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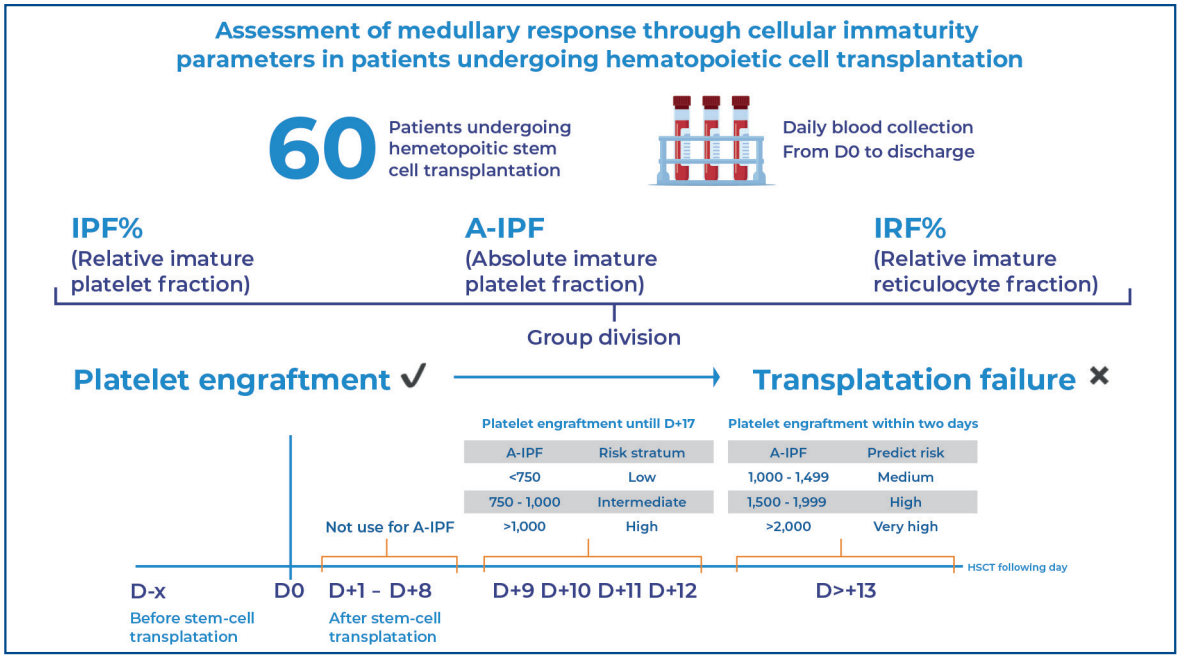
ORIGINAL ARTICLE

Assessment of medullary response through cellular immaturity parameters in patients undergoing hematopoietic stem cell transplantation



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In Brief

This prospective study enrolled 60 patients undergoing hematopoietic stem cell transplantation. Blood samples were collected and analyzed from the conditioning period through hospital discharge. Relative immature platelet fraction (IPF%), absolute immature platelet fraction (A-IPF), and relative immature reticulocyte fraction (IRF%) were compared between patients who achieved platelet engraftment and those who experienced engraftment failure. The results demonstrated that only A-IPF was useful for predicting platelet engraftment after transplantation. Specifically, A-IPF values measured between days +9 and +12 predicted the probability of platelet engraftment by day +17, and A-IPF values were also able to predict the risk of platelet engraftment within the subsequent two days. Risk stratification was established for both approaches. Furthermore, lower weekly mean A-IPF values were associated with a higher need for prophylactic platelet transfusions in the following week.

- A-IPF can be used as a biomarker for platelet engraftment after hematopoietic stem cell transplantation.
- IPF% and IRF% are not reliable biomarkers for bone marrow engraftment after hematopoietic stem cell transplantation.
- IPF%, A-IPF, and IRF% do not support safe reduction of prophylactic platelet transfusions.
- Cellular immaturity parameters lack standardized quality control measures for harmonization between clinical and research laboratories.

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ORIGINAL ARTICLE

Assessment of medullary response through cellular immaturity parameters in patients undergoing hematopoietic stem cell transplantation

