The change of lung function in children with bronchiolitis obliterans syndrome after hematopoietic stem cell transplant

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Abstract

Background: Bronchiolitis obliterans syndrome (BOS) is a life-threatening respiratory complication of allogeneic hematopoietic stem cell transplant (HSCT). Even though a lung function test is crucial in monitoring BOS, little information exists on the test's association with prognosis in children with BOS. Objectives: The purpose of this study was to determine the correlation between changes in lung function after BOS diagnosis and long term outcomes. Methods: A total of 428 children received allogeneic HSCT from January 2006 to December 2017 at Asan Medical Center. Twenty-three of those children (5.4%) were diagnosed with BOS after allogeneic HSCT, and their clinical data were reviewed. Twenty-one subjects underwent regular pulmonary function tests for 24 months after the occurrence of BOS. Results: Among the 21 children with BOS, eight died, five underwent a lung transplant (TPL), and 15 required oxygen (O2) therapy. The FEV1% predicted (pred), FVC% pred, and FEF25-75% pred were 37.8±12.7% (mean±SD), 62.2±16.2%, and 16.4±9.6%, respectively, upon BOS diagnosis. Changes in the FEV1% pred were greater in the death and lung TPL group (-24.8±22.3%) than the survival without lung TPL group (5.7±21.8%), and greater in the O2 therapy (-19.4±23.4%) group than the group without O2 therapy (14.2±20.0%) during the first three months after BOS diagnosis. Conclusion: The change of FEV1 during the first three months after BOS correlated with the prognosis including survival, lung transplantation, and O2 therapy. These results suggest more active intervention in the first three months after BOS diagnosis may be needed to improve prognosis.

Introduction

Bronchiolitis obliterans syndrome (BOS) is a life-threatening complication of allogeneic hematopoietic cell transplant (HSCT)[1]. It is characterized by an irreversible small airway obstruction caused by epithelial injury, subepithelial inflammation, and fibrosis of small airways [2]. The prevalence of BOS was reported 2%-6.5% in allogeneic HSCT recipients in adult cohort[3-5], and 2.0-2.7% in pediatric cohorts[6,7]. The prognosis of children with BOS after HSCT is poor; the five-year survival rate is 45-59% [8,9]. Since the number of patients receiving allogeneic HSCT is increasing, BOS in children will likely increase in the future.

A BOS diagnosis is based on declining FEV_1, which is measured serially after HSCT [10], and confirmed with pathology of constrictive bronchiolitis or high-resolution computed tomography (CT) showing air trapping, small airway thickening, or bronchiectasis [11]. After BOS diagnosis, pulmonary functions are measured regularly to monitor treatment efficacy and prognosis [12]. Systemic steroids have been the backbone of BOS therapy [13-17] and inhaled fluticasone, azithromycin, and montelukast (FAM) have been recently introduced[18]. However, the prognosis of BOS is still poor.

A study enlisting subjects with BOS in a multicenter prospective trial and a retrospective cohort concluded that FEV_1 declined rapidly in the 6 months prior to BOS diagnosis [19]. The current study is one of few

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studies that describe the longitudinal change of lung function after BOS diagnosis in children and clarify the clinical implications of lung function changes on BOS prognosis.

Study design and Methods

Study participants

Between January 2006 and December 2017, 428 children received allogeneic HSCT at Asan Medical Center. A detailed description for study participants is provided in the **online supplement** . In the present study, 21 children met lung function criteria modified from the National Institutes of Health consensus guidelines for diagnosis of BOS (E-figure 1) [11,20,21]. No subject has concurrent pulmonary infection. In addition, all subjects underwent chest CT scans, and 13 children showed air trapping, small airway thickening, or bronchiectasis. A lung perfusion/ventilation scan was performed on eight children who showed no clear evidence of BOS according to the CT results. Of those eight, five had heterogeneous multiple matched perfusion defects. Lung biopsies were performed on nine children, and constrictive bronchiolitis was confirmed in all nine. Echocardiograms showed that all 21 patients displayed normal heart function at the time of BOS diagnosis.

The median observation period for all subjects after BOS diagnosis was 34.4 months (IQR, 11.5-62.0 months). In our current analysis, pulmonary function tests (PFTs) were gathered during 24 months after BOS diagnosis, and CT values were gathered during 12 months after diagnosis.

