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Original Article

Pretransplant Small-airway Dysfunction is Associated with Posttransplant Complications in Adult HSCT Recipients

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ABSTRACT

OBJECTIVE: Pulmonary function testing is routinely performed before hematopoietic stem cell transplantation (HSCT), but conventional parameters may not capture subtle airway abnormalities. This study evaluated the association of pretransplant forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}) with post-HSCT complications in adults.

MATERIAL AND METHODS: This retrospective single-center cohort included 83 adults who underwent HSCT between 2016 and 2023. Reduced FEF_{25-75} was defined as <75% predicted. The primary outcome was a composite of post-HSCT complications. Multivariable logistic regression models were adjusted for age, sex, ever-smoking status, HSCT type, and reduced forced expiratory volume in 1 second (FEV_1). Discrimination was assessed using receiver operating characteristic analysis.

RESULTS: Overall, 32 patients (38.6%) experienced post-HSCT complications. Complications occurred in 50.0% of patients with reduced FEF_{25-75} versus 28.9% of those with FEF_{25-75} ≥75% predicted ($P = 0.049$). Reduced FEF_{25-75} was independently associated with higher odds of complications [odds ratio (OR): 3.58, 95% confidence interval (CI): 1.28–10.04; $P = 0.015$]. Reduced FEV_1 showed an inverse association (OR: 0.12, 95% CI: 0.02–0.71; $P = 0.019$). FEF_{25-75} showed poor standalone discrimination (area under the curve: 0.578, 95% CI: 0.450–0.705).

CONCLUSION: Reduced pretransplant FEF_{25-75} was independently associated with post-HSCT complications, but showed poor standalone discrimination. These hypothesis-generating findings suggest that FEF_{25-75} may provide information complementary to FEV_1, but they do not support its use as an independent predictive test. Larger prospective studies are required.

KEYWORDS: Hematopoietic stem cell transplantation, small-airway disease, FEF_{25-75}, pulmonary complications, FEV_1, DLCO

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INTRODUCTION

Pulmonary complications remain a leading source of morbidity after hematopoietic stem cell transplantation (HSCT). Conventional pretransplant assessment prioritizes diffusing capacity of the lung for carbon monoxide (DLCO) and forced expiratory volume in 1 second (FEV_1), yet these parameters may not capture subtle airway abnormalities that precede overt ventilatory limitation.

Small-airway disease (SAD) is now recognized as a pivotal "silent zone" in early airflow impairment, often undetectable by standard spirometric indices.[1,2] Mid-expiratory flow parameters, such as forced expiratory flow (FEF_{25-75}), are used as functional markers of peripheral airway impairment. Although variability exists, reductions in FEF_{25-75} have been shown to precede measurable reductions in FEV_1 and correlate with markers of airway inflammation and early functional impairment across various pulmonary diseases.[3,4] Although FEF_{25-75} has been associated with pulmonary complications in pediatric pretransplant cohorts and with bronchiolitis obliterans syndrome (BOS) in early posttransplant adult assessments, evidence regarding its association with subsequent post-HSCT morbidity in adults remains limited.[5-9]

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Therefore, this study aimed to evaluate the association between pretransplant FEF_{25-75} and post-HSCT complications in an adult cohort and to compare its relationship with outcomes to that of conventional pulmonary function parameters. We hypothesized that reduced FEF_{25-75} would be associated with posttransplant complications and might identify functional abnormalities not fully captured by conventional FEV_1 thresholds.

MATERIAL AND METHODS

Study Design and Population

This retrospective cohort study included adult patients who underwent HSCT at the Marmara University Bone Marrow Transplantation Unit (İstanbul, Türkiye) between January 2016 and December 2023.

A total of 120 patients were screened; 83 patients with complete pretransplant pulmonary function test (PFT) data and follow-up records were included in the final analysis.

