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Endothelial Activation and Stress Index predict GVHD-free, relapse-free survival in adults undergoing haploidentical haematopoietic stem cell transplantation

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Abstract

The Endothelial Activation and Stress Index (EASIX) is a prognostic score including creatinine, lactate dehydrogenase, and thrombocytes. Its prognostic value in the context of haploidentical SCT (haplo-HSCT) remains to be fully elucidated. To explore the significance of pre-transplant EASIX for clinical outcome, we conducted a retrospective study in 434 consecutive patients who received haplo-HSCT with ATG/G-CSF-based protocol for the treatment of hematologic malignancies In multivariate analysis, the EASIX score was independently associated with graft-versus-host disease (GVHD)-free, relapse-free survival (GRFS, (HR = 1.2, $P < 0.001$)). The cutoff value of EASIX for GRFS was 1.6, with 3-year GRFS being 63% and 72% in the high- and low-risk groups, respectively ($P < 0.001$). The cumulative incidences of grade III-IV aGVHD were 24% and 12% ($P = 0.004$), and the 3-year cumulative incidences of moderate to severe cGVHD were 40% and 20% in the high- and low-risk groups, respectively ($P < 0.001$). In the MDS subgroup, an optimal cutoff of 0.7 was established, and EASIX remained significantly associated with the GRFS (HR = 5.4, $P = 0.02$). Pre-transplant EASIX serves as an independent predictor for GRFS as an easily accessible tool.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative therapy for various malignant hematological diseases. Haploidentical HSCT (haplo-HSCT) has emerged as a widely adopted alternative, expanding donor availability for patients without a matched sibling donor or those requiring urgent transplantation (1). Graft-versus-host disease (GVHD), relapse and non-relapse mortality (NRM) have remained the long-standing clinical challenges in the field of transplantation. Thus, pre-transplant risk assessment is critically important and is intrinsically linked to clinical decision-making.

Several comprehensive risk scoring systems, such as the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) (2), the European Society for Blood and Marrow Transplantation (EBMT) score (3), and the Disease Risk Index (DRI) (4) have been developed and are widely used for pre-transplant risk stratification. While valuable, these systems often require complex clinical variables that hamper rapid use. More recently, a novel and simpler biomarker, the Endothelial Activation and Stress Index (EASIX), has shown a highly promising ability for risk stratification. It was initially validated by Luft et al. as a powerful predictor for the development of acute GVHD (aGVHD) after allo-HSCT (5). This assessment strategy has since been validated and extended by multiple centers, with accumulating evidence demonstrating that EASIX is also predictive of overall survival (OS) and NRM in broader transplant settings (6–11).

EASIX is calculated from three routinely available laboratory biomarkers—serum creatinine, lactate dehydrogenase (LDH), and platelet count (5). The simplicity and cost-effectiveness of EASIX are among its principal strengths. Although evidence for EASIX's prognostic value is growing, most studies to date have focused on its application in matched donor transplants. Data specifically validating its predictive power in the context of haplo-HSCT remain scarce. Given the distinct immunological and endothelial

injury risks in haplo-HSCT, it is crucial to evaluate whether EASIX retains its prognostic power for this specific population. Therefore, this study investigates the prognostic utility of the pre-transplant EASIX score for predicting survival, NRM, GVHD, and relapse in haplo-HSCT recipients managed under the antithymocyte globulin (ATG)/granulocyte colony-stimulating factor (G-CSF) -based protocol.

MATERIALS AND METHODS

Patients

We performed a retrospective cohort study of adult patients who underwent haplo-HCT at Peking University Institute of Hematology between January 2020 to June 2021. Clinical data were collected from the institutional medical database. Informed consent was obtained from all patients. This study was approved by the institutional review board of Peking University People's Hospital and was conducted under the Declaration of Helsinki.

