Original Article

The Role of Pre-bone Marrow Transplantation Pulmonary Function Test in Predicting Post-transplant Noninfectious Pulmonary Complications

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Abstract

Background: Pulmonary function test (PFT) is used as a tool for pre-transplant risk assessment and as a predictor of post-transplant outcomes. As there are currently few studies that discuss the role of PFT in bone marrow transplantation (BMT) patients in Saudi settings, and as the number of transplant patients with benign and malignant conditions continues to increase, this study was conducted with the aim of assessing the local practice.

Methods: This retrospective cohort study included all adult patients who underwent BMT at Princess Noorah Oncology Center, King Abdulaziz Medical City, Jeddah, between 2014 and 2020. The association between established patient-related risk factors and the incidence of pulmonary complications among autologous and allogeneic groups was assessed.

Results: A total of 186 patients were included (autologous = 143; allogenic = 43), of which 115 (61.8%) were male. At the pre-BMT phase, about 30% of the patients had comorbidities and 51% had received two rounds of salvage chemotherapy, while 16.1% had received radiation therapy. In the autologous group, the only PFT parameter that was a significant predictor of post-BMT pulmonary complications was forced vital capacity <80% ($P = 0.012$), while in the allogenic group, no parameter was significantly associated with pulmonary complications. The patient-related factors that were associated with respiratory distress in the autologous group were lung involvement ($P = 0.03$) and pre-transplant radiation ($P = 0.044$).

Conclusion: The findings of this study indicated that forced vital capacity <80% was a significant factor in predicting non-infectious complications in the autologous group. Furthermore, lung involvement and pre-transplant radiation were the patient-related factors associated with pulmonary complications.

Keywords: Bone marrow transplantation, complications, forced expiratory volume, pulmonary function test, respiratory distress, Saudi Arabia, treatment outcome

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INTRODUCTION

Bone marrow transplantation (BMT) is a lifesaving procedure for malignant and nonmalignant disorders. BMT has evolved and advanced over the years;[1] yet, BMT remains associated with several significant complications. Practitioners should be aware of the effect of chemotherapy and radiation exposure during previous treatments, as such exposures are substantial risk factors for the development of toxicity during and after BMT.[2] After stem cell transplantation, about 40–60% of patients develop infectious and non-infectious pulmonary complications.[3]

The Hematopoietic Cell Transplantation-specific Comorbidity Index is a routinely used scoring system that uses pulmonary function tests (PFTs) to determine patient outcomes after hematopoietic cell transplantation. Forced expiratory volume exhaled in 1 second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) are used to determine the severity of lung dysfunction; furthermore, they can predict the risk of developing lung graft-versus-host disease (GVHD).[4] In addition, history of smoking, pre-transplant restrictive PFT, and pre-existing small airway disease are important risk factors for mortality following allogeneic BMT.[5]

Typically, PFTs are used to determine lung volumes, bronchial obstruction, gas exchange, lung compliance, and ventilatory capacity. The test includes spirometry and lung volume measurement. Spirometry measures the ability to inhale and exhale air relative to time, and it is used to monitor the progression of various respiratory disorders. Spirometry parameters include forced vital capacity (FVC), FEV1, and the FEV1/FVC ratio. Lung volume measurement is important to detect changes in lung volume independent of effort, especially when FVC is decreased on spirometry. The variables include functional reserve capacity, vital capacity, slow vital capacity, expiratory reserve volume, and residual volume. Pulmonary diffusion capacity describes the diffusion of gases across the alveolar–capillary membrane, and it is calculated using carbon monoxide (CO). The DLCO is interpreted in conjunction with spirometry and lung volumes; the quality of the test must be ensured before interpreting the results. An FEV1/FVC ratio <0.7 defines an obstructive ventilatory defect. A mixed defect can also present with low total lung capacity, in which case, the patient has a mixed obstructive and restrictive pattern.[6] This indicates the importance of performing pre-transplant PFT to detect pulmonary abnormalities. In light of this, the current study was conducted with the aim of determining the role of pre-BMT PFT in predicting post-transplant noninfectious pulmonary complications in an adult Saudi population due to a lack of data demonstrating the impact of the current practice. The correlation between established patient-related risk factors and the incidence of pulmonary complications among autologous (auto) and allogeneic (allo) groups was assessed.