All subjects started treatment immediately upon diagnosis. All subjects received 6 to 17 cycles of methylprednisolone (mPD) (i.v. 20mg/kg/day for 3 days, with an interval of 1 month) except one subject who died within 6 months after BOS diagnosis. The median mPD pulse therapy period for all subjects was 12.0 months (IQR: 7.5-12.0 months) (E-table 1). A detailed description is provided in the **online supplement** . Diagnosis and treatment of BOS and lung function monitoring followed the Pediatric Hemato-oncology Division of Asan Medical Center protocol regarding BOS after HSCT, which was developed with the Pediatric Pulmonology Division in 2011.

We divided subjects into two groups according to BOS prognosis and compared the clinical characteristics, lung function parameters, and chest CT findings between the good and poor prognosis groups. The poor prognosis group included patients who had died or required lung TPL (hereafter labeled Group 1) and Group that had required O_2 therapy after BOS diagnosis (hereafter labeled Group 3), and the good prognosis group included survivors that did not require lung TPL (hereafter labeled Group 2) or Group that did not require O_2 therapy after BOS diagnosis (hereafter labeled Group 4). O_2 therapy was defined as O_2 therapy for more than 1 day due to dyspnea after BOS diagnosis and O_2 therapy was applied when dyspnea was accompanied by less than 90% of S_PO_2[22].

Lung Function Tests

Detailed descriptions for measuring PFT, IOS, FeNO, and 6MWT are provided in the **online supplement** .

Chest CT

Patients underwent CT examinations upon BOS diagnosis and 3, 6, and 12 months after diagnosis of BOS using various CT systems (see**online supplement**).

Statistical analysis

Statistical analyses were conducted using SPSS version 23 (SPSS, Chicago, IL) (see **online supplement**).

Results

Clinical characteristics

The clinical characteristics of the subjects are shown in Table 1. Of the 21 subjects, eight were male and 13 were female. Their age at the time of diagnosis with hemato-oncological diseases was 10.4±4.7 years (mean ± standard deviation), and their age at the time of HSCT was 11.6±4.1 years. Their age at the time of BOS

diagnosis was 12.7±4.0 years, and the average time to BOS diagnosis after HSCT was 14.0±10.1 months (Table 1). Clinical characteristics did not show statistical differences between Groups 1 and 2 and Groups 3 and 4 (Table 2).

Prognosis

Eight subjects (8/21, 38.1%) died; six (6/21, 28.6%) died due to respiratory failure after BOS diagnosis, one died from fungal infection, and one died from acute renal failure. The mean time before death after BOS diagnosis was 18.6±15.1 months. Five subjects (5/21, 23.8%) underwent lung transplantation, and the mean time before lung transplantation after BOS diagnosis was 30.4±28.0 months. In addition, 15 subjects (15/21, 71.4%) underwent O_2 therapy, and the mean time before O_2 therapy after BOS diagnosis was 17.6±19.8 months (Table 1). We used O_2 therapy and death or lung TPL to analyze the prognosis of BOS.

Lung function during the study period

Data gathered after lung TPL were excluded because they did not represent the original characteristics of the subjects. E-figure 1 shows the change in lung function caused by BOS. FEV_1% pred, FVC% pred and FEF_{25-75}% pred showed statistical significance during study period in linear mixed modeling, and FEV_1% pred, FVC% pred, and FEF_{25-75}% pred decreased significantly upon BOS diagnosis compared to pre-HSCT ($P < 0.001$). FEV% pred, FVC% pred, and FEF_{25-75}% pred were 92.8±13.0%, 87.9±14.7%, and 113.0±24.2%, respectively, before HSCT, and FEV_1% pred, FVC% pred, and FEF_{25-75}% pred at the time of BOS diagnosis were 37.8±12.7%, 62.2±16.2%, and 16.4±9.6%, respectively. Among these values, FEF_{25-75}% pred decreased the most from pre-HSCT (111.7±24.2%) to BOS diagnosis (16.0±3.3%). After BOS diagnosis, FEV_1% pred, FVC% pred, and FEF_{25-75}% pred were significantly reduced at each time point with an interval of 3 months during study period when compared to pre-HSCT (E-table 2).

Comparison of lung function during the study period according to the prognosis

Twenty-one subjects repeated PFTs regularly for 24 months after BOS occurred. Among them, nine children did not complete PFTs because they are died or underwent lung TPL within 24 months after BOS diagnosis. The events were defined as death or lung TPL, and O_2 therapy. The median pre-event period for PFTs in all subjects was 24.0 months (interquartile range [IQR] 7.5-24.0 months) (E-table 1).