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ABSTRACT

Objective: This study aimed to evaluate relative immature platelet fraction (IPF%), absolute immature platelet fraction (A-IPF), and relative immature reticulocyte fraction (IRF%) as biomarkers of bone marrow recovery after hematopoietic stem cell transplantation and to assess their potential role in reducing prophylactic platelet transfusions. **Methods:** Sixty hematopoietic stem cell transplantation recipients (mean age, 50 years) were analyzed, and sex-specific reference ranges for IPF%, A-IPF, and IRF% were established. The predictive performance for platelet engraftment and transfusion requirements was assessed using receiver operating characteristic curve analysis, logistic regression, Fine-Gray competing risks models, Cox regression, and negative binomial modeling. **Results:** Only A-IPF differed significantly between groups. An A-IPF threshold greater than 1,450 predicted platelet engraftments within two days with a sensitivity of 82.1% and a specificity of 80.0%. Logistic regression demonstrated a 2.3-fold increase in the likelihood of platelet engraftment for every 1,000-unit increase in A-IPF, and Fine-Gray analysis confirmed a higher cumulative incidence of engraftment in the intermediate and high A-IPF strata (subdistribution hazard ratios, 2.71 and 3.58; $p<0.001$). All patients required platelet transfusions (149 events). Cox regression identified A-IPF as an independent risk factor for transfusion (hazard ratio, 1.0001; $p=0.027$), whereas platelet count showed a protective effect (hazard ratio, 0.959; $p<0.001$). Negative binomial modeling demonstrated that higher weekly mean A-IPF was associated with fewer subsequent transfusions. **Conclusion:** A-IPF is a robust biomarker for early platelet engraftment and a clinically relevant predictor of platelet transfusion requirements in patients undergoing hematopoietic stem cell transplantation.

Keywords: Platelet count; Reticulocyte count; Hematopoietic stem cell transplantation; Complete blood count

INTRODUCTION

New technologies already available in standard clinical blood cell laboratories have the potential to introduce meaningful innovation into the clinical practice of hematopoietic stem cell transplantation (HSCT). Hematopoietic stem cell transplantation is a complex procedure that involves the collection of hematopoietic stem cells, administration of conditioning therapy, infusion of hematopoietic stem cells, and subsequent reconstitution of the hematopoietic and immune systems.[1] Hematopoietic stem cell transplantation treats a wide range of diseases, most commonly neoplasms of hematopoietic and lymphoid tissues. Other indications include solid tumors, myelodysplastic syndromes, and various forms of anemia.[2]

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The diagnosis of leukemia, whether acute or chronic, relies on a combination of laboratory investigations, including molecular biology techniques, flow cytometry, and cytogenetic analyses. However, the complete blood count remains the standard initial screening test. Key findings suggestive of leukemia include anemia, thrombocytopenia, leukocytosis, and the presence of immature cells or blasts.[3-5] The complete blood count also plays a central role in monitoring hematopoietic recovery after HSCT. Neutrophil engraftment is defined as a sustained peripheral blood neutrophil count greater than 500 × 10^6/L for more than three consecutive days,[6] whereas platelet engraftment is achieved when the platelet count remains above 20 × 10^9/L for seven consecutive days in the absence of platelet transfusion.[7]

The complete blood count has proven to be a valuable tool for the diagnosis and monitoring of patients with leukemia undergoing HSCT.[8] Cell-counting techniques have evolved from manual microscopic methods using counting chambers to modern automated systems based on flow cytometry with fluorescent markers for cell population differentiation.[9] The most advanced automated analyzers now provide additional parameters that were not previously attainable with microscopy.[10] Among these are the immature platelet fraction (IPF) and immature reticulocyte fraction (IRF), which represent cell populations with high nucleic acid content in their cytoplasm and are measured using the Sysmex XN analyzer. These immature populations are identified by nucleic acid-specific fluorescent markers through flow cytometry, and increases in their peripheral blood levels may reflect bone marrow recovery after HSCT.[11,12] Several studies have explored the clinical utility of these parameters, including their role in predicting platelet engraftment before conventional blood cell count recovery[13,14] and in estimating the duration of hospital stay.[15]

OBJECTIVE

The present study aims to determine cutoff values for both the percentages and absolute counts of immature platelet fraction and immature reticulocyte fraction to distinguish patients who achieve bone marrow engraftment from those who experience engraftment failure after hematopoietic stem cell transplantation. In addition, the study evaluates whether immature platelet fraction or immature reticulocyte fraction can predict bone marrow engraftment earlier than conventional complete blood count-based criteria. Finally, the study seeks to establish a reference limit for immature platelet fraction to support assessment of platelet transfusion requirements in patients undergoing hematopoietic stem cell transplantation and to aid in predicting the need for additional transfusions.

METHODS

This prospective observational study included complete blood count and reticulocyte count data from 60 consecutive patients undergoing HSCT at *Hospital Israelita Albert Einstein* (HIAE).

The study was conducted in accordance with the principles of the Declaration of Helsinki and followed Good Clinical Laboratory Practice guidelines. Approval was obtained from the local ethics committee (CAAE: 80893417.7.0000.0071; #2.955.985)

Reference values for relative immature platelet fraction (IPF%), absolute immature platelet fraction (A-IPF), and relative immature reticulocyte fraction (IRF%) were established using samples from 70 healthy donors. A 95% reference interval was defined, with stratification by sex.