Transplant procedures

The myeloablative conditioning (MAC) was consisted of: cytarabine 4 g/m^2 per day at days − 10 and − 9, busulfan 3.2 mg/kg a day intravenously at days − 8 to -6, cyclophosphamide 1.8 g/m^2 a day at days − 5 and − 4, semustine 250 mg/m^2 orally at day − 3, and rabbit ATG 2.5 mg/kg a day at days − 5 to -2. For recipients over 55 years old or with a HCT-CI score ≥ 3 points, a reduced toxicity conditioning (RTC) regimen was performed, which consisted of cytarabine 2 g/m2 per day at days − 10 and − 9, fludarabine 30 mg/m^2 per day from day − 6 to day − 2, cyclophosphamide 1.0 g/m^2 a day at days − 5 and − 4, together with the same busulfan, semustine and ATG doses as mentioned above (12, 13). The GVHD prophylaxis regimen comprised cyclosporine A (CsA), mycophenolate mofetil (MMF), and short-term methotrexate (MTX). CsA 2.5 mg/kg a day intravenously with trough concentration adjusted to 150 to 250 ng/mL, and was switched to the oral route when the gastrointestinal function of patients recovered. MMF was administered 0.5 g every 12 hours from day − 9 until neutrophil engraftment; MTX was administered intravenously at 15 mg/m^2 on day + 1 and at 10 mg/m^2 on days + 3, +5, and + 11 (12). We followed the consensus recommendations for the monitoring, treatment, and prevention of leukemia relapse after allo-HSCT in China (14). All patients received G-CSF 5 μg/kg from day + 6 to neutrophil engraftment.

EASIX score assessment

EASIX was calculated by the formula: lactate dehydrogenase (U/L) × creatinine (mg/dL)/ thrombocytes (10^9 cells/L) (5). A $\log_2$ transformation was applied to reduce skewness (5, 8). We evaluated the last EASIX score, which was obtained within 5 days before initiating conditioning (9).

Definitions and Study Endpoints

Neutrophil engraftment was defined as the first of three consecutive days with an absolute neutrophil count ≥ 0.5 × 10^9/L. Platelet engraftment was defined as the first of seven consecutive days with a platelet count ≥ 20 × 10^9/L without requiring transfusion support. Overall survival (OS) was defined as the time from the date of transplantation to the date of death from any cause. Non-relapse mortality (NRM) was defined as death in the absence of relapse. Relapse was defined as recurrence of bone marrow blasts of more than 5%, or any extramedullary site after complete remission. GVHD-free, relapse-free survival (GRFS) was defined as survival without the following events: grade III–IV aGVHD, cGVHD requiring systemic immunosuppressive treatment, relapse, or death from any cause after transplantation (15). Acute GVHD (aGVHD) was graded according to the modified Glucksberg's criteria (16), and chronic GVHD (cGVHD) was graded according to the National Institute of Health criteria (17).

Statistical analysis

For descriptive information, continuous variables were compared using the Mann-Whitney U test; categorical variables were compared using the chi-square or Fisher's exact test. The Kaplan–Meier method was used to estimate the probability of OS and GRFS. Cumulative incidences of NRM, relapse, and GVHD were calculated by a competing risk setting. Hazard ratios for OS and GRFS were estimated by the COX regression model. Fine and Gray's proportional subdistribution hazards model was utilized for the competing risks regression (18). Factors included in the regression model were $\log_2$-EASIX score, age of recipient, donor age, disease risk index, conditioning intensity (MAC vs. RTC), and female to male recipient (no vs. yes). Variables with a $P < 0.1$ in univariate analysis were included in the multivariate analysis to evaluate the impact of $\log_2$-EASIX on clinical outcomes. Maximally selected log-rank statistics were used to determine the optimal $\log_2$-EASIX cutoff value for OS and GRFS (19). All of the tests were two-tailed, and $P < 0.05$ was considered statistically significant. All analyses were conducted using SPSS (version 22.0; Chicago, IL) and R software (version 4.5.0; http://www.r-project.org).

Results

Patient characteristics and EASX value distribution

Our cohort included 434 patients, and their details are shown in Table 1. Median $\log_2$-EASIX was − 0.20 (range, -2.69–6.33) for the overall population. This corresponds to a value of the original value of 0.87. Given that MDS patients are prone to thrombocytopenia, and acute leukemia recipients account for 71.9% of the total cohort, with 95.5% of them being in complete remission before transplantation, we analyzed the impact of EASIX in the MDS subgroup. Median $\log_2$-EASIX was 1.31 (range, -1.71–6.33) for the MDS subgroup and − 0.40 (range, -2.69–5.11) for the remaining population (2.48 and 0.76 on the original EASIX values, respectively, $P < 0.001$).

