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Utility of Bronchoscopy with Bronchoalveolar Lavage among Hematologic Transplant Recipients in the Era of Noninvasive Testing

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Abstract
Background: Pulmonary complications are common among hematologic stem cell transplant (HSCT) recipients. Their evaluation can be pursued through bronchoscopy with bronchoalveolar lavage (BAL) and a variety of available noninvasive studies, which include newer molecular markers for detecting a variety of infectious agents. ***Objective:*** The objective of this study is to evaluate the diagnostic yield of BAL among HSCT patients relative to the yield of noninvasive testing. ***Method:*** This is a retrospective analysis of HSCT recipients who underwent both BAL and noninvasive testing at a cancer center in 2013 and 2014. ***Results:*** There were 210 diagnostic results among 98 HSCT recipients. There were 84 unique findings on noninvasive testing that were not evident on BAL, and 36 unique findings on BAL that were not evident on noninvasive testing. Noninvasive testing tended to yield bacterial and viral infections more commonly, while BAL yielded mycobacterial isolates more commonly. ***Conclusion:*** While both noninvasive testing and BAL are helpful in this population, each appeared more precise than the other with individual lung diseases. Bronchoscopy with BAL and noninvasive testing should be considered complementary strategies in the workup of pulmonary complications among HSCT patients.

Introduction

Since its inception about 50 years ago, hematologic transplantation has offered a cure to thousands of patients whose underlying diseases, typically including leukemia, lymphoma, and multiple myeloma, had previously been considered fatal. Recipients of hematologic stem cell transplants (HSCT), the most common mode of hematologic transplant delivery, remain prone to a variety of posttransplant pulmonary complications. Infection, consequent to impaired immunity caused by the underlying disease and the transplant itself, is common, and the lungs are a frequent target. Pulmonary complications are associated with high morbidity and mortality and have been reported in up to 70% of transplanted patients [1–3].

Flexible bronchoscopy with bronchoalveolar lavage (BAL) is a commonly employed diagnostic tool among these patients and allows a safe means of sampling the

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lower respiratory tract. The reported diagnostic yield of BAL in this population is variable, ranging between 31 and 89% [4, 5]. Though many studies suggest that the BAL results can influence medical management, there is a paucity of data supporting the idea that utilizing this procedure among HSCT patients has any significant effect on outcomes [6–9]. Moreover, the last decade has seen advances in less invasive serologic tests for some infections, including viral and fungal PCR and molecular serum markers [10–12]. As diagnostic approaches to these patients have changed, it is conceivable that many patients, for whom BAL would traditionally have been helpful, may now achieve a diagnosis by other means. As a result, the relative benefit of this procedure in the transplant population has become less clear.

The objective of this study is to evaluate the diagnostic yield of BAL among HSCT patients and to express its utility when used in combination with noninvasive testing. We hypothesize that BAL remains a useful tool that can be additive to noninvasive testing in identifying the etiology of pulmonary infiltrates in this population.

Materials and Methods

Patient Population

This is a retrospective analysis of HSCT patients who underwent bronchoscopy with BAL between January 2013 and December 2014 at Memorial Sloan Kettering Cancer Center (MSK), a tertiary care cancer center in New York City. Patients who underwent bronchoscopy without BAL, who underwent bronchoscopy immediately preceding video-assisted thoracoscopic surgery, or who did not have computed tomography (CT) scans performed prior to their bronchoscopy were excluded. After approval by the Institutional Review Board, cases were identified by a registry maintained by the Adult Bone Marrow Transplant Service at MSK.

Demographic and Clinical Data

MSK contains an institutional transplant registry, storing basic demographic and historical data of hematologic transplant recipients. Data were extracted from this registry retrospectively for the purposes of this analysis, including age; gender; type of underlying malignancy requiring HSCT; type of transplant; dates of birth, transplantation, BAL, and death (if applicable); length of hospital stay; and the presence or absence of graft-versus-host disease (GVHD). For the purpose of this analysis, an early bronchoscopy was defined as a bronchoscopy with BAL performed 4 days or less from presentation. Late bronchoscopy was defined as a bronchoscopy with BAL performed more than 4 days after presentation. Other clinical information was extracted from the medical record, including the use of mechanical ventilation and the absolute neutrophil count. Radiological data, microbiology results, the presence or absence of complications, and the type of management change subsequent to BAL, if any, were determined by chart review.

Chart review was conducted by 2 of the investigators (I.H. and M.F.). Data were combined after collection, and a sample of 8 patients was mutually reviewed to ensure consistency and accuracy. Radiographic information was acquired from official radiology reports of chest CT scans. Potential complications of bronchoscopy with BAL included hemorrhage requiring a transfusion, pneumothorax, respiratory failure requiring intubation within 24 h of the procedure, and ICU admission. For patients who ultimately underwent multiple bronchoscopies during their course, only the first with BAL was analyzed.