Demographic data, underlying hematologic diagnoses, transplant type (autologous or allogeneic), and comorbidity profiles were retrieved from institutional electronic medical records. Baseline comorbidity burden was evaluated using a validated transplantation-specific comorbidity scoring system.[10] Follow-up duration was calculated from the date of HSCT to death or the administrative censoring date (January 1, 2024), whichever occurred first.

Smoking history (ever-smoking status and cumulative pack-years) and physician-diagnosed asthma or chronic obstructive pulmonary disease were retrieved from the electronic medical records when available, and were included in the baseline characteristics. Because information on obstructive airway disease was unavailable for a subset of patients, the number of available observations was reported.

Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki and approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (decision no.: 09.2023.669, date: 05/05/2023).

Because of the retrospective study design, the Ethics Committee waived the requirement for informed consent. All patient data were anonymized prior to analysis.

Pulmonary Function Testing

All pretransplant PFTs were performed at the Marmara University Respiratory Physiology Laboratory in accordance with the American Thoracic Society and the European Respiratory Society technical standards. DLCO was measured using the single-breath technique.[11,12]

PFT included FEV_1, forced vital capacity (FVC), the FEV_1/FVC ratio, and FEF_{25-75} (forced expiratory flow between 25% and 75% of FVC). Gas transfer function was assessed using DLCO and DLCO per unit of alveolar volume. Pulmonary function parameters were expressed as percentages of predicted values, where applicable, using the reference equations employed by the laboratory.[13]

Reduced FEF_{25-75} was operationally defined as <75% of predicted. Although no universally accepted diagnostic threshold exists for FEF_{25-75}, this cut-off was selected a priori based on previous evidence identifying values of approximately 75% predicted as thresholds associated with airway hyperresponsiveness in individuals with otherwise preserved conventional spirometric indices.[14] Accordingly, FEF_{25-75} <75% predicted was used as an operational research definition of reduced mid-expiratory flow rather than an established clinical lower limit of normal.

For categorical analyses, reduced FEV_1 and FVC were defined as <80% predicted, airflow obstruction as FEV_1/FVC <0.70, and reduced DLCO as <80% predicted.[15] These thresholds were used for analytical categorization and were not intended to substitute for comprehensive physiologic interpretation.

Definition of Outcomes

Clinical outcomes were extracted from standardized transplant follow-up records. Early complications were defined as events occurring within 100 days post-HSCT, whereas late complications were defined as those occurring after day 100, until the end of follow-up. All-cause mortality was recorded as a major endpoint. Complications included infectious, pulmonary, hepatic, gastrointestinal, and graft-related events. Diagnostic consistency was ensured through review by hematologists and pulmonologists.

Statistical Analysis

All statistical analyses were performed using Jamovi software.[16] The distribution of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables were summarized as mean ± standard deviation or median [interquartile range (IQR)], as appropriate, and categorical variables as frequencies and percentages. Between-group comparisons were performed using Student's t-test or the Mann-Whitney U test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables, as appropriate.

Given the limited number of events, a parsimonious multivariable logistic regression model was used to evaluate factors associated with any post-HSCT complication. The final model included age, sex, ever-smoking status, HSCT type (autologous vs. allogeneic), reduced FEV_1 (<80% predicted), and reduced FEF_{25-75} (<75% predicted). Adjusted odds ratios (OR) with 95% confidence intervals (CI) were reported. Overall model significance was assessed using the likelihood-ratio χ^2 test. Multicollinearity among included covariates was evaluated using variance inflation factors (VIFs) and tolerance values, and model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Receiver operating characteristic (ROC) curve analysis was used to assess the discriminatory performance of individual pretransplant pulmonary function parameters in predicting any post-HSCT complication, with results reported as area under the curve (AUC) and 95% CIs.