METHODS

Study design, setting, and participants

This is a retrospective correlational cohort study that used purposive sampling and included all auto and allo adult patients who underwent autologous BMT at Princess Noorah Oncology Center, King Abdulaziz Medical City, Jeddah, Saudi Arabia, between January 1, 2014, and December 31, 2020.

All data were collected from the electronic patient records following a uniform data collection sheet that included patients' demographic data and PFT parameters.

Statistical analysis

Data were recorded onto an Excel sheet prior to data analysis process. The SPSS (version 25) software was used for analyses. Frequency, percentage, and bar chart were used for categorical variables. The log-rank test was used for the bivariate analysis of demographic variables and PFT parameters for the development of post BMT respiratory distress. Analysis was done separately for auto and allo groups. *P* value ≤0.05 was considered significant.

RESULTS

A total of 186 patients who underwent BMT were included (auto: 143; allo: 43), of which 115 (61.8%) were male. Pre-BMT comorbidities were present in approximately 30% of the patients, with the most common being diabetes, hypertension, and heart failure. Among both the auto and allo groups, there were 21 smokers; 25% had lung involvement and they were all lymphoma patients (auto group). In the pre-BMT phase, 95 (51%) patients had received two rounds of salvage chemotherapy, 102 (54.8%) had received chemotherapy that predisposed them to lung toxicity, and 30 (16.1%) had received radiation therapy [Table 1].

In terms of the most common complications, in the auto group, the major causes of respiratory stress post-BMT were pneumonia and engraftment syndrome [Table 2]. In the allo group, patients primarily experienced skin GVHD and only five patients experienced respiratory distress after transplant [Table 3].

Table 1: Characteristics of the patients (*N*=186)

Variable	Auto (*n*=143), *n* (%)	Allo (*n*=43), *n* (%)
Gender		
Male	94 (65.7)	21 (48.8)
Female	49 (34.3)	22 (51.1)
Comorbidities		
Yes	20 (14.0)	7 (16.3)
No	123 (86.0)	36 (83.7)
Smoking		
Yes	16 (11.2)	5 (11.6)
No	127 (88.8)	38 (88.4)
Diagnosis		
Relapsed/lymphoma	93 (65.0)	1 (2.3)
MM	44 (30.8)	1 (2.3)
ALL	3 (2.1)	10 (23.3)
AML	3 (2.1)	25 (58.2)
Aplastic anemia		1 (2.3)
CML		4 (9.3)
Myelofibrosis		1 (2.3)
Lung involvement by disease		
Yes	23 (25.0)	
No	69 (75.0)	
Pre-BMT chemotherapy		
Yes	142 (99.3)	38 (88.4)
No	1 (0.7)	5 (11.6)
Lines of chemotherapy		
1 line	35 (24.6)	19 (50.0)
2 lines	78 (54.9)	17 (44.7)
3 or more	29 (20.4)	2 (5.3)
Chemotherapy with lung toxicity		
Yes	84 (58.7)	18 (47.4)
No	59 (41.3)	20 (52.6)
Radiation		
Yes	27 (18.9)	3 (7.0)
No	116 (81.1)	40 (93.0)

BMT – Bone marrow transplant; Auto – Autologous; Allo – Allogeneic; MM – Multiple myeloma; ALL – Acute lymphoblastic leukemia; AML – Acute myeloid leukemia; CML – Chronic myeloid leukemia

Table 2: Post-transplant complications in the autologous group

Variable	Auto (*n*=143), *n* (%)
Type of conditioning	
BEAM	87 (60.8)
Melphalan	44 (30.8)
BU/CY	5 (3.5)
CY/TBI	2 (1.4)
BU/CY/thiotepa	3 (2.1)
Etoposide	2 (1.4)
Respiratory distress	
Yes	12 (8.4)
No	131 (91.6)
Cause of respiratory distress	
Pneumonia	4 (33.3)
Edema	1 (8.3)
Hemorrhage	1 (8.3)
Engraftment syndrome	4 (33.3)
Radiation pneumonitis	1 (8.3)
Drug/chemotherapy	1 (8.3)
SCT result	
Complete response	109 (76.2)
Partial response	6 (4.2)
Refractory	25 (17.5)
Relapsed	3 (2.1)