Figure 1 illustrates the comparison of lung function during the study period between Group 1 versus Group 2 and Group 3 versus Group 4. FEV_1% pred, FVC%, pred, and FEF_{25-75}% pred were lower in Group 1 than in Group 2 at all time points after BOS diagnosis. However, these differences were significant at only the 6, 9, and 18 month time points for FEV_1% pred and the 9 month time point for FEF_{25-75}% pred after BOS diagnosis (all P <0.05, Figure 1a, E-table 3a). When comparing Groups 3 and 4, FEV_1% pred and FVC% pred were significantly lower in Group 3 than in Group 4 at 3 months post-BOS diagnosis and afterward. The levels of FEF_{25-75}% pred were also significantly lower in Group 3 than in Group 4 at 3, 6, 9, 15, 18, and 21 months after BOS diagnosis (all P <0.05, Figure 1b, E-table 3b).

Lung function change during the study period according to the prognosis

We compared changes in FEV_1% pred between Groups 1 and 2 and between Groups 3 and 4 during the study period (Table 3). A detailed description for the calculation is provided in the**online supplement** . There was no significant difference in FEV_1% pred change from pre-transplant to BOS diagnosis between Groups 1 and 2 and Groups 3 and 4. We compared changes in FEV_1% pred at each time point with an interval of 3 months after BOS diagnosis during the study period, and there was a significant difference between Group 1 (-24.8±22.3%) and Group 2 (5.7±21.8%) (P =0.016) and between Group 3 (-19.4±24.4%) and Group 4 (8.6±21.9%) (P =0.041) during the first 3 months after BOS diagnosis. Likewise, there was a significant difference in the change of $FEF_{25-75\%}$ pred between Group 1 (-32.4±23.6%) and Group 2 (11.7±37.1%) (P=0.007) and between Group 3 (-19.4±24.4%) and Group 4 (16.8±39.6%) (P=0.026) during the first 3 months after BOS diagnosis (E-table 4a). Detailed descriptions for additional analysis are provided in the **online supplement** (E-table 4b).

The prognosis of BOS according to the slope of FEV_1 change during the first 3 months after BOS diagnosis

When death or lung TPL was defined as an event, the median pre-event period 13.5 months (IQR, 8.4-30.9 months) for Group 1 after BOS diagnosis, and the observation period for Group 2 was 59.7 months (IQR, 43.0-85.6 months). When O_2 therapy was defined as an event, 10.2 months (IQR, 5.8-17.9 months) for Group 3, and the observation period for Group 4 was 59.8 months (IQR, 33.9-102.0 months).

When comparing the Kaplan-Meier estimates between groups with positive and negative slopes of FEV_1 change during the first 3 months after BOS diagnosis, the group with a negative slope had a higher likelihood of being Group 1 with a marginal significance when compared to the group with a positive slope ($P = 0.057$ according to the log-rank test) (Figure 2a). Also, the group with a negative slope of FEV_1 change during the first 3 months after BOS diagnosis had a significantly higher probability of being Group 3 when compared to the group with a positive slope ($P = 0.014$ according to the log-rank test) (Figure 2b).

The occurrence of air trapping on chest CTs during the first 12 months after BOS diagnosis according to the prognosis

We compared changes in air trapping percent at each time point during the first 12 months after BOS diagnosis. Detailed description for the calculation and analysis are provided in the **online supplement** .

Airway resistance and reactance, FeNO, and 6MWT according to prognosis

We compared IOS, FeNO, and 6MWT values upon BOS diagnosis. Detailed description for the analysis are provided in the **online supplement** .

Discussion

A major finding regarding BOS is the decrease of lung function, especially reduced airway function including FEV_1 and $FEF_{25-75}\%$. However, no study has examined the relationship between prognosis and lung function change in patients with BOS. Our current study is the first to discover the clinical implications of lung function change in BOS, especially during the first 3 months after BOS diagnosis. In the current study, 21 children were diagnosed with BOS, treated, and monitored with regular PFTs prospectively on the basis of our protocol, and accumulated data were analyzed retrospectively. The good prognosis groups (Groups 2 and 4) showed different changes in $FEV_1\%$ pred and $FEF_{25-75}\%$ pred during the first 3 months after BOS diagnosis when compared to the poor prognosis groups (Groups 1 and 3).