No missing data were imputed. Analyses used the available data, and the multivariable model was based on complete cases (82/83 patients). All tests were two-sided, and *P* values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Of the 120 patients screened, 83 met the inclusion criteria and were included in the analysis, as shown in the study flow diagram (Figure 1). The median follow-up duration was 1,527 days (IQR: 889–1,911 days), with a range of 5–2,532 days. The mean age of the cohort was 49.0±14.3 years, and 57.8% were male. Multiple myeloma was the most common indication for HSCT (47.0%), followed by lymphomas (32.5%) (Table 1).

Most patients underwent autologous HSCT (79.5%). Baseline pulmonary function was generally preserved, with mean FEV_1 and FVC values of approximately 96% predicted, while mean FEF_{25-75} was 78.9±24.7% predicted (Table 2).

Early complications (≤100 days after HSCT) occurred in 27.7% of patients. Baseline FEF_{25-75} and DLCO did not significantly differ according to early complication status, whereas time to neutrophil recovery differed significantly (*P* = 0.014) (Supplementary Table 1).

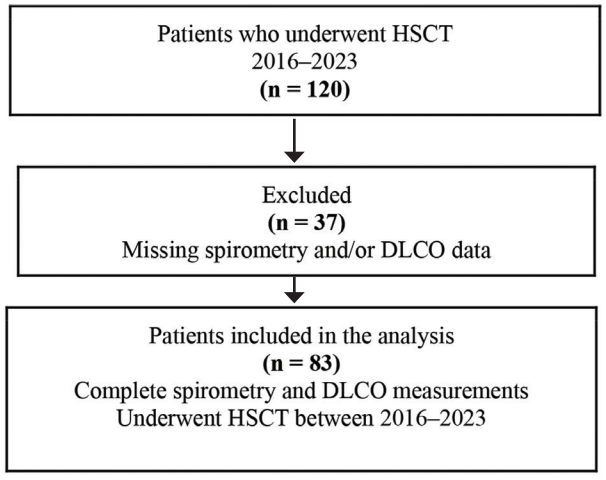


Figure 1. Study flow diagram

HSCT: hematopoietic stem cell transplantation, DLCO: diffusing capacity of the lung for carbon monoxide

Table 1. Distribution of hematological diagnoses in the study population

Diagnosis	n	%
Acute lymphoblastic leukemia	4	4.8
Acute myeloid leukemia	12	14.5
Hodgkin lymphoma	10	12.0
Multiple myeloma	39	47.0
Non-Hodgkin lymphoma	17	20.5
Myelofibrosis	1	1.2
Total	**83**	**100.0**

During follow-up, all-cause mortality was 12.1%. No baseline spirometric or diffusion parameter, including FEF_{25-75}, was significantly associated with mortality (Supplementary Table 2).

Association Between FEF_{25-75} and Post-HSCT Complications

Conventional pulmonary function parameters, including FEV_1, FVC, and DLCO, did not differ significantly between patients with and without post-HSCT complications (all $P > 0.05$) (Table 3).

Complications occurred in 19 of 38 patients (50.0%) with reduced FEF_{25-75} (<75% predicted), compared with 13 of 45 patients (28.9%) with FEF_{25-75} ≥75% predicted (χ^2: 3.88, *P* = 0.049) (Table 4).

Table 2. Baseline demographic, clinical, and pulmonary function characteristics of the study population (n = 83)

Variable	Value
Demographic characteristics	
Male sex, n (%)	48 (57.8)
Age, years	49.0±14.3
Body mass index, kg/m^2	28.5±5.2
Ever smoker, n (%)	31 (37.3)
Smoking exposure among ever smokers, pack-years†	20 (20–30)
Pre-existing obstructive airway disease‡, n (%)	4 (4.8)
Baseline comorbidity	
HCT-CI risk group	
• Low (=0)	48 (57.8)
• Intermediate (1–2)	26 (31.3)
• High (≥3)	9 (10.8)
Pulmonary function parameters	
FEV_1, % predicted	95.7±19.7
FVC, % predicted	96.8±20.6
FEF_{25-75}, % predicted	78.9±24.7
DLCO, % predicted	76.1±19.9
DLCO/VA, % predicted	92.3±17.8
Transplant characteristics and outcomes	
Autologous HSCT, n (%)	66 (79.5)
Time to neutrophil recovery, days	10.7±3.5
Early HSCT complication, n (%)	23 (27.7)
Late HSCT complication, n (%)	12 (16.7)
Any HSCT complication, n (%)	32 (38.6)
All-cause mortality, n (%)	10 (12.1)