SCT – Stem cell transplantation; Auto – Autologous; BU/CY – Busulfan and cyclophosphamide; CY-TBI: Cyclophosphamide with total body irradiation; BEAM – BCNU, etoposide, cytarabine and melphalan

Table 4 describes the PFT parameters as predictors of post-BMT pulmonary complications in the auto group. The parameters, namely, pre-DLCO, pre-FEV, and FEV1/FVC ratio were not significantly associated with complications, except for pre-BMT FVC <80%, which was associated with increased complications ($P = 0.012$). Table 5 describes the pre-BMT PFT as predictors of post-BMT pulmonary complications in the allo group. None of the measured parameters (DLCO, TLCO, FEV, FVC, and FEV1/FVC ratio) were significantly associated with complications.

Table 6 shows the correlation between established patient-related risk factors and the incidence of pulmonary complications in the auto group. Two variables were found to be significantly correlated with post-BMT respiratory distress: lung involvement and radiation ($P < 0.05$ for both). No other factor was significantly associated with complications. Table 7 shows the correlation between established patient-related risk factors and the incidence of pulmonary complications in the allo group. None of the factors were significantly associated with complications.

DISCUSSION

The study aimed to investigate the role of pre-BMT PFT in predicting post-BMT non-infectious pulmonary complications in BMT patients. In the auto group, all PFT parameters were insignificant, except for pre-FVC <80%, which was associated with increased complications. Among the allo group, no significant associations were noted between PFT parameters and post-BMT complications. Kaya *et al.*[7] reported a significantly increased risk of early respiratory failure with reduced pre-transplant FEV1 or FVC in a pediatric allo group ($P = 0.001$). In contrast, Penna *et al.*[8] found that less active or physically disabled survivors presented inferior PFT values and poor performance on the 6-minute walking (6MW) test. In their study, the most physically active individuals had the most optimal FEV_1 (L), FEV_1 (% from the expected), and FEV1/FVC (absolute), and walked longer distances on the 6MW test. There were no significant differences between the auto and allo groups in their study. Similarly, Scarlata *et al.*[9] found that a lower respiratory volume and lung diffusion index predicted worse overall survival and a shorter infection-free period.

At our center, the practice is to perform a thorough evaluation for all patients with low PFT parameters in pre-BMT PFT, especially low DLCO. Based on the pulmonologist's recommendations, patients are assigned as ineligible for transplant or their conditioning chemotherapy is altered. For example, we changed to melphalan/

Table 3: Post-transplant complications in the allogenic group

Variable	Allo (*n*=43), *n* (%)
Type of conditioning	
BU/CY	21 (48.8)
RIC	5 (11.6)
FU/BU/TBI	3 (7.0)
CY/ATG	1 (2.3)
CY/TBI	11 (25.6)
Etoposide/TBI	2 (4.7)
Acute GVHD	
Yes	13 (30.2)
No	30 (69.8)
Type of GVHD	
Skin	5 (35.7)
Gut	4 (28.6)
2 sites	5 (35.7)
Respiratory distress	
Yes	5 (11.6)
No	38 (88.4)
Cause of respiratory distress	
Pneumonia	4 (80.0)
Edema	1 (20.0)
Post-PFT	
Yes	18 (41.9)
Not done	25 (58.1)
Reason for post-PFT	
Symptoms	4 (22.2)
Surveillance	14 (78.8)

Allo – Allogeneic; PFT – Pulmonary function test; GVHD – Graft-versus-host disease; BU/CY – busulfan and cyclophosphamide; RIC Reduced intensity conditioning; FU/BU/TBI – Fludarabine/Busulfan/Total body irradiation; ATG – antithymocyte globulin (rabbit); CY/TBI –cyclophosphamide/Total body irradiation

Table 4: Univariate analysis of pulmonary function test parameters related to post-bone marrow transplant respiratory distress in the autologous group