Noninvasive Microbial Data and Bronchoscopy Data

Noninvasive microbial data were collected if they were performed within 10 days prior to the bronchoscopy with BAL. Whenever available, these included blood culture, sputum culture, nasopharyngeal PCR of viral organisms, *Aspergillus galactomannan*, β-D-glucan, and urine antigen detection of Legionella, Mycoplasma, and Streptococcus organisms. BAL results and any consequent change in medical management were also recorded. *Pneumocystis jiroveci* was tested by PCR and direct fluorescent antibody from sputum, which was sometimes induced, and BAL. A positive result was defined as identification of a pathogenic organism by culture, positive molecular studies, or evidence of alveolar hemorrhage at BAL. A therapeutic change was defined as any addition, withdrawal, or change in antibiotics or glucocorticoids as a result of the procedure, as documented in daily progress and/or physician notes.

Fiberoptic Bronchoscopy

There is no standardized protocol at MSK on performing bronchoscopy with BAL. All patients were seen in consultation by an attending physician on the staff of the institution's pulmonary service. Contraindications to bronchoscopy and BAL were at the discretion of the pulmonary attending physician, but typically included hemodynamic instability or the requirement of more than 4 L/min of supplemental oxygen, unless mechanically ventilated. Thrombocytopenia or abnormal coagulation studies were not a contraindication to BAL unless the platelet count could not be corrected to 30,000, or the INR could not be corrected to 1.5 with suitable transfusions, or if there was ongoing bleeding or hemoptysis.

After obtaining informed consent, every bronchoscopy with BAL was performed by a fellow and attending physician in a dedicated endoscopy unit or, for intubated and critically ill patients, in an intensive care unit. Patients were monitored with continuous cardiac telemetry and pulse oximetry. Blood pressure was measured every 5–10 min. Monitored sedation was administered by an anesthesiologist on staff.

For each case, the bronchoscope was introduced through a laryngeal mask airway or endotracheal tube. In mechanically ventilated patients, ventilation was performed with 100% oxygen, and the bronchoscope was advanced through a swivel-Y adaptor. Topical anesthesia of the oropharynx, vocal cords, and major airways was obtained with lidocaine (2% for upper airways and 1% for lower airways). BAL was performed in the lung segment(s) most affected on CT scan and/or chest X-ray. If no such segment was identified, BAL was performed in the right middle lobe and/or lingula.

Table 1. Baseline characteristics of 98 HSCT patients who underwent both bronchoscopy and noninvasive testing

Patients, *N*	98
Median age, years (range)	55 (13–75)
Female	38 (40)
Stem cell source	
Allogeneic*	86 (88)
Autologous	12 (12)
HLA matching (allogeneic transplants only)	
Matched related	21 (21)
Mismatched related	1 (1)
Matched unrelated	31 (32)
Mismatched unrelated	17 (17)
Cord and Cord haplo	16 (16)

Values denote *N* (%) unless specified otherwise. HSCT, hematologic stem cell transplant. * T-depleted peripheral stem cell transplant (43 patients), unmodified peripheral stem cell transplant (23 patients), bone marrow transplant (4 patients), and umbilical cord transplant (16 patients).

Statistical Analysis

Descriptive statistics were used to summarize patient demographic and clinical characteristics. Kaplan-Meier method was used to present the probability of 1-year overall survival and compare the 1-year OS between the timings of receiving bronchoscopy (≤4 vs. >4 days) as well as the presence or absence of management change by the bronchoscopy results. We used SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) in all analyses. All statistical tests were 2-tailed, and p values <0.05 will be considered statistically significant.

Results

Characteristics of the 98 patients undergoing bronchoscopy with BAL are summarized in Table 1. More than half, 86 patients (88%) had undergone allogeneic peripheral stem cell transplants, of whom 43 patients (50% of allogeneic stem cell transplants) were T-cell depleted. The underlying conditions necessitating transplant are summarized in Table 2. AML was the most common. Relevant clinical data at the time of the procedure are included in Table 3. Twenty-six patients (27% of all patients) suffered from GVHD. Among them, 17 had chronic GVHD (65% of GVHD patients), 7 patients had acute GVHD (27% of GVHD patients), and 2 patients had overlap GVHD (8% of GVHD patients). The most common organ affected was the GI tract (16 patients), skin (13 patients), liver (3 patients), mucosa (2 patients), and eyes (2 patients). Only one patient had bronchiolitis obliterans, a manifestation of rejection involving the lung.