IPF%, A-IPF, and IRF% were measured in venous blood samples collected throughout the treatment period, with follow-up extending until hospital discharge. Samples were collected in ethylenediaminetetraacetic acid tubes (Sarstedt®). Complete blood count and reticulocyte analyses were performed using the Sysmex XN9000 series analyzer (Sysmex-Roche®), following the standard laboratory workflow at HIAE. All samples were processed within a maximum of two hours after collection.

To evaluate the impact of platelet transfusions on IPF%, A-IPF, and IRF, linear mixed-effects models were fitted to account for correlations arising from repeated measurements within individual patients. Each immaturity parameter was analyzed separately as a continuous outcome using longitudinal daily data collected over the entire observation period. The primary exposure of interest was platelet transfusion, modeled as a binary variable indicating whether a transfusion occurred on a given follow-up day. To assess both immediate and delayed effects, additional models incorporated lagged transfusion variables (1-day, 2-day, and 3-day lags) to represent the influence of transfusions administered on preceding days.

To accommodate the repeated-measures structure, all models included platelet transfusion variables (immediate and lagged), platelet count, and follow-up day as covariates.

The potential effect of inflammation was evaluated using a separate set of mixed-effects models with A-IPF as the dependent variable. In these models, C-reactive

protein, platelet count, and follow-up day were included as fixed effects, with a random intercept specified for each patient to account for inter-individual variability.

All models were fitted using restricted maximum likelihood. Statistical significance was defined as a two-sided α level of 0.05 ($p<0.05$).

The predictive performance of IPF and IRF for platelet engraftment was evaluated by comparing immaturity parameter trajectories with the standard bone marrow response assessment methodology used by the HSCT service at HIAE.

The sample was divided into two groups: Group 1 comprised patients who achieved platelet engraftment, and Group 2 comprised patients who did not achieve engraftment. For intergroup comparisons, the interquartile ranges of IPF%, A-IPF, and IRF% in Group 1 were evaluated on the day of platelet engraftment and at two and five days before engraftment, and were compared with the interquartile ranges of the highest observed values for each analyte in Group 2. This approach was selected because the data showed non-Gaussian distributions, as assessed by the Shapiro-Wilk test. Hypothesis testing for all parameters was performed using the Mann-Whitney U test with a significance level of $\alpha=0.05$.

For each parameter that demonstrated an association with platelet engraftment, an optimal cutoff value was established to differentiate Group 1 from Group 2. Cutoff points were determined using Youden's index, corresponding to the best balance between sensitivity and specificity derived from receiver operating characteristic curve analysis.

The probability of platelet engraftment over time was estimated using the cumulative incidence function (CIF). The effects of predictor variables on the cumulative incidence of platelet engraftment was evaluated using competing risks regression based on the Fine-Gray model, with results reported as subdistribution hazard ratios (sHRs) and corresponding 95% confidence intervals (95%CIs).

Model discrimination was assessed using a concordance index adapted for competing risks, whereas calibration was evaluated using calibration plots and calculation of the Brier score for censored data.

For each patient, A-IPF measured between days +9 and +12 was used as the exposure variable. Patients were subsequently stratified into three risk groups based on prespecified cutoff values, corresponding to low, intermediate, and high IPF strata. These cutoffs were selected through exploratory analysis of the IPF distribution within the cohort and their association with the cumulative incidence of platelet engraftment.

Competing risks analysis was then conducted using CIFs to account for death without engraftment as a competing event. Fine-Gray regression models were applied to estimate hazard ratios with 95%CIs for each IPF stratum, using the low IPF group as the reference category.

The study also evaluated whether A-IPF and IPF% could serve as biomarkers to support reductions in prophylactic platelet transfusions. To this end, A-IPF and IPF% values were correlated with inflammatory and clinical parameters defined by the Association for the Advancement of Blood & Biotherapies, including C-reactive protein levels greater than 7 mg/L, fever, presence of active bleeding, and platelet counts below 20,000 cells/μL.[X4] Samples were stratified into three groups: Control: platelet count >20,000 cells/μL; Group 10-19A: platelet count between 10,000 and 19,999 cells/μL, without inflammatory abnormalities or active bleeding and Group 10-19B: platelet counts between 10,000 and 19,999 cells/μL, with inflammatory abnormalities and/or active bleeding.

Comparisons among the three groups were performed using the Kruskal-Wallis test. Subsequently, Groups 10-19A and 10-19B were compared using the Mann-Whitney U test to assess whether they differed significantly.

Longitudinal data were transformed into a counting process format to accommodate time-dependent covariates. For each patient, multiple records were created to represent time intervals between sequential measurements, during which covariates remained constant. Survival analyses were performed using Cox proportional hazards regression with time-dependent covariates to assess the association between A-IPF and the risk of platelet transfusion.