Because BOS is characterized by the narrowing of small airways via a fibroproliferative process [23,24], the reduction in FEV_1 and $FEF_{25-75}\%$ may be more prominent than in FVC, as in our current analysis. In a cohort study of adult patients with BOS, lung function trajectory was examined, and it concluded that FEV_1 decreased rapidly 6 months before BOS diagnosis and stabilized after BOS diagnosis [19]. Also, a study examining BOS after lung transplantation[25] concluded that subjects with higher FEV_1 or 6MWT values (measured at 3, 6, and 12 months and annually after lung transplantation) had a better chance of survival and a lower risk of developing BOS. However, these studies focused on pulmonary function before BOS diagnosis and did not show a relationship between lung function trajectory after BOS diagnosis and BOS prognosis. In the current study, we analyzed spirometric parameters over time after BOS diagnosis, and we investigated impulse oscillometric values, 6MWT and FeNO values at BOS diagnosis.

The pathogenesis of BOS after HSCT is associated with alloreactivity (e.g. graft-versus-host disease) [26,27], and systemic steroids and other anti-inflammatory agents are typically used to treat BOS; however, peri-bronchial inflammation can still progress into fibrosis causing a poor prognosis [18]. Our current study showed that a rapid decline in FEV_1 in the first 3 months after BOS correlates with poor prognosis (i.e. death or the need for a lung transplant or O_2 therapy). Moreover, the slope of $FEV_1\%$ pred level change during the first 3 months after BOS diagnosis determined BOS prognosis in Kaplan-Meier estimates even though all patients with BOS received the same treatment. Our first hypothesis that may explain this phenomenon is that airway inflammation in patients with a rapid FEV_1 decline may be too severe to be controlled by anti-inflammatory

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treatment. Our second hypothesis posits that the rate of lung function reduction after BOS development in some patients is faster because it rapidly progresses into fibrosis in the airway, which can no longer respond to anti-inflammatory treatment. This progression may depend on an individual's susceptibility to fibrosis after injury in the airway[28]. This study is the first to show that changes in pulmonary function during early disease processes can predict BOS prognoses. New treatment modalities during the first 3 months after BOS diagnosis are needed for patients with a poor prognosis.

This study found different changes in $FEV_1\%$ pred and $FEF_{25\text{-}75}\%$ pred during the first 3 months after BOS diagnosis between good and poor prognosis groups. However, changes in PFTs could not be compared across all periods because of death or lung TPL. Lung function likely declines persistently in patients with a poor prognosis, and if their data were included, a significant difference in the change of $FEV_1\%$ pred after the first 3 months after BOS would likely occur. However, the data from subjects with a poor prognosis (Groups 1 and 3) were all present except for one subject until 6 months after BOS diagnosis. Furthermore, PFT changes from 3 to 6 months after BOS diagnosis were not significant. Therefore, the first 3 months after BOS diagnosis should be considered a meaningful period for determining prognosis. In addition, Figure 1a shows that FEV_1 in Group 1 tended to increase after 18 months from BOS diagnosis, but not in a significant manner. However, this analysis was distorted because subjects with low lung functions died early. In this group, only two subjects completed PFTs during the 24 months after BOS diagnosis, and others dropped out due to death or lung TPL within 24 months after BOS diagnosis. We analyzed the PFT trajectories of two subjects who consistently performed PFTs until 24 months after BOS diagnosis (E-table 5, E-figure 3). Both subjects eventually received lung TPL because of decreasing lung function. One received lung TPL at 34.4 months after BOS diagnosis and the other received lung TPL at 68.5 months after BOS diagnosis. E-figure 3 illustrates that FEV_1 steadily decreased during the first 24 months after BOS diagnosis in both subjects.

In this study, subjects performed IOS upon BOS diagnosis, and we found that the Xrs5% value in Group 3 was significantly higher than in Group 4. Reactance implies tissue elastance and inertance, especially at lower frequencies (e.g. 5 Hz), with a close association with capacitance, which better reflects the elasticity of the lung periphery[29]. No study has clarified the effect of IOS on the prognosis of BOS after HSCT. Studies using patients with diffuse interstitial lung disease and emphysema showed pulmonary fibrosis and emphysema can cause changes in Xrs5% pred due to lung stiffness, hyperinflation and a loss of lung elastic recoil, respectively[30,31]. Another study examining children with postinfectious bronchiolitis obliterans (PIBO) showed greater differences in Xrs5 than Rrs5 in children with PIBO compared to other groups [32]. These findings are consistent with our current findings, and it suggests that Xrs5% pred may better reflect small airway obstruction than Rrs5% pred due to peribronchial fibrosis of lung periphery in children with PIBO and BOS [29-31]. This study showed that IOS can predict BOS prognosis in young children who cannot undergo spirometry.