Survival

The median follow-up time among survivors after HCT was 1150 days (range, 66–1772 days). By adopting maximally selected log-rank statistics, an EASIX score of 1.6 stratified patients into high- and low-risk groups for GRFS (HR: 1.9; 95% CI: 1.4–2.7; $P < 0.001$). Kaplan-Meier analysis demonstrated that the high-risk group (EASIX ≥ 1.6) exhibited significantly lower 3-year GRFS compared to the low-risk group (63% (95% CI: 54–74) vs. 72% (95% CI: 67–77); $P < 0.001$, Fig. 1a). Multivariate analysis confirmed that the $\log_2$-EASIX score was independently associated with GRFS (HR: 1.2; 95% CI: 1.1–1.3; $P = 0.001$). However, we could not find an optimal EASIX cutoff value for OS. There was no statistically significant difference in OS between the groups (HR: 1.0; 95% CI: 0.9–1.2; $P = 0.69$).

For the MDS sub-group, an optimal cutoff of 0.7 was established for the original EASIX score to stratify patients into high- (EASIX ≥ 0.7) and low-risk (EASIX < 0.7) groups for GRFS. It has significantly inferior 3-year GRFS in the high-risk group compared to the low-risk group (63% (95% CI: 53–76) vs. 83% (95% CI: 64–100), $P = 0.02$, Fig. 1b). In univariate analysis, $\log_2$-EASIX emerged as a significant predictor for GRFS (HR: 5.4; 95% CI: 1.3–22.2; $P = 0.02$). Meanwhile, in the subgroup of recipients aged ≥ 55 years, $\log_2$-EASIX was associated with GRFS (HR: 1.4; 95% CI: 1.1–1.7; $P = 0.01$), however, we could not identify a cutoff value for GRFS in this population.

Engraftment

Two patients died before + 28 days. Among patients who achieved engraftment, the median time to neutrophil engraftment was 12 days (range, 9–25), and the median time to platelet engraftment was 16 days (range, 7-278). The cumulative incidence of neutrophil engraftment was 99.5% (95% CI: 98.7–100.0) at + 28 days for the cohort. The cumulative incidence of platelet engraftment was significantly different between the high- and low-risk groups (87% (95% CI: 78–92) vs. 95% (95% CI: 93–97), $P = 0.02$, Fig. 2) at + 60 days (20). $\log_2$-EASIX score was associated with decreased cumulative incidence of platelet engraftment (HR: 0.9; 95% CI: 0.8–1.0; $P = 0.004$) in univariate analysis (Table 2). Furthermore, the association remained statistically significant after multivariable adjustment (HR: 0.8; 95% CI: 0.6–1.0; $P = 0.04$). This significant difference was not observed in the MDS subgroup and the subgroup of recipients aged ≥ 55 years.

GVHD

By + 100 days after HSCT, the cumulative incidences of grade II-IV aGVHD were 40% (95% CI: 30–49) and 31% (95% CI: 26–36) for high-risk (EASIX ≥ 1.6) and low-risk (EASIX < 1.6) groups, respectively ($P = 0.28$, Fig. 3a). While the cumulative incidences of grade III-IV aGVHD were 24% (95% CI: 16–34) and 12% (95% CI: 8–16), respectively ($P = 0.004$, Fig. 3b). The high-risk group was associated with an increased risk of grade III-IV aGVHD in multivariate analysis (HR: 2.4; 95% CI: 1.3–4.2; $P = 0.004$).

Increasing log_2-EASIX score, was also associated with increased cumulative incidence of moderate to severe cGVHD (HR: 1.3; 95% CI: 1.2–1.5; $P < 0.001$). This association remained significant after adjustment for covariates in multivariate analysis (HR: 2.4; 95% CI: 1.6–3.8; $P < 0.001$). In addition, an EASIX cutoff of 1.6 effectively stratified patients into high- and low-risk groups for both cGVHD (57% (46–67) vs. 45% (39–50); $P = 0.035$, Fig. 4a) and moderate to severe cGVHD (40% (29–52) vs. 20% (15–25); $P < 0.001$, Fig. 4b]).

In multivariate analysis, EASIX was observed as a risk factor for moderate to severe cGVHD for the MDS subgroup (HR: 1.4; 95% CI: 1.1–1.8; $P = 0.02$) and for the subgroup of recipients aged ≥ 55 years (HR: 3.2; 95% CI: 1.2–8.9; $P = 0.02$).

Relapse and NRM

Overall, there were 47 cases of NRM. The 3-year cumulative incidence of NRM was 11% (95% CI: 9–15), and the cumulative incidence of relapse was 11% (95% CI: 8–14). EASIX was not associated with either NRM (HR: 1.1; 95% CI: 0.9–1.4; $P = 0.35$) or REL (HR: 0.9; 95% CI: 0.7–1.1; $P = 0.20$).