Table 2. Primary diagnosis requiring transplant

Type of malignancy	*N* (%)
AML	28 (29)
Non-Hodgkin's lymphoma	17 (17)
Multiple myeloma	14 (14)
ALL	13 (13)
Myelodysplastic syndrome	10 (10)
Hodgkin's lymphoma	5 (5)
Myeloproliferative disease	3 (3)
CML	3 (2)
CLL/prolymphocytic leukemia	2 (2)
Plasmacytoid dendritic cell leukemia	1 (1)
Amyloid	1 (1)
Aplastic anemia	1 (1)

Table 3. Clinical characteristics at the time of bronchoscopy

Clinical data	*N* (%)
Intubated	23 (23)
Absolute neutrophil count <1,000	21 (21)
GVHD present	26 (27)
Pulmonary infiltrates on imaging	
Nonfocal	77 (79)
Focal	21 (21)
Timing of BAL to development of infiltrates	
Early BAL (0–3 days)	64 (65)
Late BAL (>3 days)	34 (35)
Timing of BAL to HCST	
Pre-engraftment (<30 days)	23 (23)
Intermediate post-engraftment (30–90 days)	12 (12)
Late post-engraftment (>90 days)	63 (64)

GVHD, graft-versus-host disease.

The median time to BAL from transplant was 161 days. All patients had CT scans showing new pulmonary infiltrates, and most pulmonary infiltrates were diffuse. The median time between CT scan and BAL was 3 days. Twenty-three patients (23% of all patients) were mechanically ventilated at the time of the procedure. Twenty-six patients (27% of all patients) died within 30 days of bronchoscopy, and 57 (58.2%) died within 1 year (Fig. 1a). Seventy patients received bronchoscopy early (≤4 days) and 28 received bronchoscopy late (>4 days). One-year overall survival was similar in the early and late groups (log-rank $p = 0.83$) (Fig. 1b).

Overall, there were 210 diagnostic results among the 98 patients who underwent noninvasive testing and bronchoscopy. Many patients had more than 1 diagnosis. The specific diagnoses, as well as the numbers uniquely iden-

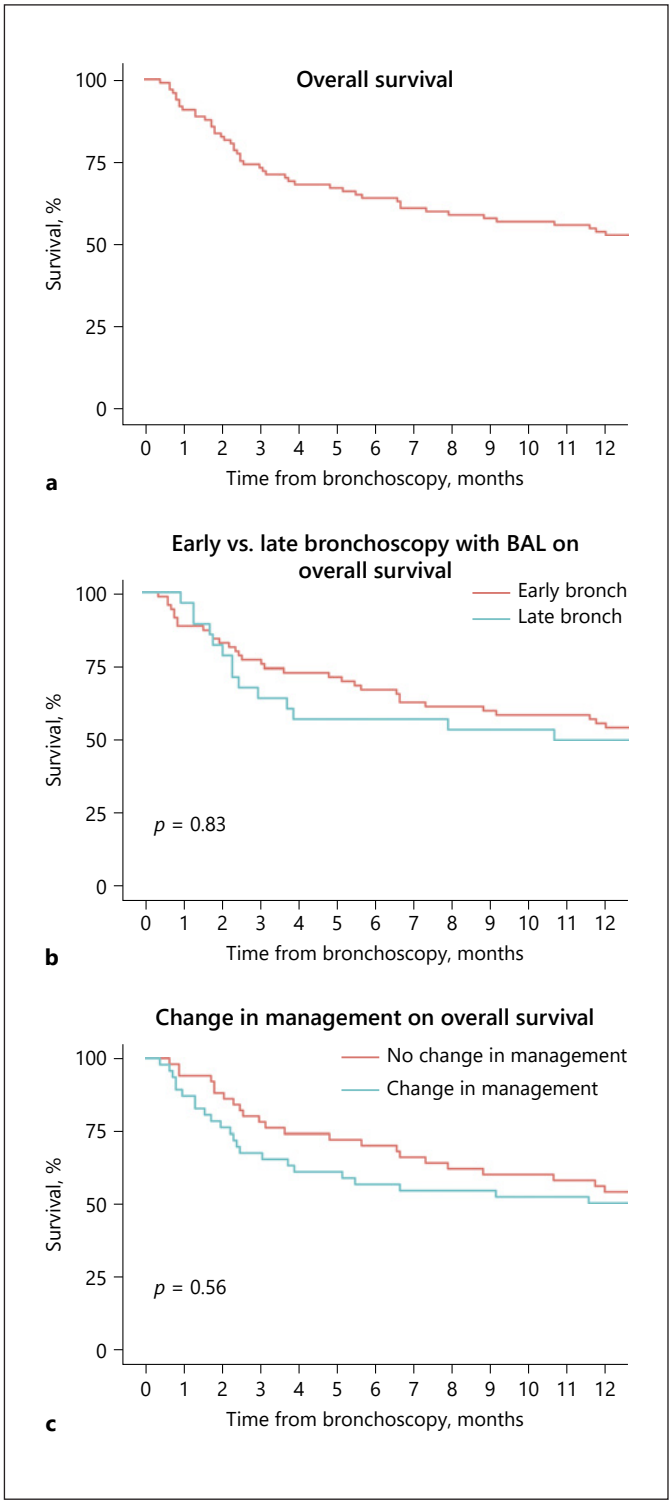

Fig. 1. Kaplan-Meier plot for overall 1-year overall survival from time of bronchoscopy (**a**). Kaplan-Meier plot for 1-year overall survival by the timing of bronchoscopy (**b**). Kaplan-Meier plot for 1-year overall survival by the presence or absence of any management changed based on bronchoscopy results (**c**). BAL, bronchoalveolar lavage.