Values are presented as mean ± standard deviation, median (interquartile range), or number (percentage), as appropriate

†Smoking exposure is presented only for ever-smokers

‡Includes physician-diagnosed asthma or chronic obstructive pulmonary disease

HCT-CI: hematopoietic cell transplantation–comorbidity index, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, FEF_{25-75}: forced expiratory flow between 25% and 75% of forced vital capacity, DLCO/VA: diffusing capacity of the lung for carbon monoxide adjusted for alveolar volume, HSCT: hematopoietic stem cell transplantation

Overall Complications

Among the 83 HSCT recipients, 32 (38.6%) experienced at least one posttransplant complication during follow-up. These included 14 episodes of pneumonia, 7 pulmonary thromboembolic events, 6 episodes of neutropenic fever, 4 graft-versus-host disease (GVHD) events, and 4 non-infectious complications (3 thrombophlebitis and 1 posterior reversible encephalopathy syndrome). Because some patients experienced more than one complication, the total number of events exceeded the number of patients with complications.

Multivariable Analysis

In the multivariable logistic regression model adjusted for age, sex, ever-smoking status, HSCT type, and reduced FEV_1, reduced FEF_{25-75} (<75% predicted) was independently associated with higher odds of any post-HSCT complication (OR: 3.58, 95% CI: 1.28–10.04; P = 0.015). Reduced FEV_1 (<80% predicted) showed an inverse association (OR: 0.12, 95% CI: 0.02–0.71; P = 0.019), whereas age, sex, ever-smoking status, and HSCT type were not significantly associated with the outcome (Table 5).

The overall model was statistically significant [likelihood-ratio $\chi^2(6) = 14.7$, $P = 0.023$]. The Hosmer-Lemeshow test showed no significant lack of fit [$\chi^2(8) = 13.74$, $P = 0.089$]. No problematic multicollinearity was detected among the covariates (VIF range: 1.13–1.36; Supplementary Table 3).

Table 3. Comparison of clinical and pulmonary parameters between patients with and without any HSCT complication

Variable	Without complication (n = 51) mean ± SD	With complication (n = 32) mean ± SD	*P* value
Age (years)	47.7±15.4	51.0±12.2	0.443
Smoking (pack-years)	7.4±13.6	13.5±17.0	0.062
BMI (kg/m^2)	28.6±5.0	28.3±5.7	0.796
FEV_1/FVC (%)	82.9±8.0	81.3±6.8	0.362
FEV_1 (%)	95.7±21.7	95.7±16.3	0.998
FVC (%)	96.6±21.3	97.2±19.9	0.910
FEF_{25-75} (%)	80.6±24.5	76.1±25.1	0.238
Dysanapsis ratio (FEF_{25-75}/FVC)	0.88±0.42	0.81±0.29	0.477
$DLCO_{SB}$ (%)	76.3±22.1	75.8±16.0	0.914
DLCO/VA (%)	91.4±14.9	93.8±21.8	0.562
Neutrophil recovery (days)	11.4±3.8	9.8±2.6	0.058

HSCT: hematopoietic stem cell transplantation, SD: standard deviation, BMI: body mass index, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, FEF_{25-75}: forced expiratory flow between 25% and 75% of forced vital capacity, DLCO_SB: single-breath diffusing capacity of the lung for carbon monoxide, DLCO/VA: diffusing capacity of the lung for carbon monoxide adjusted for alveolar volume