Discussion

In this study, we investigated the prognostic value of the pre-transplant EASIX score in adults undergoing haplo-HSCT at our institution. We found that the log_2-EASIX pre-transplant was a significant predictor of adverse outcomes, associated with lower cumulative incidence of platelet engraftment, higher incidence of high grade GVHD, and lower GRFS. The cutoff value of EASIX for GRFS was 1.6 in the context of a G-CSF/ATG-based regimen. In contrast, the EASIX score was not associated with OS and NRM.

cGVHD presents a double-edged sword in HSCT. While non-severe cGVHD is frequently associated with a beneficial graft-versus-leukemia effect, which reduces the risk of disease relapse (21). Our results, demonstrating a significant association between pre-transplant EASIX and cGVHD, stand in contrast to the findings of prior studies by Liu et al (22) and Penack et al. (11). We propose that distinct transplant methodologies and patient populations give rise to different biological pathways for cGVHD, thereby altering the predictive power of EASIX. Primary, and most critically, there is a stark contrast in T-cell depletion strategies. The conditioning employed in our cohort was the ATG-based haplo-HSCT, which was developed as a T-cell replete protocol, whereas the study conducted by Penack et al., 66% of patients underwent in vitro T depletion. Additionally, different conditioning intensity likely further contributed. Our cohort was conditioned with MAC regimens, whereas the reference cohort largely received RIC conditioning (59%). The more intense tissue damage and inflammatory state associated with MAC (23). Furthermore, our study differed from previous reports in several respects: our recipients were younger, our cohort exclusively comprised haploidentical transplant recipients (compared to only 55% in the study by Penack et al. (11)), and a higher proportion (74% vs. 45% in Liu et al.'s cohort (22)) had a low/intermediate DRI. Moreover, we identified that a higher EASIX score was a risk factor for the grade III-IV aGVHD and moderate-to-severe cGVHD occurrence in this study, which significantly impairs quality of life, diminishes GRFS. To the best of our knowledge, this study is the first to investigate the

association of pre-transplant EASIX with the development of moderate-to-severe GVHD and GRFS. Multiple studies have consistently shown its value in predicting both NRM and OS when assessed during pre-transplant evaluation (6, 8, 22, 24–26). However, except for a recent study by Liu et al.(22), where the prognostic ability of EASIX was validated in elderly patients undergoing RIC regimen, our observation appears to conflict with prior evidence, suggesting a potential heterogeneity that may exist in treatment protocols and patient populations as mentioned above.

The high neutrophil engraftment rate, exceeding 99% and only two pre-engraftment deaths limited the feasibility of analyzing the effect of EASIX on engraftment; it was thought to have little practical value. For platelet is included in the EASIX formula and prior identification as a predictor of engraftment (27), we explored the association between pre-transplant EASIX and engraftment probability. The negative impact of a high pre-transplant EASIX score on platelet engraftment, as confirmed in our cohort, has also been documented by Fujita et al. (6). The reason for the discrepancy with the study by Peña et al. (26) is unclear, but it may be related to differences in conditioning intensity (MAC + RTC vs. predominated by RIC).

Given that thrombocytopenia is a characteristic feature of MDS, we specifically assessed the impact of the EASIX score on outcomes in this sub-population. As hypothesized, the distinct disease characteristics of MDS patients resulted in a different pattern of EASIX utility compared to the overall cohort. The median log_2-EASIX was higher in the MDS subgroup, and its prognostic cutoff values were lower than those for the overall population. Notably, the log_2-EASIX cutoff for predicting GRFS in MDS patients was − 0.6. However, EASIX failed to predict the occurrence of cGVHD in this subgroup. A potential explanation for this discrepancy lies in the distribution of cutoff values between the groups. In the overall population, the EASIX cutoffs for GRFS, cGVHD, and moderate-to-severe cGVHD were closely clustered (0.7, 0.95, and 1.0, respectively). In contrast, the corresponding cutoffs in the MDS subgroup were relatively dispersed (-0.6, -0.015, and − 0.015, respectivly). Similarly, Acosta-Medina et al. studied the predictive ability of EASIX in myelofibrosis; their findings did not support its routine use in this population(28). This shows the necessity for future studies to explore the disease-specific prognostic value of EASIX.