Parameter	Yes, *n* (%)	No, *n* (%)	Log rank *P*
Pre-DLCO			
≤65	8 (12.5)	56 (87.5)	0.280
>65	4 (5.1)	75 (94.9)	
Pre-FEV			
≤80	7 (14.3)	42 (85.7)	0.360
>80	5 (5.3)	89 (94.7)	
Pre-FVC			
≤80	9 (17.6)	42 (82.4)	0.012*
>80	3 (3.3)	89 (96.7)	
FEV1/FVC ratio			
≤80	1 (2.6)	38 (97.4)	0.205
>80	11 (10.6)	93 (89.4)	

*Significant at 5%. FEV – Forced expiratory volume; FVC – Forced vital capacity; DLCO – Diffusion lung capacity for carbon monoxide

Table 5: Univariate analysis of pulmonary function test parameters related to post-bone marrow transplant respiratory distress in the allogeneic group

Parameter	Yes, *n* (%)	No, *n* (%)	Log rank *P*
Pre-DLCO			
≤65	0	7 (100)	0.421
>65	5 (13.9)	31 (86.1)	
Pre-TLCO			
≤80	3 (11.1)	24 (89.9	0.872
>80	2 (12.5)	14 (87.5)	
Pre-FEV			
≤80	1 (7.1)	13 (92.9)	0.553
>80	13 (13.8)	25 (86.2)	
Pre-FVC			
≤80	0	15 (100)	0.106
>80	5 (17.9)	23 (82.1)	
FEV1/FVC ratio			
≤80	0	6 (100)	0.254
>80	5 (13.5)	32 (88.4)	

FEV – Forced expiratory volume; FVC – Forced vital capacity; DLCO – Diffusion lung capacity for carbon monoxide; TLCO – Transfer factor for carbon monoxide

Table 6: Univariate analysis of factors related to post-bone marrow transplant respiratory distress in the autologous group

Variable	Yes, *n* (%)	No, *n* (%)	Log rank *P*
Gender			
Male	9 (9.6)	85 (90.4)	0.582
Female	3 (6.1)	46 (93.9)	
Comorbidities			
Yes	10 (8.1)	113 (91.9)	0.920
No	2 (10.0)	18 (90.0)	
Smoking			
Yes	1 (6.3)	15 (93.8)	0.731
No	11 (8.7)	116 (91.3)	
Diagnosis			
Relapsed/lymphoma	9 (9.7)	84 (90.3)	0.935
MM	3 (6.8)	41 (93.2)	
High risk ALL	0	3 (100)	
Relapsed/AML	0	3 (100)	
Lung involvement/lymphoma			
Yes	5 (21.7)	18 (78.3)	0.030*
No	4 (5.8)	65 (94.2)	
Chemotherapy pre-BMT			
Yes	12 (8.5)	130 (91.5)	0.759
No	0	1 (100)	
Lines of chemotherapy			
1	3 (8.6)	32 (91.4)	0.959
2	6 (7.7)	72 (92.3)	
≥3	3 (10.3)	26 (89.7)	
Chemotherapy with lung toxicity			
Yes	6 (7.1)	78 (92.9)	0.409
No	6 (10.2)	53 (89.8)	
Pre-BMT radiation			
Yes	5 (18.5)	22 (81.5)	0.044*
No	7 (6.0)	109 (94.0)	

*Significant at 5%. BMT – Bone marrow transplant; MM – Multiple myeloma; ALL – Acute lymphoblastic leukemia; AML – Acute myeloid leukemia

etoposide instead of BEAM conditioning regimen for several patients with Hodgkin's lymphoma. In other cases, additional testing, such as ventilation/perfusion scans, had to be performed. These changes might explain the lack of significance in most of the PFT parameters in pre-BMT PFT in our study. Chien and Sullivan[10] conducted a study that included 56 auto and 165 allo BMT patients who had pre-transplant DLCO between 40% and 60% and found no significant association with the risk for respiratory failure or non-relapse mortality. Although low DLCO may indicate increased risk of poor outcomes, a more thorough risk stratification method should be used. In addition, Le Bourgeois *et al.*[11] suggested that the diffusing capacity of the lung for nitric oxide (DLNO) and the

Table 7: Univariate analysis of factors related to post-bone marrow transplant respiratory distress in the allogeneic group