In addition, daily A-IPF measurements and platelet transfusion events were aggregated into weekly units. For each patient-week, the total number of transfusions received, weekly mean A-IPF, and lagged A-IPF from the preceding week were calculated. Associations between A-IPF parameters and transfusion requirements were modeled using negative binomial regression for count data, with a patient-level random effect included to account for intra-individual correlation.

RESULTS

A total of 60 patients were enrolled, including 27 women and 33 men, with a mean age of 49.96 years (range, 19-71 years). Complete blood count data obtained two days before platelet engraftment were unavailable for 16 patients. Among the remaining 44 patients,

IRF data two days before platelet engraftment were missing for three individuals. Regarding indications for HSCT, 17 patients had acute myeloid leukemia, seven had myelodysplastic syndrome, and five had chronic myeloid leukemia or myelofibrosis. Four patients each had acute lymphoblastic leukemia (B-lineage), acute lymphoblastic leukemia (T-lineage), mantle cell lymphoma, and acute monoblastic leukemia. Single cases were observed for blastic plasmacytoid dendritic cell neoplasm, unspecified lymphoid leukemia, acute promyelocytic leukemia, Burkitt lymphoma, Hodgkin lymphoma, B-cell non-Hodgkin lymphoma, T/NK-cell non-Hodgkin lymphoma, chronic myelomonocytic leukemia, mycosis fungoides, multiple myeloma, and aleukemic myeloid sarcoma.

Reference values for the three parameters were established with stratification by sex. For men, reference ranges were IPF% 1.6-11.0, A-IPF 3,800-22,500, and IRF% 2.4-14.3. For women, reference ranges were IPF% 1.1-11.0, A-IPF 2,900-24,100, and IRF% 2.0-10.0.

Group 1 included 55 patients, whereas Group 2 included five patients. Among the evaluated parameters, only A-IPF showed a statistically significant difference between groups according to the Mann-Whitney test (p=0.011). Receiver operating characteristic curve analysis yielded an area under the curve of 0.821 and identified an optimal cutoff value of A-IPF >1,450, corresponding to a sensitivity of 82.1% and a specificity of 80.0%. The predictive value of cellular immaturity parameters was further assessed by comparing A-IPF, IPF%, and IRF values measured two and five days before platelet engraftment in Group 1 with the highest observed values for each parameter in Group 2 (Table 1).

Table 1. Comparative analysis of platelet immaturity parameters between Groups 1 and 2 on the day of platelet engraftment and at two and five days before engraftment

Comparison between groups at five days before engraftment			
	Group 1	**Group 2**	**p value**
IPF%	2.2-4.65	2.8-5.5	0.4630
A-IPF	600-2,075	700-1,700	0.8642
IRF%	1.6-23.35	0.85-19.25	0.7816
Comparison between groups at two days before engraftment			
	Group 1	**Group 2**	**p value**
IPF%	2.8-6.375	2.8-5.5	0.9656
A-IPF	1,700-4,225	700-1,700	0.0218
IRF%	14.22-28.95	0.85-19.25	0.3328
Comparison between groups at the day of engraftment			
	Group 1	**Group 2**	**p value**
IPF%	2.9-7.48	2.8-5.5	0.8583
A-IPF	1,990-4,100	700-1,700	0.0110
IRF%	11.15-27	0.85-19.25	0.5098

IPF%: relative immature platelet fraction; A-IPF: absolute immature platelet fraction; IRF%: relative immature reticulocyte fraction.

An A-IPF cutoff value greater than 1,450 predicted platelet engraftment within two days with a sensitivity of 82.1% and a specificity of 80.0%, yielding an overall accuracy of 82.82% (p=0.02). This cutoff demonstrated a high positive predictive value of 97%, but a low negative predictive value of 36.4%. None of the evaluated parameters reliably predicted platelet engraftment beyond a two-day window, reflecting the absence of a fixed time point for platelet engraftment, as illustrated in figures 1 and 2.

Binary logistic regression demonstrated a marginally significant association between A-IPF and the prediction of platelet engraftment within two days (p=0.0576). The odds ratio of 2.32 (95%CI=1.35-18.1) indicated a 132% increase in the odds of platelet engraftment within two days for every 1,000-unit increase in A-IPF.