We examined CT results, which are another crucial factor in diagnosing BOS. Some studies attempted to predict lung function via CT scan in BOS patients, but this is challenging in young children because no consensus exists regarding reference values that define air trapping in chest CTs. In a pilot feasibility study of children (6-17 years of age), quantitative computed tomography assessments in children with BOS showed a correlation between their lung function and air trapping as defined by the individualized threshold ([attenuation values of normal lung parenchyma + attenuation values of air trapping area] / 2)[33]. In our current analysis, we used this as a cut-off value to distinguish air trapping lungs from normal lungs on CT scans. The percent of air trapping total lung volume according to CT measurements (air trapping volume/total lung volume) at 3, 6, and 12 months after BOS diagnosis was calculated, and Groups 1 and 2 as well as Groups 3 and 4 were compared. The change in air trapping during the first 3 months after BOS diagnosis was greater in poor prognosis groups (Groups 1 and 3), but the result was not significant. This suggests that the critical period for determining the prognosis of BOS is the first 3 months after BOS diagnosis, which agrees with the analysis of lung function change during BOS. In addition, these results suggest that PFTs are more sensitive to predict the prognosis of BOS even though CT scans may be helpful in tracking the prognosis of BOS. However, we could not perform expiration chest CTs to identify air trapping

because children with dyspnea had difficulty completing expiration CTs, and frequent radiation exposure was a concern [34].

The major limitations of the current study are a small sample size and the use of different observation periods for each subject. However, there are very few studies examining pulmonary function in children diagnosed with BOS because of its low prevalence after hematopoietic stem cell transplantation. This is also the first study to show that changes in pulmonary function after BOS diagnosis can predict the prognosis. In the survival analysis, we also showed that PFT changes during the first 3 months after BOS diagnosis in children may influence their prognosis. Furthermore, when the observation periods of all subjects were unified to 24 months after BOS diagnosis in the analysis, there was a significant difference in the change of FEV_1 during the first 3 months after BOS diagnosis between Groups 3 and 4 (E-table 6). As another possibility to affect the results, the difference in the diagnosis time of BOS after HSCT or the difference in lung function change before BOS diagnosis among study subjects could be considered to affect the change in lung function after diagnosis of BOS. However, lung function changes during 6 months before BOS diagnosis had no effect on the prognosis (data was not shown).

In conclusion, the change of FEV_1 during the first 3 months after BOS diagnosis was significantly different between good and poor prognosis groups. Our current analysis shows that the phase right after BOS diagnosis is the most critical in determining the prognosis of BOS. These results suggest that an active intervention strategy is needed during the first 3 months after BOS diagnosis to improve its prognosis

Figure Legends

Figure 1. *Comparison of lung function during the study period according to the prognosis* . (a) Lung function between death or lung transplant (TPL) (Group 1) and survival without lung TPL (Group 2). (b) Lung function between Group with O_2 therapy (Group 3) and group without O_2 therapy (Group 4). BOS, bronchiolitis obliterans syndrome. *$P<0.05$.

Figure 2. *The prognosis of bronchiolitis obliterans syndrome (BOS) according to the slope of FEV_1 change during the first 3 months after BOS diagnosis* . Group A was defined as subjects with negative slope of FEV1 change during the first 3 months after diagnosis of BOS, and Group B was defined as Subjects with positive slope of FEV1 change during the first 3 months after diagnosis of BOS. (a) Cumulative probability of an event according to the slope of FEV1 change during the first 3 months after BOS diagnosis. Death or lung transplant (TPL) was defined as an event. (b) Cumulative probability of an event according to the slope of FEV1 change during the first 3 months after BOS diagnosis. O_2 therapy was defined as event