Our study has several limitations inherent to its retrospective design. First, potential for selection bias and unmeasured confounding factors, such as transfusion, changes in kidney, liver, and heart function, could impact EASIX values. Second, this was a single-center study, conducted at our institution that our patient population, treatment protocols, and institutional practices may limit the utility of our findings to other centers. Third, the sample size, while substantial, limited the statistical power for extensive MDS subgroup analyses, which may have different characteristics from acute leukemia. Finally, for EASIX itself, due to its susceptibility to various transplantation-related factors such as transfusion, conditioning regimen, and its intensity, GVHD prophylaxis, and probably disease entities as mentioned above, no standardized cut-off values have been established to date. This presents an opportunity for us to explore future prospective, multi-center, large-scale studies to validate our findings, as well as to adopt multi-timepoint dynamic EASIX scores for precisely predicting transplantation outcomes.

In summary, we demonstrated that EASIX is a powerful prognostic tool for platelet engraftment, high grade GVHD, and GRFS in haplo-HSCT under ATG/G-CSF-based protocol. The prognostic cutoff value for the overall cohort and MDS differed. EASIX, as a cost-effective and readily applicable method, is a useful tool for identifying the high-risk population.

Declarations

Competing Interests

The authors declare no competing interests.

Author Contributions

YW: conception and design. FMZ, XJS, YQS, XDM, ML, YFC, LPX, ZXH, and XJH: data collection and/or assembly, analysis and interpretation of the data, and manuscript preparation. YW and XJH: funding and administrative support, and approval of the final manuscript version.

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Tables

Tables 1 and 2 are available in the Supplementary Files section.