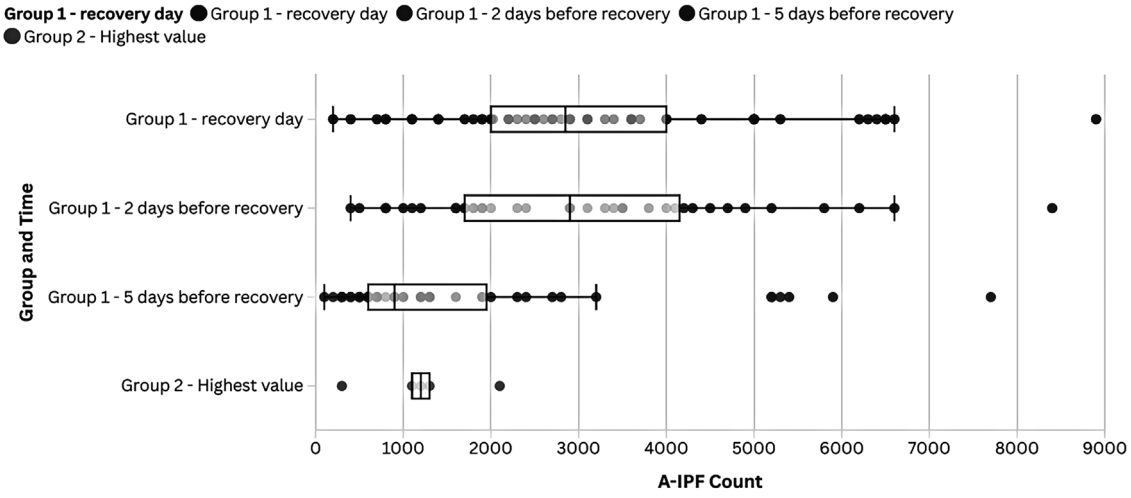
Using CIFs, predicted risk estimates for platelet engraftment within two days were derived, as presented in table 2.

The mean day of platelet engraftment in the study cohort was day +22, with a median of day +19. Day +17 was selected as the target time point for platelet engraftment because no patients achieved engraftment on day +18. In contrast, at least one patient achieved platelet engraftment on days +19, +20, and +22. This gap at day +18 therefore provided a clearer separation between early and later engraftment groups.

Across the analyzed time points, differences in both IPF parameters were observed between groups. Accordingly, all parameters were subjected to receiver operating characteristic curve analysis to identify optimal cutoff values. Day +12 showed the best performance, with an A-IPF cutoff >750 (area under the curve, 0.932; positive predictive value, 93.1%; negative predictive value, 92.0%). DeLong tests demonstrated no significant differences in discriminative performance between days +9 and +12 (day +9 vs. day +12, p=0.223; day +10 vs. day +12, p=0.085; day +11 vs. day +12, p=0.626), indicating that an A-IPF cutoff >750 could be applied between days +9 and +12 to predict platelet recovery by day +17.

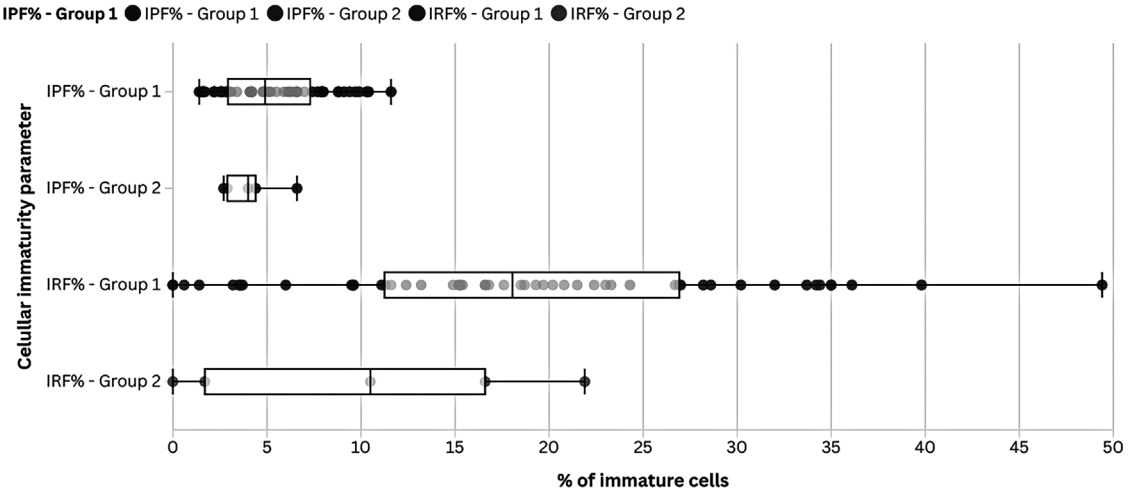
Gray's test showed statistically significant differences among risk strata (p<0.001). The cumulative incidence of platelet engraftment varied according to IPF levels (Table 3).

In the Fine-Gray regression analysis, patients in the intermediate- and high-risk groups exhibited significantly higher probabilities of platelet engraftment compared with the low-risk group. The sHR for the intermediate-risk group was 2.71 (95%CI=1.97-3.74; p<0.001), whereas the sHR for the high-risk group was 3.58 (95%CI=2.82-4.54; p<0.001).