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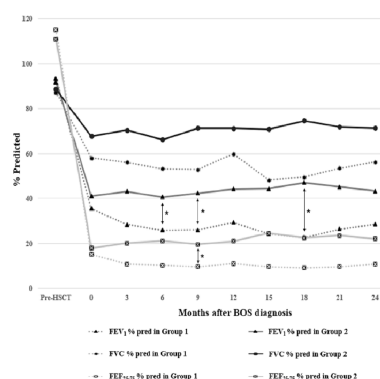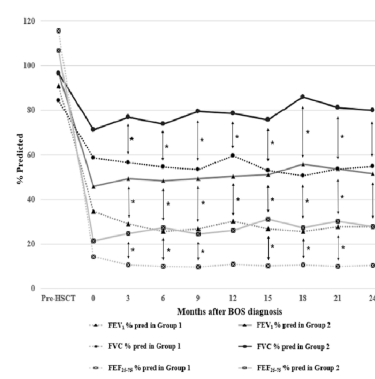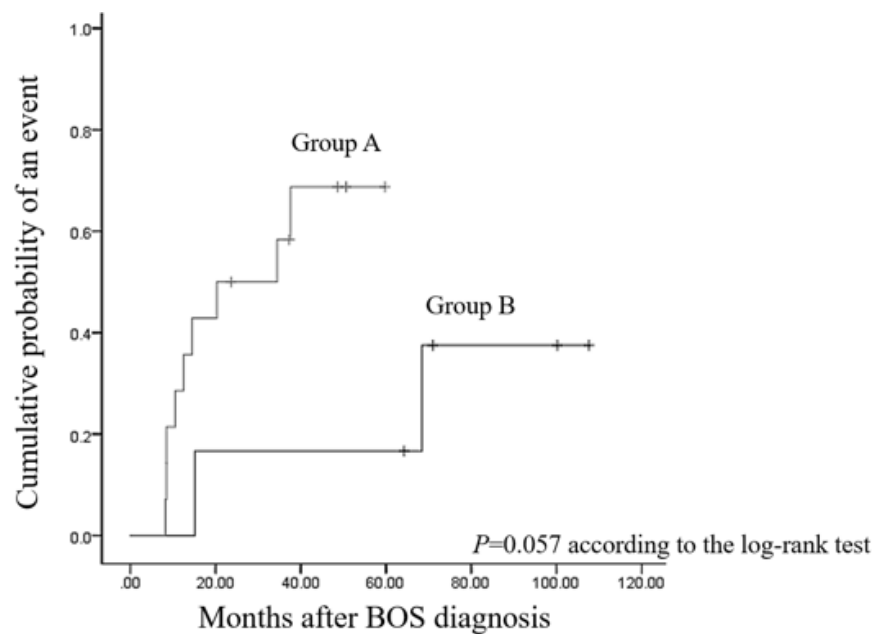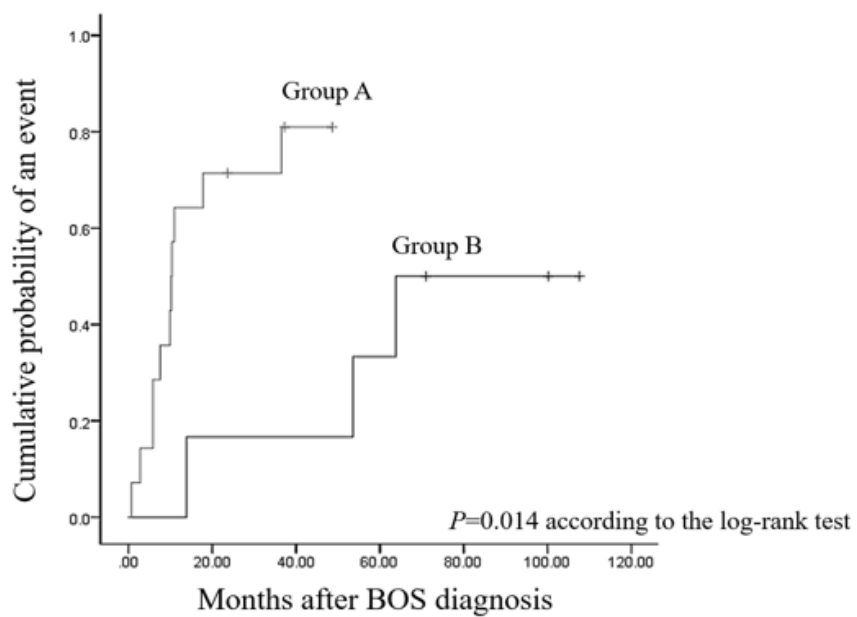

Figure 1 (a)

Figure 1 (b)

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(b)

Figure 2