Variable	Yes, *n* (%)	No, *n* (%)	Log rank *P*
Gender			
Male	2 (9.5)	19 (90.5)	0.734
Female	3 (13.6)	19 (86.4)	
Comorbidities			
Yes	0	7 (100)	0.144
No	5 (13.9)	31 (86.1)	
Smoking			
Yes	1 (20.0)	4 (80.0)	0.836
No	4 (10.5)	34 (89.5)	
Pre-BMT chemotherapy			
Yes	4 (10.5)	34 (89.5)	0.662
No	1 (20.0)	4 (80.0)	
Lines of chemotherapy			
1	2 (10.5)	17 (89.5)	0.931
2	2 (11.5)	15 (88.2)	
≥3	0	2 (100)	
Chemotherapy with lung toxicity			
Yes	3 (16.7)	15 (83.3)	0.268
No	1 (50.0)	19 (95.0)	
Radiation			
Yes	1 (33.3)	2 (66.7)	0.101
No	4 (10.0)	36 (90.0)	

BMT – Bone marrow transplant

DLNO/DLCO ratio were more accurate predictors of post-allo-BMT pulmonary complications than DLCO and that they should be used instead of DLCO to determine transplant eligibility.

The current study reported a correlation between established patient-related risk factors and the incidence of pulmonary complications. We found that among the auto group, lung involvement in lymphoma patients and radiation exposure prior to transplantation significantly predicted post-BMT complications. In contrast, among the allo group, none of the factors were significantly associated with post-BMT complications. Scarlata *et al.*[9] reported that patients who were exposed to pneumotoxic agents before BMT had increased risk of pulmonary function abnormalities, and the exposure affected the infection-free interval, event-free survival, and overall survival. In addition, Bruce *et al.*[12] reported that patients who were treated with bortezomib and thalidomide were at a higher risk of developing PFT abnormalities; 47 (13.7%) patients had an obstructive pattern, and 76 (22.1%) had restrictive patterns on PFT. These findings highlight the influence of pre-BMT therapy or salvage therapy on PFT results. Moreover, Le Bourgeois *et al.*[11] reported that the type of disease impacted pulmonary outcomes, as lymphoid patients had an increased risk of developing acute respiratory distress syndrome in the allo group.

According to Kiefer *et al.*,[13] there are racial and ethnic disparities in various aspects of lung function. For example, 15% of the difference in vital capacity is attributable to race and ethnicity. In a similar context, Zavorsky *et al.*[14] revealed that racial differences accounted for approximately 5%–10% of the total variance, and about 73% of the variance in DLCO was accounted for by gender (~57%), race (10%), age (~4%), and height (2%). This highlights the importance in confirming the influence of patient characteristics on PFT results. Furthermore, it highlights the importance of establishing baseline data for the Saudi population, and consideration of such differences is important to prevent incorrect diagnoses.

Limitations

A limitation of this study was that it was conducted at a single center with a relatively small number of patients, which might limit its generalizability. Furthermore, the majority of the sample were auto patients, and the study did not address lung GVHD and its association with pre-BMT PFT. All patients were assigned as eligible for BMT, and no patient with low DLCO was eligible for BMT. Nonetheless, the findings of this study are important because there are few recent studies examining the role of pre-BMT PFT in predicting post-BMT pulmonary complications.

CONCLUSION

This study highlighted the role of pre-BMT PFT in predicting pulmonary complications in auto and allo patient groups. The findings of this study may help redefine the eligibility criteria of pre-transplant PFT evaluation, and they can be used as evidence to expand the inclusion of what were considered non-eligible patients. Future multicenter studies are crucial to guide local practice and the development of guidelines.

Ethical consideration

The study was approved by the King Abdullah International Medical Research Center (Ref. no.: NRJ21J-074-03; date: July 13, 2021). Requirement for informed consent was waived owing to the study design. The study adhered to the principles of Declaration of Helsinki, 2013, and no identifying information was recorded.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: A.S.A., R.S.G.; Methodology: R.S.G., G.A.O., A.S.A., A.N.A., S.M.A., M.D.A., M.M.K., S.K.D.,

I.Y.H., W.A.R.; Data analysis: M.E.A.; Writing–original draft preparation: R.S.G.; Writing – review and editing: A.S.A.

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Conflicts of interest

There are no conflicts of interest.

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