Figures

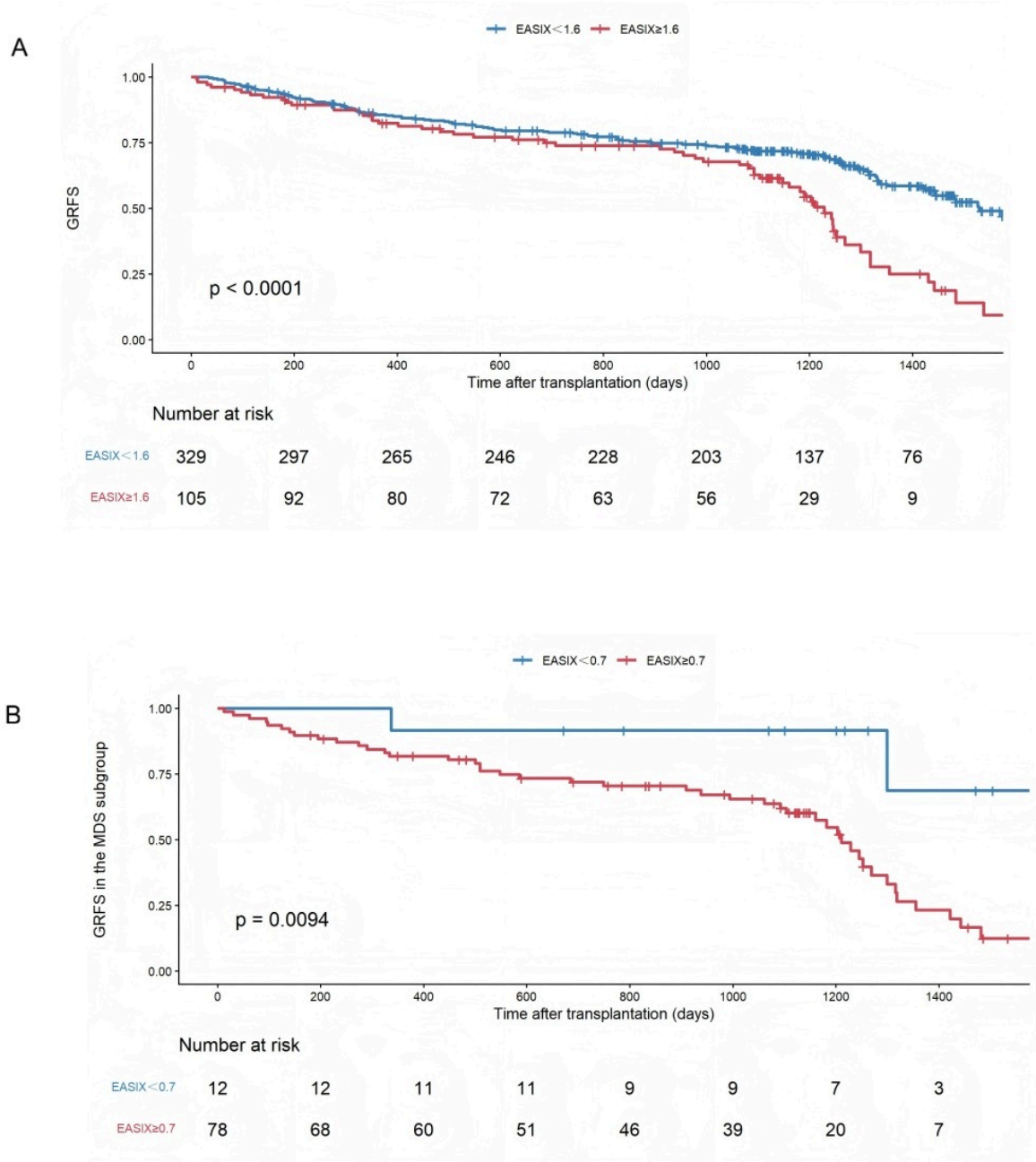


Figure 1

a. Univariable effect of **endothelial activation and stress index (**EASIX) on cumulative incidence of graft-versus-host disease-free, relapse-free survival (GRFS) in the overall population.

b. Univariable effect of EASIX on cumulative incidence of GRFS in the (myelodysplastic syndrome) MDS subgroup.

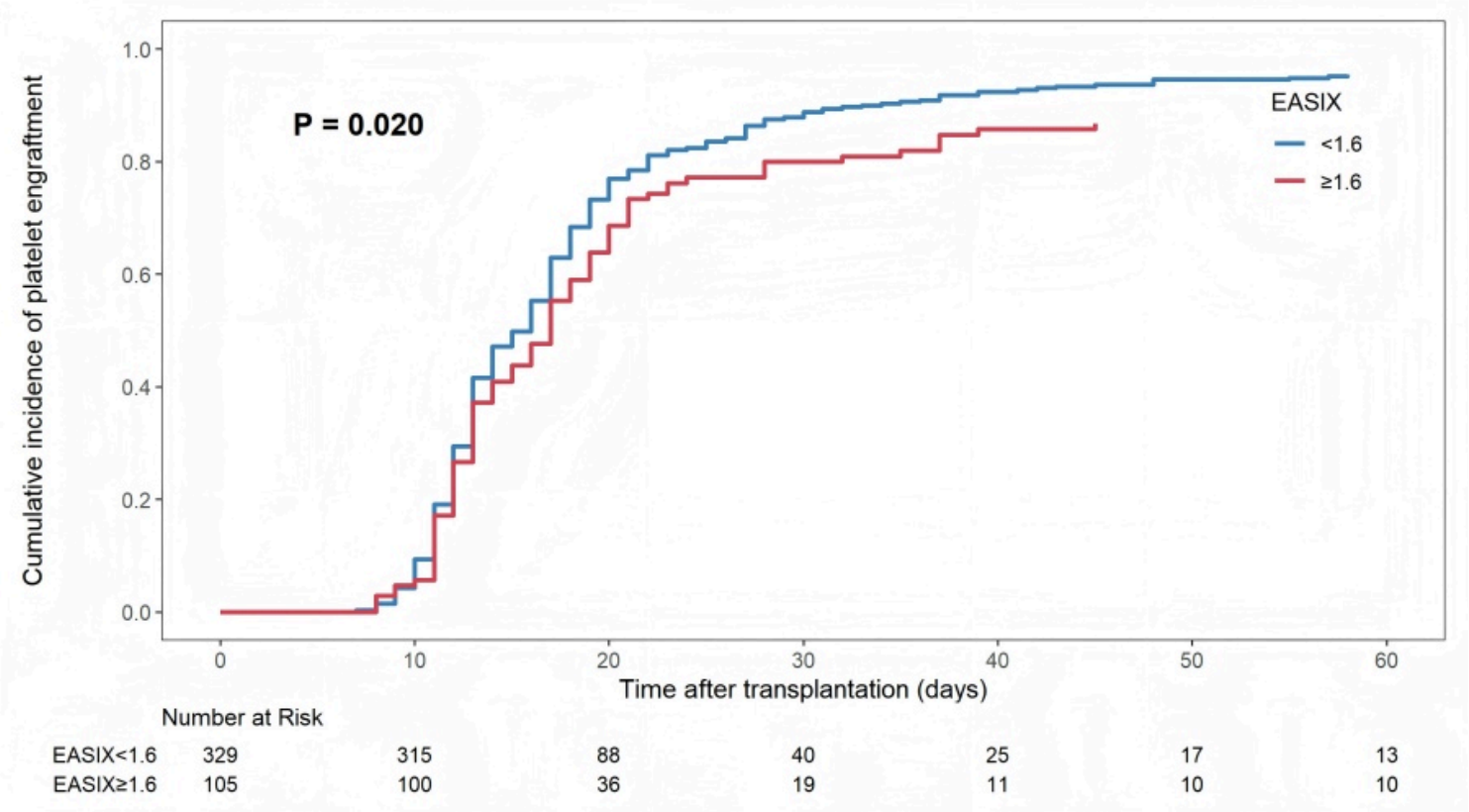


Figure 2

Univariable effect of EASIX on cumulative incidence of platelet engraftment in the overall population.

