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# Optimal Threshold and Time of Absolute Lymphocyte Count Assessment for Outcome Prediction after Bone Marrow Transplantation

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The recovery pace of absolute lymphocyte count (ALC) is prognostic after hematopoietic stem cell transplantation. Previous studies have evaluated a wide range of ALC cutoffs and time points for predicting outcomes. We aimed to determine the optimal ALC value for outcome prediction after bone marrow transplantation (BMT). A total of 518 patients who underwent BMT for acute leukemia or myelodysplastic syndrome between 1999 and 2010 were divided into a training set and a test set to assess the prognostic value of ALC on days 30, 60, 90, 120, 180, as well as the first post-transplantation day of an ALC of 100, 200, 300, 400, 500, and 1000/μL. In the training set, the best predictor of overall survival (OS), relapse-free survival (RFS), and nonrelapse mortality (NRM) was ALC on day 60. In the entire patient cohort, multivariable analyses demonstrated significantly better OS, RFS, and NRM and lower incidence of graft-versus-host disease (GVHD) in patients with an ALC >300/μL on day 60 post-BMT, both including and excluding patients who developed GVHD before day 60. Among the patient-, disease-, and transplant-related factors assessed, only busulfan-based conditioning was significantly associated with higher ALC values on day 60 in both cohorts. The optimal ALC cutoff for predicting outcomes after BMT is 300/μL on day 60 post-transplantation.


## INTRODUCTION

Relapse, infectious complications, and graft-versus-host-disease (GVHD) are the major reasons for treatment failure after allogeneic hematopoietic stem cell transplantation (SCT). The last decade has seen numerous attempts to reduce relapse incidence [1] and treatment-related morbidity/mortality associated with SCT [2,3]; however, such interventions are costly and have side effects, and thus may be better suited for patients at high risk for treatment failure. One way of identifying high-risk patients is through evaluation for delayed immune reconstitution post-transplantation, an important cause of morbidity and mortality. Most methods for assessing immune recovery are complex, require special knowledge, and are not part of clinical practice, however. Consequently, there is considerable need for a simple and reliable prognostic marker for evaluating the recovery of immune function as a whole and can be widely used to identify patients at high risk for treatment failure.

Immune reconstitution after SCT is a stepwise process in which the innate immune system starts to recover before the adaptive system [4]. Natural killer (NK) cells recover during the first weeks post-SCT, constituting the major part of the lymphocyte count early after transplantation [5]. Whereas thymus-independent donor memory T cells start expanding immediately after SCT, thymus-dependent development of new T cells from progenitors may take up to 1 to 2 years [6]. In addition, B cell numbers are low during at least the first 2 months post-SCT [7], and reconstitution of the B compartment may take up to 2 years [8].

Patient age, in vivo or ex vivo T cell depletion, and donor type may affect immune reconstitution early after SCT [9,10]; however, graft source is considered the most important factor affecting reconstitution [11]. Peripheral blood (PB)

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**Table 1**
Published Studies Assessing the Associations of Post-BMT ALC with Clinical Outcomes

