

	Chronic Anemia					
	No		Yes		Total	
	N	%	N	%	N	%
Total[†]	784	100.0	242	100.0	1026	100.0
Age at Transplant (years)						
< 1	164	20.9	50	20.7	214	20.9
1–4	338	43.1	72	29.8	410	40.0
5–12	206	26.3	67	27.7	273	26.6
13+	76	9.7	53	21.9	129	12.6
Race						
White	456	58.2	125	51.7	581	56.6
Black	104	13.3	50	20.7	154	15.0
Hispanic	128	16.3	36	14.9	164	16.0
Other	84	10.7	27	11.2	111	10.8
Gender						
Male	369	47.1	111	45.9	480	46.8
Female	415	52.9	131	54.1	546	53.2
Primary Diagnosis						
Biliary atresia	333	42.5	73	30.2	406	39.6
Other cholestatic	105	13.4	37	15.3	142	13.8
Fulminant liver failure	105	13.4	34	14.0	139	13.5
Metabolic disease	126	16.1	45	18.6	171	16.7
Cirrhosis	37	4.7	16	6.6	53	5.2
Other	78	9.9	37	15.3	115	11.2
Immunosuppression at Transplant						
CSA Base	59	7.5	24	9.9	83	8.1
Tac Base	633	80.7	193	79.8	826	80.5
Other	65	8.3	12	5.0	77	7.5
Steroid Usage at Transplant						

	Chronic Anemia					
	No		Yes		Total	
	N	%	N	%	N	%
No	78	9.9	25	10.3	103	10.0
Yes	706	90.1	217	89.7	923	90.0
cGFR < 90 at Transplant						
No	591	75.4	178	73.6	769	75.0
Yes	71	9.1	32	13.2	103	10.0

CSA – cyclosporine; Tac – Tacrolimus; cGFR – calculated glomerular filtration rate

†Distribution of demographics and characteristics may not equal 100% due to missing data

Table 2

Univariate Analysis of Risk Factors Associated with Chronic Anemia

Factor	Comparison Group	Reference Group	Odds Ratio	Confidence Interval	*P* Value	Overall *P* Value
Age at Transplant	1–4 years	< 1 year	0.70	(0.47, 1.05)	0.0836	**< 0.0001**
	5–12 years		1.07	(0.70, 1.62)	0.7627	
	13+ years		2.29	(1.43, 3.67)	0.0006	
Race	Black	White	1.75	(1.19, 2.59)	0.0049	**0.0406**
	Hispanic		1.03	(0.67, 1.56)	0.9045	
	Other		1.17	(0.73, 1.89)	0.5127	
Gender	Female	Male	1.05	(0.79, 1.40)	0.7442	0.7442
ABO Incompatibility	Compatible	Identical	1.04	(0.69, 1.58)	0.8421	0.4207
	Incompatible		1.98	(0.71, 5.53)	0.1900	
Patient Status at Transplant	ICU	Not hospitalized	1.25	(0.87, 1.79)	0.2260	0.3123
	Hospitalized, not in ICU		1.27	(0.86, 1.90)	0.2341	
Primary Diagnosis	Other cholestatic	Biliary atresia	1.61	(1.02, 2.53)	0.0397	**0.0151**
	Fulminant liver failure		1.48	(0.93, 2.35)	0.0982	
	Metabolic disease		1.63	(1.07, 2.49)	0.0242	
	Cirrhosis		1.97	(1.04, 3.74)	0.0371	
	Other		2.16	(1.36, 3.45)	0.0012	
PELD Score at Transplant	0–10	< 0	0.89	(0.57, 1.39)	0.6154	0.7089
	10–20		0.97	(0.62, 1.53)	0.8998	
	≥ 20		1.14	(0.75, 1.73)	0.5324	
Height Deficit at Transplant	> 2 Std. Dev. Below Mean	Above Mean or within 2 Std. Dev.	0.96	(0.69, 1.35)	0.8291	0.8291
Weight Deficit at Transplant	> 2 Std. Dev. Below Mean	Above Mean or within 2 Std. Dev.	0.81	(0.56, 1.15)	0.2336	0.2336
Immunosuppression at Transplant	CSA Base	Tac Base	1.33	(0.81, 2.20)	0.2595	0.1376
	Other		0.61	(0.32, 1.14)	0.1224	
Steroids at Transplant	Yes	No	0.96	(0.60, 1.54)	0.8617	0.8617
cGFR < 90 at Transplant	Yes	No	1.50	(0.95, 2.35)	0.0788	0.0788
Aplastic Anemia at last follow-up	Yes	No	6.56	(1.19, 36.01)	0.0305	**0.0305**
Leukopenia at last follow-up	Yes	No	7.74	(3.61, 16.60)	< 0.0001	**< 0.0001**
CMV Disease up to last follow-up	Yes	No	1.11	(0.64, 1.93)	0.7166	0.7166
EBV Disease up to last follow-up	Yes	No	0.80	(0.42, 1.53)	0.5009	0.5009
PTLD Disease up to last follow-up	Yes	No	1.43	(0.58, 3.52)	0.4360	0.4360
Anti-hypertensive at last follow-up	Yes	No	2.71	(1.96, 3.75)	< 0.0001	**< 0.0001**
GI bleeding at last follow-up	Yes	No	4.45	(1.53, 12.95)	0.0062	**0.0062**
Immunosuppression at last follow-up	CSA Base	Tac Base	3.37	(1.81, 6.29)	0.0001	**0.0004**
	Other		0.65	(0.27, 1.59)	0.3462	