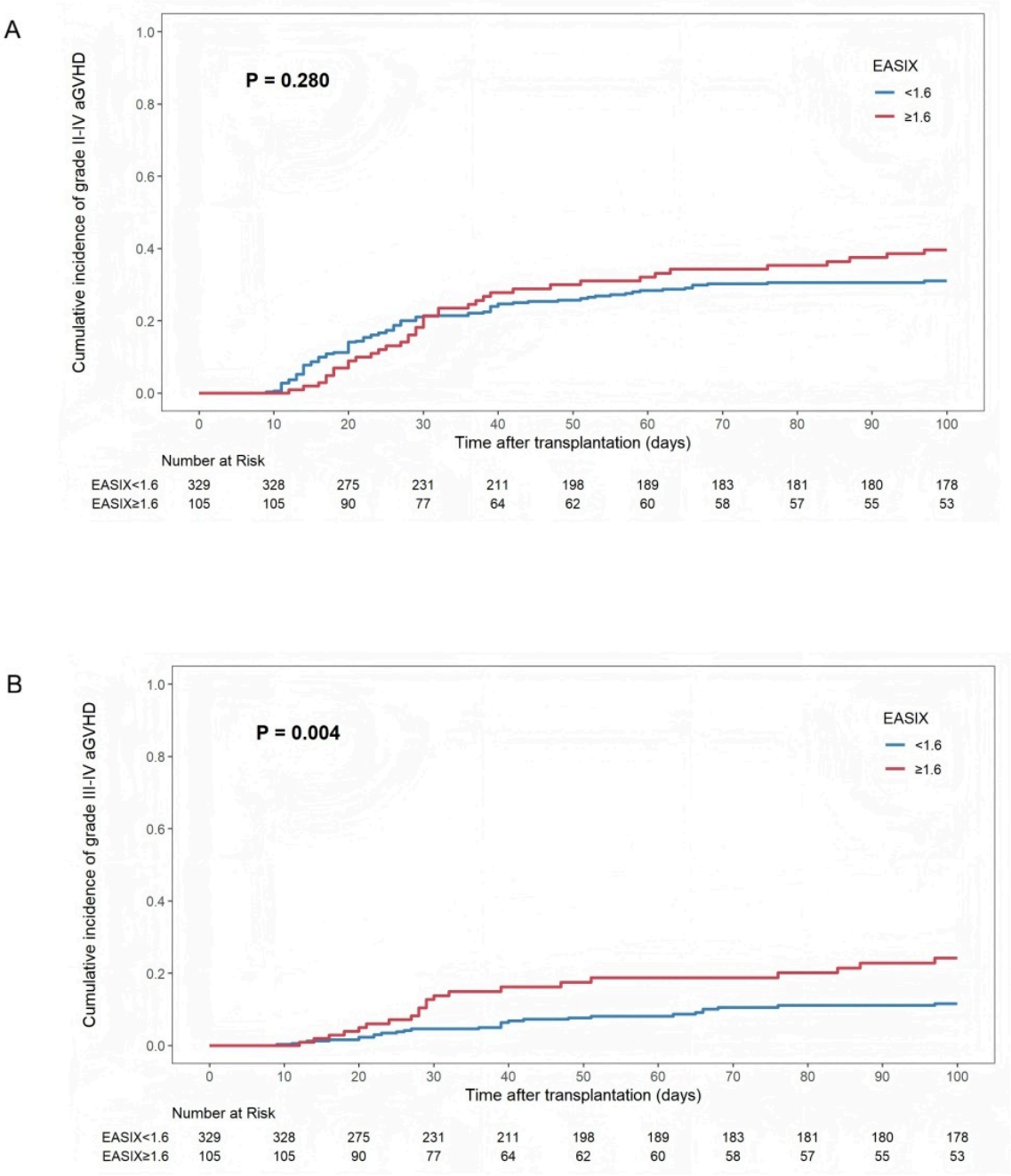


Figure 3

a. Univariable effect of EASIX on cumulative incidence of grade II–IV acute graft-versus-host disease (GVHD) in the overall population.

b. Univariable effect of EASIX on cumulative incidence of grade III–IV acute GVHD in the overall population.