Table 4. Association between reduced FEF_{25-75} (< 75%) and any post-HSCT complication

FEF_{25-75} group	No complication (n = 51)	Any complication (n = 32)	Total (n = 83)
≥75% predicted	32 (62.7%)	13 (40.6%)	45 (54.2%)
<75% predicted	19 (37.3%)	19 (59.4%)	38 (45.8%)
Total	51	32	83

χ^2: 3.88, df = 1, P = 0.049

FEF_{25-75}: forced expiratory flow between 25% and 75% of forced vital capacity, HSCT: hematopoietic stem cell transplantation, χ^2: chi-square, df: degrees of freedom

Table 5. Multivariable logistic regression analysis of factors associated with any post-HSCT complication

Predictor	OR (95% CI)	*P* value
Age, per year	1.00 (0.97–1.05)	0.827
Male sex	1.32 (0.45–3.89)	0.609
FEF_{25-75} <75% predicted	3.58 (1.28–10.04)	0.015
Autologous HSCT	1.67 (0.40–6.95)	0.483
FEV_1 <80% predicted	0.12 (0.02–0.71)	0.019
Ever smoker	1.57 (0.53–4.63)	0.410

Model fit: Deviance = 95.0; AIC = 109; McFadden R^2 = 0.134; overall likelihood-ratio $\chi^2(6) = 14.7$, $P = 0.023$; Hosmer-Lemeshow $\chi^2(8) = 13.74$, $P = 0.089$.

Note: Estimates represent the odds of developing any post-HSCT complication (1 = complication)

HSCT: hematopoietic stem cell transplantation, OR: odds ratio, CI: confidence interval, FEF_{25-75}: forced expiratory flow between 25% and 75% of forced vital capacity, FEV_1: forced expiratory volume in one second, AIC: Akaike information criterion, χ^2: chi-square

Discriminative Performance (ROC Analysis)

ROC analysis demonstrated poor standalone discriminatory ability of pretransplant pulmonary function parameters for predicting any post-HSCT complication (Supplementary Table 4). FEF_{25-75} had an AUC of 0.578 (95% CI: 0.450–0.705), while FEV_1, FVC, and DLCO had AUCs of 0.504, 0.506, and 0.495, respectively. None demonstrated statistically significant discrimination (all $P > 0.05$).

DISCUSSION

This single-center study identified an association between reduced pretransplant FEF_{25-75} and the composite endpoint of post-HSCT complications. After adjustment for age, sex, ever-smoking status, HSCT type, and reduced FEV_1, FEF_{25-75} <75% predicted remained independently associated with higher odds of complications. However, its standalone discriminative performance was poor (AUC: 0.578), indicating that the observed association should not be interpreted as evidence of clinical predictive utility. Reduced FEV_1 was unexpectedly inversely associated with complications. Collinearity diagnostics did not indicate problematic multicollinearity between FEF_{25-75} and FEV_1, but this finding should be interpreted with caution because of the small number of patients with reduced FEV_1 and the small number of outcome events.

FEF_{25-75} in the Context of Previous HSCT Studies

FEF_{25-75} reflects expiratory flow during the middle portion of forced expiration and has been used as a functional marker of the small airways, where abnormalities may occur before conventional spirometric indices become impaired.[17-21] However, the clinical significance of FEF_{25-75} in the transplant setting remains incompletely established.

Our findings are consistent with previous pediatric evidence. Srinivasan et al.[5] demonstrated that children who subsequently developed pulmonary complications had significantly lower pretransplant FEF_{25-75} values. Although differences in age, underlying diseases, and outcome definitions limit direct comparison, our primary endpoint was a broader composite comprising pulmonary and non-pulmonary complications. Therefore, the observed association should not be interpreted as evidence of a direct mechanistic relationship between reduced FEF_{25-75} and individual components of the composite.