Factor	Comparison Group	Reference Group	Odds Ratio	Confidence Interval	*P* Value	Overall *P* Value
Steroids at last follow-up	Yes	No	3.32	(2.45, 4.50)	< 0.0001	< **0.0001**
cGFR < 90 at last follow-up	Yes	No	4.73	(2.81, 7.97)	< 0.0001	< **0.0001**

PELD – pediatric end-stage liver disease; cGFR – calculated glomerular filtration rate; CMV – cytomegalovirus; EBV – Epstein Barr virus; PTLD – post-transplant lymphoproliferative disorder; CSA – cyclosporine; Tac – Tacrolimus

Table 3

Multivariate Analysis of Risk Factors Associated with Chronic Anemia

Factor	Comparison Group	Reference Group	Odds Ratio	Confidence Interval	*P* Value	Overall *P* Value
Race	Black	White	1.89	(1.12, 3.19)	**0.0164**	0.1123
	Hispanic		1.31	(0.74, 2.31)	0.3485	
	Other		1.31	(0.69, 2.51)	0.4131	
Age at Transplant	1–4 years	< 1 year	0.59	(0.35, 1.01)	0.0556	**0.0007**
	5–12 years		1.31	(0.76, 2.27)	0.3285	
	13+ years		1.86	(0.97, 3.58)	0.0637	
Leukopenia at last follow-up	Yes	No	9.55	(3.71, 24.62)	--	**< 0.0001**
GI Bleeding at last follow-up	Yes	No	11.83	(2.08, 67.49)	--	**0.0054**
Anti-hypertensive Medication at last follow-up	Yes	No	1.89	(1.23, 2.91)	--	**0.0039**
Immunosuppression at last follow-up	CSA Base	Tac Base	3.69	(1.56, 8.76)	**0.0039**	**0.0012**
	Other		0.24	(0.06, 0.93)	**0.0315**	
Steroids at last follow-up	Yes	No	2.90	(1.94, 4.33)	--	**< 0.0001**
cGFR < 90 at last follow-up	Yes	No	4.62	(2.47, 8.67)	--	**< 0.0001**

cGFR – calculated glomerular filtration rate; CSA – cyclosporine; Tac – Tacrolimus