A-IPF: absolute immature platelet fraction.

Figure 1. Comparison of A-IPF at two and five days before platelet engraftment and on the day of platelet engraftment in Group 1 *versus* the highest corresponding values observed in Group 2



IPF%: relative immature platelet fraction; IRF%: relative immature reticulocyte fraction.

Figure 2. Comparison of IPF% and IRF% at the day of platelet engraftment in Group 1 *versus* the highest corresponding values observed in Group

Table 2. Predicted risk of platelet engraftment within two days according to A-IPF values

A-IPF	Predicted risk (%)	Standard error	95%CI
1,000 - 1,499	72.8	0.1117	50.9-94.7
1,500 - 1,999	83.3	0.0741	68.8-97.8
>2,000	90.3	0.0690	78.6-100

A-IPF: absolute immature platelet fraction; 95%CI: 95% confidence interval.

Table 3. sHR values for A-IPF measured between days +9 and +12 for prediction of platelet engraftment by day +17

A-IPF	Risk stratum	Cumulative incidence at day +17 (%)	sHR (95% CI)	p value
<750	Low	40.7	Reference	-
750-1,000	Intermediate	62.4	2.71 (1.97-3.74)	<0.001
>1,000	High	75.9	3.58 (2.82-4.54)	<0.001

A-IPF: absolute immature platelet fraction; sHR: subdistribution hazard ratio; 95%CI: 95% confidence interval.

These findings indicate that higher IPF levels are strongly associated with an increased cumulative incidence of platelet engraftment, supporting the role of IPF as a clinically relevant prognostic biomarker in this setting.

All patients undergoing HSCT in this study required platelet transfusions during treatment; therefore, comparison with patients who did not require transfusions was not feasible. A total of 149 platelet transfusion events were analyzed.

Kruskal-Wallis testing demonstrated significant intergroup differences for A-IPF ($p<0.0001$), whereas IPF% showed no significant differences between groups ($p=0.533$). Subsequent Mann-Whitney U testing between Groups 10-19A and 10-19B revealed no

statistically significant differences for either parameter (A-IPF, p=0.741; IPF%, p=0.878).

To account for the longitudinal structure of the data and multiple observations per patient, a Cox proportional hazards regression model with time-dependent covariates and robust standard errors clustered by patient ID was applied.

The results of the multivariate analysis are presented in table 1. A-IPF showed a significant association with the risk of requiring platelet transfusion.

After adjustment for concurrent platelet count, each unit increase in IPF was associated with a small but statistically significant increase in the instantaneous risk of platelet transfusion (adjusted hazard ratio, 1.0001; 95%CI=1.0000-1.0002; p=0.027). In contrast, platelet count showed a strong inverse association with transfusion risk, with each unit increase associated with a 4.1% reduction in risk (adjusted hazard ratio, 0.959; 95%CI=0.938-0.982; p<0.001).

The overall model demonstrated good discriminative performance, with a concordance index of 0.752 (standard error, 0.052). Global model fit tests confirmed strong statistical significance (likelihood ratio test: χ^2=29.61, df=2, p<0.001; Wald test: χ^2=13.42, df=2, p=0.001).

In addition, A-IPF showed a meaningful association between the mean A-IPF over the preceding seven days and the number of platelet transfusions required in the subsequent seven days. Results from the negative binomial regression analysis are presented in table 4.

Table 4. Negative binomial regression model using weekly mean A-IPF to predict the number of platelet transfusions over the subsequent seven days

Weekly mean A-IPF	Predicted weekly transfusions (n)	95% CI	Reduction in transfusions within one week (%)
155	2.53	1.62-3.44	0
1,173	1.08	0.77-1.40	57.3
2,192	0.46	0.25-0.67	81.8
3,210	0.20	0.06-0.33	92.2
4,228	0.08	0-0.17	96.7

A-IPF: absolute immature platelet fraction; 95% CI: 95% confidence interval.

The model showed that higher weekly mean A-IPF values were significantly associated with a reduction in the number of platelet transfusions in the subsequent week (β=-0.000847; p<0.001), indicating a lower expected transfusion burden at higher A-IPF levels.

The model included a patient-level random intercept (standard deviation, 0.72), reflecting substantial individual heterogeneity in transfusion requirements.

DISCUSSION

Current evidence does not support a consensus on the use of IPF and IRF for predicting platelet engraftment after HSCT. Previous attempts to establish fixed cutoff values, particularly in the early post-transplant period, have produced inconsistent results, largely owing to high biological variability and dilution effects related to platelet transfusions.[16,17] Reported cutoff values – including IPF% >10%,[13,18,19] IPF% >2%,[20] and IRF% >12%[13] – have shown poor specificity (<50%) and high false-positive rates, thereby limiting their clinical applicability.