| Study | Patient Characteristics | ALC Time Point and Cutoffs Assessed, with Rationale for Their Selection | OS | RFS | NRM | RI | aGVHD | cGVHD |
|---|---|---|---|---|---|---|---|---|
| Rigoni et al, 2015 [15] | 100 chemoresponsive patients with AML/ALL/MDS; all sources and donors; 78% MA, 22% RIC | Time points and cutoff chosen arbitrarily | OS longer in high-ALC group | | | | | |
| | | 300 at day 21 (30%) | HR, 1.3 (95% CI, 0.7-2.6) | | HR, 1.2 (95% CI, 0.6-2.6) | 25% versus 26% ($P = NS$) | 76% versus 52% ($P = NS$) | 33% versus 36% ($P = NS$) |
| | | 300 at day 30 (18%) | HR, 2.2 (95% CI, 1.0-4.7) | | HR, 2.0 (95% CI, 0.9-4.4) | 12% versus 29% ($P = NS$) | 94% versus 50% ($P = .003$) | 46% versus 34% ($P = NS$) |
| Kim et al, 2015 [13] | 1109 patients; all diseases; UCB and haplo excluded; 48% MA, 52% RIC | Time points chosen arbitrarily; cutoff based on RFS curves | At 5 yr: | At 5 yr: | At 5 yr: | Patients with <200 at any time point (14% of all patients) versus >200 at month 1, month 2, and month 3:40% versus 43% ($P = NS$) | | |
| | | 200 at month 1 (8%) | 30% versus 45% ($P < .001$) | 19% versus 38% ($P < .001$) | 33% versus 20% ($P = .002$) | | | |
| | | 200 at month 2 (6%) | 28% versus 49% ($P < .001$) | 25% versus 41% ($P < .001$) | 44% versus 19% ($P < .001$) | | | |
| | | 200 at month 3 (6%) | 27% versus 53% ($P < .001$) | 22% versus 45% ($P < .001$) | 41% versus 18% ($P < .001$) | | | |
| Yamamoto et al, 2014 [16] | 206 patients with AML/ALL/MDS; MA and RIC; all sources and donors | Time point of day 100 selected to exclude aGVHD effect; cutoff based on OS curves | OS longer in high-ALC group: HR, 2.4 (95% CI, 1.3-4.5) | | NRM lower in high-ALC group: HR: 2.8 (95% CI, 1.1-6.8) | HR, 1.4 (95% CI, 0.7-3.0) | | |
| | | 500 at day 100 (18%) | | | | | | |
| Michelis et al, 2014 [17] | 191 patients with AML in CR; MRD or MUD; PB only; MA and RIC | Cutoff chosen arbitrarily; time point based on the median number of days to achieve ALC500 | | | | RI lower in high-ALC group: HR, 0.49 (95% CI, 0.26-0.92) | | |
| | | 500 at day 28 (42%) | $P = NS$ in multivariable analysis | | $P = NS$ in multivariable analysis | | | |
| Han et al, 2013 [18] | 69 children with hematologic malignancies; 64 MA, 5 RIC; all sources and donors | Cutoff based on preliminary analyses of ALC200, 300, 400, and 500 | At 5 yr: 62% versus 67% ($P = NS$) | | At 5 yr: 19% versus 16% ($P = NS$) | At 5 yr: 20% versus 22% ($P = NS$) | Grade II-IV incidence: 29% versus 17% ($P = NS$) | Extensive: 14% versus 15% ($P = NS$) |
| | | 500 at day 21 (41%) | | | | | | |
| | | 500 at day 30 (28%) | 53% versus 71% ($P = .043$) ($P = NS$ on multivariable analysis) | | 34% versus 11% ($P = .019$) | 20% versus 22% ($P = NS$) | | 11% versus 16% ($P = NS$) |
| DeCook et al, 2012 [19] | 118 patients with hematologic malignancies; RIC with Flu/Mel; PB and BM; all donors | Rationale not provided | Univariate OS analyses; on multivariable analysis, only day 100 was significant ($P = .049$) | | | | | |
| | | 300 at d day15 (57%) | $P = .25$ | | | | | |
| | | 300 at day 30 (6%) | $P < .001$ | | | | | |
| | | 300 at day 60 (11%) | $P < .001$ | | | | | |
| | | 300 at day 100 (18%) | $P < .001$ | | | | | |
| Le Blanc et al, 2009 [20] | 102 patients with AML/CML/MDS only; MA only; MUD only; PB and BM | Multivariable analysis performed with ALC on day 30 as a continuous variable; day 30 chosen | $P = NS$ on multivariable analysis | Significance increases with ALC ($P = .04$) | Significance decreases with ALC ($P < .05$) | | | |