Evidence from adult HSCT studies also supports the relevance of assessing the small airways, although previous investigations have focused predominantly on posttransplant pulmonary outcomes. Jamani et al.[6] reported that early posttransplant reductions in FEF_{25-75} were associated with subsequent BOS. Similarly, Yang et al.[7] associated pretransplant pulmonary function abnormalities with chronic pulmonary GVHD after allogeneic HSCT, while Walter et al.[9] linked pulmonary function abnormalities with long-term posttransplant outcomes. In contrast, our study evaluated pulmonary function before transplantation and used overall post-HSCT complications; therefore, pulmonary-specific findings cannot be directly extrapolated to non-pulmonary complications.

Parimon et al.[8] demonstrated the prognostic importance of conventional pretransplant pulmonary function, particularly FEV_1 and DLCO, for respiratory failure and mortality after HSCT. Our findings should not be interpreted as evidence that FEF_{25-75} replaces established pulmonary function parameters. Whether the observed association reflects pulmonary-specific vulnerability or residual confounding cannot be determined.

Although the association was not restricted to pulmonary complications, potential links between impaired respiratory health and systemic outcomes have been described. Chronic inflammatory lung diseases have been associated with venous thromboembolism, with inflammation, coagulation activation, and immunothrombotic pathways proposed as links between pulmonary diseases and thrombotic events.[22] However, this literature provides biological context rather than evidence that reduced FEF_{25-75} is mechanistically related to thrombotic events. Such mechanisms were not evaluated in our study and remain speculative.

Interpretation of the FEV_1 Findings

The inverse association with reduced FEV_1 should be interpreted cautiously and should not be considered evidence of a protective effect. FEV_1 and FEF_{25-75} represent related but distinct aspects of expiratory function. Reduced FEV_1 and FEF_{25-75} were significantly associated ($\chi^2 = 7.29$, $P = 0.007$); however, substantial discordance between the measures was observed. Among 38 patients with FEF_{25-75} <75% predicted, 27 (71.1%) had preserved FEV_1 (≥80% predicted), indicating that reduced mid-expiratory flow frequently occurred despite preserved FEV_1. Collinearity diagnostics showed low VIFs for FEF_{25-75} (VIF: 1.13) and FEV_1 (VIF: 1.25), indicating no problematic multicollinearity (Supplementary Table 3).

FEV_1 did not differ by complication status in unadjusted analyses, whereas reduced FEV_1 showed an inverse association with complication status after multivariable adjustment. Given that only 14 patients had FEV_1 <80% predicted, this unexpected association may reflect small-sample instability, categorization effects, or residual confounding rather than a protective effect (Supplementary Table 5).

These findings suggest that reductions in FEF_{25-75} and FEV_1 may provide different information in this cohort; however, the association for FEF_{25-75} should not be interpreted as evidence of superior predictive performance, particularly given its poor standalone discrimination.

Clinical Implications

The present findings suggest that FEF_{25-75} may provide complementary information during pretransplant pulmonary assessment, particularly when FEV_1 remains preserved. Because FEF_{25-75} is derived from standard spirometry, it can be evaluated without additional testing.[23,24] However, its poor standalone discriminative performance (AUC: 0.578) indicates that FEF_{25-75} should not be considered an independent clinical decision-making tool or a replacement for established pretransplant risk assessment. Rather, reduced FEF_{25-75} may represent a candidate functional marker warranting further investigation within broader risk-assessment approaches. Prospective studies are needed to determine whether FEF_{25-75} provides incremental prognostic information beyond established risk factors.

Strengths and Limitations

This study has several strengths. To our knowledge, it is the first adult HSCT cohort to specifically evaluate pretransplant FEF_{25-75} in relation to overall posttransplant complications, extending previous observations from pediatric cohorts and adult studies focused on pulmonary outcomes. Standardized pretransplant PFT allowed direct comparison of FEF_{25-75} with conventional spirometric and diffusion parameters. The relatively long follow-up enabled the assessment of complications beyond the early posttransplant phase. The multivariable analysis accounted for age, sex, smoking history, and transplant type; multicollinearity and model calibration were formally assessed.