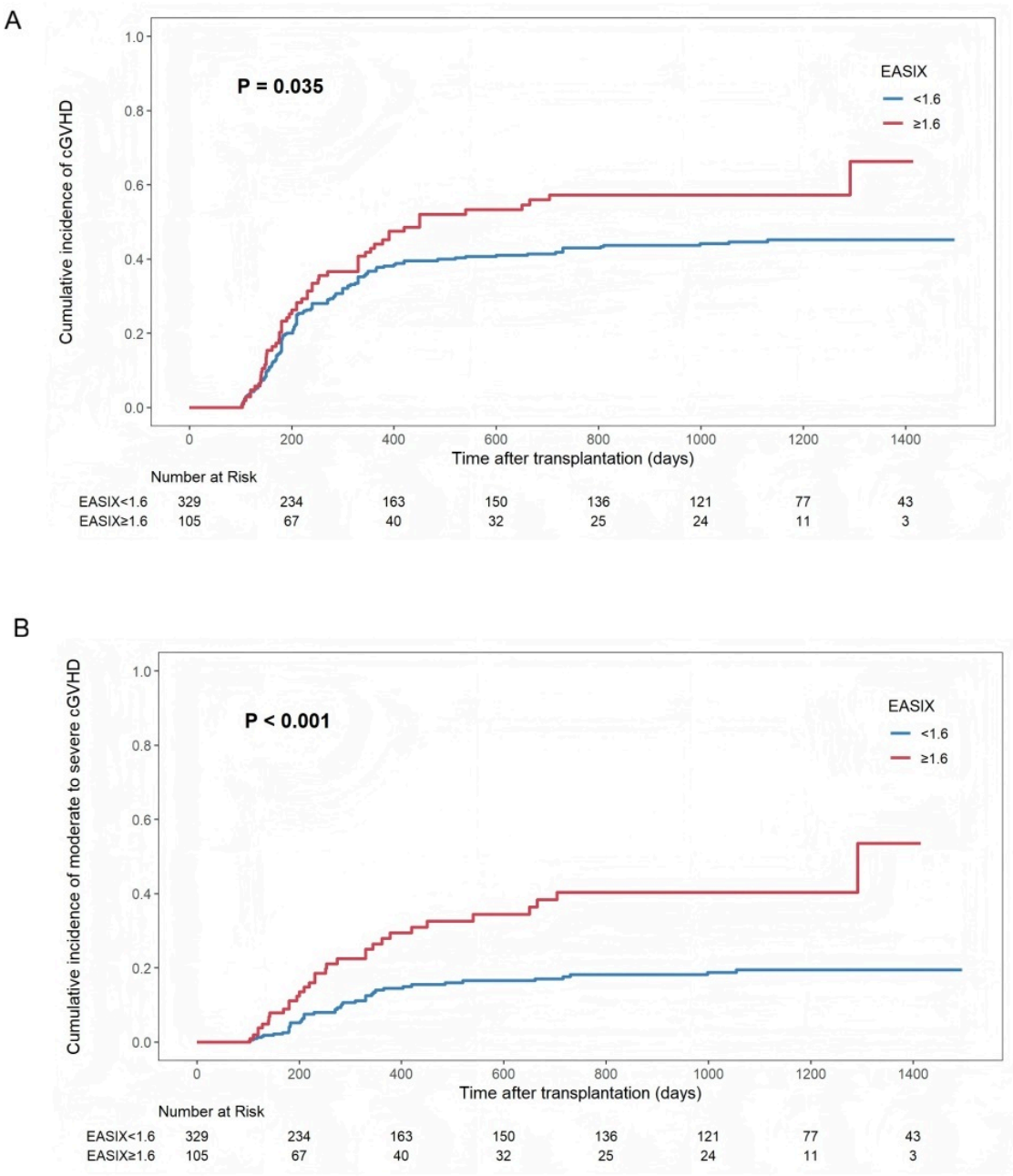


Figure 4

a. Univariable effect of EASIX on cumulative incidence of chronic GVHD in the overall population.

b. Univariable effect of EASIX on cumulative incidence of moderate to severe chronic GVHD in the overall population.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1Patientandtransplantationcharacteristic.xlsx
- Table2.Univariateanalysisofriskfactors.xlsx