Our findings confirm that platelet transfusions substantially influence IPF%, whereas A-IPF remains unaffected, in agreement with prior reports.[21] Because IPF% represents a relative measure, abrupt changes in platelet count can distort its values, whereas A-IPF, as an absolute parameter, provides greater robustness. However, the relatively low negative predictive value of A-IPF (36.4%) limits its use as a standalone marker, highlighting the importance of clinical context and risk stratification when interpreting this parameter.

Importantly, this study demonstrates that A-IPF is a more stable marker than IPF% or IRF%, with a cutoff >750 at day +12 predicting platelet engraftment by day +17 (positive predictive value, 93.1%; negative predictive value, 92.0%). Unlike earlier studies, the present grouping strategy distinguished patients who achieved engraftment by day +17 from those who achieved engraftment later or experienced engraftment failure, thereby improving predictive accuracy. These findings support A-IPF as a superior parameter, in agreement with recent reports,[22] although some studies have questioned its utility,[23] likely because transfusion-related interference was not adequately accounted for.

This study also provides the first evidence that A-IPF can predict platelet transfusion requirements. Higher weekly mean A-IPF values were inversely associated with subsequent transfusion burden, with reductions of up to 96.7%, suggesting a novel role for A-IPF in guiding supportive care. In contrast, the data did not support the use of IPF% or IRF% to safely reduce prophylactic platelet transfusions in patients with thrombocytopenia, consistent with previously conflicting reports.[13,20,24,25]

A key limitation involves the absence of standardized quality control procedures for IPF-derived parameters across hematology analyzers. Current quality control protocols ensure analytical validity for platelet counts but not for IPF%, A-IPF, or IRF%, leaving these measures susceptible to systematic and random errors. Harmonization efforts and inter-laboratory validation remain essential to reduce variability and to enable reliable comparisons and meta-analyses.

In summary, A-IPF outperforms IPF% and IRF% as a biomarker for predicting platelet engraftment and transfusion requirements after HSCT. Integration of A-IPF into clinical practice warrants further validation in larger cohorts using standardized analytical frameworks.

CONCLUSION

A-IPF demonstrates utility as a biomarker for predicting platelet engraftment following hematopoietic stem cell transplantation. A stratified probability model based on A-IPF enables prediction of platelet engraftment within two days, independent of the post-transplant day, and A-IPF values can also be used to predict platelet engraftment at specific time points after cell infusion. In contrast, the relative parameters IPF% and IRF% did not perform adequately as biomarkers of platelet engraftment. None of the evaluated immaturity parameters outperformed platelet count in triggering platelet transfusion decisions; however, mean A-IPF showed good accuracy in predicting the number of platelet transfusions required over the subsequent seven days. For reliable clinical implementation, the development of dedicated quality control and proficiency testing protocols is essential to harmonize results across different analyzers and laboratories. Finally, these cellular immaturity parameters did not demonstrate the ability to safely reduce prophylactic platelet transfusion requirements.

DATA AVAILABILITY

The underlying content is contained within the manuscript.

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AUTHORS' CONTRIBUTION

Bruno Gabriel Nardini Fogo: investigation, data curation, and writing - original draft. Iracema Esteves: methodology. Nelson Hamerschlak: resources. Carolina Bonet Bub: project administration and patient management. Rosana Moreira Cosentino Penteado: writing - review and editing. Andréa Aparecida Rocco Vilarinho: validation. João Carlos de Campos Guerra: supervision, funding acquisition, and resources.