Several limitations should be considered. First, the retrospective, single-center design introduces selection bias and limits generalizability. The cohort was small; only 32 patients experienced complications, which constrained multivariable adjustment. Although a parsimonious model was used, overfitting and model instability cannot be excluded, and the findings require validation in larger independent cohorts.

Second, the cohort was heterogeneous with respect to underlying hematologic diagnoses and transplant types. Autologous and allogeneic HSCT differ in their complication profiles, particularly with respect to GVHD, and the small size of the allogeneic subgroup limited transplant-specific analyses. Although transplant type was included in the multivariable model, complications specific to allogeneic transplants could not be adequately analyzed. Detailed transplant-related variables, particularly conditioning regimens and CMV serostatus, had substantial missing data and could not be reliably incorporated. GVHD-related risk factors and immunosuppressive treatments were not comprehensively accounted for. Consequently, residual confounding by disease-, transplant-, and treatment-related factors remains possible.

Third, although pretransplant PFT was standardized, FEF_{25-75} exhibits greater variability than conventional spirometric indices and is influenced by lung volumes and expiratory effort. The <75% predicted threshold was an operational research definition and should not be interpreted as a universally established diagnostic threshold for SAD. Imaging correlates were not systematically available, precluding physiologic–radiologic validation.

Fourth, information on chronic respiratory medications, including bronchodilators and inhaled corticosteroids, was not consistently available. Although smoking history was included in the multivariable model and physician-diagnosed obstructive airway disease was assessed, these data were unavailable for a subset of patients. Therefore, residual confounding related to baseline respiratory characteristics cannot be excluded.

Fifth, the primary outcome was a clinically heterogeneous composite of pulmonary and non-pulmonary complications. This heterogeneity limits mechanistic and organ-specific interpretation.

Although the Hosmer-Lemeshow test showed no significant lack of fit and collinearity diagnostics did not identify problematic multicollinearity, these diagnostics do not eliminate the possibility of model instability arising from the modest sample size and limited number of events. Moreover, the poor discriminative performance of FEF_{25-75} (AUC: 0.578) indicates that it should not be considered a clinically useful standalone predictive marker. Prospective, multicenter studies with larger cohorts, comprehensive transplant-specific covariates, standardized respiratory characterization, and external validation are needed.

CONCLUSION

Reduced pretransplant FEF_{25-75} was independently associated with the composite endpoint of post-HSCT complications after adjustment for relevant clinical factors, including reduced FEV_1. However, its poor discriminative performance (AUC: 0.578) indicates that FEF_{25-75} should not be considered a standalone predictive test or used to guide clinical decision-making. Reduced FEF_{25-75} was frequently observed despite preserved FEV_1, suggesting that these measures may provide different information. These findings are hypothesis-generating, and larger prospective studies that incorporate comprehensive transplant-specific covariates and include external validation are needed to determine its clinically meaningful incremental prognostic information.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (decision no.: 09.2023.669, date: 05/05/2023).

Informed Consent: Because of the retrospective study design, the Ethics Committee waived the requirement for informed consent. All patient data were anonymized prior to analysis.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: C.Ç., A.M.Y., Concept: C.Ç., Z.M., C.Y., I.A., S.E.E., Design: C.Ç., Z.M., T.T., S.K., Data Collection or Processing: C.Ç., A.M.Y., C.Y., Analysis or Interpretation: C.Ç., Literature Search: C.Ç., A.M.Y., Writing: C.Ç., A.M.Y., Z.M.

Conflict of Interest: No conflict of interest was declared by the authors.

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Supplementary Tables 1-5 Link: https://d2v96fxpocvxx.cloudfront.net/1dda20c2-8b22-466b-a98e-85ecfb39ceaf/content-images/bb8ee4a8-8b88-401f-93bd-cbbdb0b051da.pdf

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