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REFERENCES

1. Balassa K, Danby R, Rocha V. Haematopoietic stem cell transplants: principles and indications. Br J Hosp Med (Lond). 2019;80(1):33-9. Review.
2. Bazinet A, Popradi G. A general practitioner's guide to hematopoietic stem-cell transplantation. Curr Oncol. 2019;26(3):187-91.
3. Kassim AA, Chinratanalab W, Ferrara JL, Mineishi S. Reduced-intensity allogeneic hematopoietic stem cell transplantation for acute leukemias: "what is the best recipe?" Bone Marrow Transplantation. 2005;4;36(7):565-74.
4. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet. 2009;373(9674):1550-61.
5. Arnaout K, Patel N, Jain M, El-Amm J, Amro F, Tabbara IA. Complications of Allogeneic Hematopoietic Stem Cell Transplantation. Cancer Investigation. 2014;5;32(7):349-62.
6. Blackburn LM, Bender S, Brown S. Acute Leukemia: diagnosis and Treatment. Semin Oncol Nurs. 2019;35(6):150950.
7. Wolff SN. Second hematopoietic stem cell transplantation for the treatment of graft failure, graft rejection or relapse after allogeneic transplantation. Bone Marrow Transplant. 2002;29(7):545-52.
8. Teltschik HM, Heinzelmann F, Gruhn B, Feuchtinger T, Schlegel P, Schumm M, et al. Treatment of graft failure with TNI-based reconditioning and haploidentical stem cells in paediatric patients. Br J Haematol. 2016;175(1):115-22.
9. Hutt D. Engraftment, Graft Failure, and Rejection. 2017 Nov 22. In: Kenyon M, Babic A, editors. The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT. Cham (CH): Springer; 2018. Chapter 13. Review.
10. Vembadi A, Menachery A, Qasaimeh MA. Cell Cytometry: Review and Perspective on Biotechnological Advances. Front Bioeng Biotechnol. 2019;7:147. Review.
11. Lecompte TP, Bernimoulin MP. Novel parameters in blood cell counters. Clin Lab Med. 2015;35(1):209-24.
12. Sakuragi M, Hayashi S, Maruyama M, Kiyokawa T, Nagamine K, Fujita J, et al. Immature platelet fraction (IPF) as a predictive value for thrombopoietic recovery after allogeneic stem cell transplantation. Int J Hematol. 2018;107(3):320-6.
13. Morkis IV, Farias MG, Rigoni LD, Scotti L, Gregianin LJ, Daudt LE, et al. Assessment of immature platelet fraction and immature reticulocyte fraction as predictors of engraftment after hematopoietic stem cell transplantation. Int J Lab Hematol. 2015;37(2):259-64.
14. Saigo K, Sakota Y, Masuda Y, Matsunaga K, Takenokuchi M, Nishimura K, et al. Automatic detection of immature platelets for decision making regarding platelet transfusion indications for pediatric patients. Transfus Apher Sci. 2008;38(2):127-32.
15. Grabek J, D'Elia N, Kelsey G. Immature platelet fraction as a predictor of platelet count recovery following allogeneic bone marrow transplantation. Pathology. 2021;53(4):493-7.

16. Park SH, Park CJ, Kim MJ, Han MY, Lee BR, Cho YU, et al. Evaluation of parameters obtained from the Sysmex XN-2000 for predicting the recovery of the absolute neutrophil count and platelets after hematopoietic stem cell transplantation. Int J Lab Hematol. 2016;38(2):198-208.
17. Meintker L, Fritsch JD, Ringwald J, Krause SW. Immature platelets do not reliably predict platelet recovery in patients with intensive chemotherapy or stem cell transplantation. Vox Sanguinis. 2017;25;112(2):132-9.
18. Grabek J, D'Elia N, Kelsey G. Immature platelet fraction as a predictor of platelet count recovery following allogeneic bone marrow transplantation. Pathology. 2021;53(4):493-7.
19. Zainab Ghias, Zaidi U, Munira Borhany, Shafaq Abdul Samad, Durrani N, Fatima M, et al. Is post-transplant day + 14 immature reticulocyte fraction (IRF) a reliable surrogate marker for predicting early platelet engraftment in pediatric hematopoietic stem cell transplant? Translational Med Commun. 2023;27;8(1):1-8.
20. Morkis IV, Farias MG, Rigoni LD, Scotti L, Gregianin LJ, Daudt LE, et al. Assessment of immature platelet fraction and immature reticulocyte fraction as predictors of engraftment after hematopoietic stem cell transplantation. Int J Lab Hematol. 2015;37(2):259-64.
21. Sakuragi M, Hayashi S, Maruyama M, Kiyokawa T, Nagamine K, Fujita J, et al. Immature platelet fraction (IPF) as a predictive value for thrombopoietic recovery after allogeneic stem cell transplantation. Int J Hematol. 2018;107(3):320-6.
22. van der Linden N, Klinkenberg LJ, Meex SJ, Beckers EA, de Wit NC, Prinzen L. Immature platelet fraction measured on the Sysmex XN hemocytometer predicts thrombopoietic recovery after autologous stem cell transplantation. Eur J Haematol. 2014;93(2):150-6.
23. Gonçalo AP, Barbosa IL, Campilho F, Campos A, Mendes C. Predictive value of immature reticulocyte and platelet fractions in hematopoietic recovery of allograft patients. Transplant Proc. 2011;43(1):241-3.
24. Yamaoka G, Kubota Y, Nomura T, Inage T, Arai T, Kitanaka A, et al. The immature platelet fraction is a useful marker for predicting the timing of platelet recovery in patients with cancer after chemotherapy and hematopoietic stem cell transplantation. Int J Lab Hematol. 2010;32(6 Pt 1):e208-16.
25. Hennel E, Kentouche K, Beck J, Kiehntopf M, Boeer K. Immature platelet fraction as marker for platelet recovery after stem cell transplantation in children. Clin Biochem. 2012;45(10-11):749-52.