tified by BAL and noninvasive testing, are summarized in Table 4. Viral infections, especially HHV6 and CMV, were the most common type of infection found. The most common bacterial findings were *Staphylococcus aureus* and coagulase-negative Staphylococcus. There were 174 positive results found among 93 patients via noninvasive means, and 127 positive results among 77 patients via BAL. Overall, noninvasive testing more commonly yielded bacterial and viral diagnoses. There were 84 unique findings on noninvasive testing that were not evident on bronchoscopy with BAL. Of 43 bacterial diagnoses, 42 were found noninvasively and 19 by BAL. Only one bacterial diagnosis was evident uniquely by BAL. Of 109 viral diagnoses, 101 were found noninvasively and 71 by BAL, and only 8 were not evident noninvasively.

In contrast, there were 36 unique findings on BAL that were not evident on noninvasive testing. Seven of these were diffuse alveolar hemorrhage, a condition that is not testable noninvasively. Most mycobacterial isolates could only be found at bronchoscopy with BAL. Nine of 11 patients with mycobacterial isolates (82% of all mycobacterial isolates) had organisms identified by BAL alone. Only 2 mycobacterial isolates were detected by noninvasive means, and only one was not evident by BAL.

Of the 77 patients among whom bronchoscopy with BAL yielded at least 1 positive result, 42 patients (55% of patients with positive BAL results) had a management change attributed to the procedure. Management change was not associated with overall mortality (log-rank $p = 0.56$) (Fig. 1c). Twelve patients received new antibiotics based on BAL results that were not seen on noninvasive testing. Among them were 3 patients who began new antifungal medications (1 receiving amphotericin and 2 receiving voriconazole). Of the remaining 21 patients in whom BAL was not diagnostic, 5 patients had a management change attributed to the procedure (24% of patients with negative bronchoscopy results). All five were the withdrawal of antibiotics.

Discussion/Conclusion

We examined 98 hematologic transplant recipients who underwent noninvasive testing along with a diagnostic bronchoscopy with BAL. Among these patients, 210 positive results were detected overall. When examining noninvasive testing and BAL individually, each yielded positive findings not found in the other. There were 36 diagnoses (17% of all diagnoses made) uniquely detected via BAL, and 84 diagnoses (40% of all diagnoses made)

Table 4. Diagnoses established by noninvasive testing and bronchoscopy

Infection type	Diagnoses among all patients, *n*	By noninvasive testing, *n*	Uniquely identified by noninvasive testing, *n*	By BAL, *n*	Uniquely identified by BAL, *n*
Bacteria					
Staphylococcus aureus	6	5	2	4	1
Coagulase-negative staphylococcus	3	3	2	1	0
Enterococcal species	5	5	4	1	0
Other Gram-positive rod	1	1	0	1	0
Pseudomonas aeruginosa	5	5	1	4	0
Klebsiella pneumonia	2	2	1	1	0
Escherichia coli	7	7	4	3	0
Legionella pneumophila	1	1	0	1	0
Other Gram-negative rod	1	1	0	1	0
Actinomyces	1	1	0	1	0
Mycoplasma	4	4	4	0	0
Burkholderia cepacia	1	1	1	0	0
Hemophilus influenzae	1	1	1	0	0
Nocardia	1	1	1	0	0
Moraxella catarrhalis	1	1	1	0	0
Strep viridians	1	1	1	0	0
Ehrlichia chaffeensis	1	1	1	0	0
Total bacteria	**43**	**42**	**24**	**19**	**1**
Viral					
CMV	31	30	12	19	1
HHV6	34	31	13	21	3
Rhinovirus/enterovirus	12	11	4	8	1
Influenza A	1	1	0	1	0
Influenza B	2	1	0	2	1
Adenovirus	8	8	2	6	0
Respiratory syncytial virus	5	4	1	4	1
Parainfluenza	4	4	1	3	0
Coronavirus (non-COVID-19)	3	2	0	3	1
Metapneumovirus	2	2	0	2	0
Bordetella pertusis	1	1	0	1	0
EBV	6	6	5	1	0
Total virus	**109**	**101**	**38**	**71**	**8**
Mycobacteria					
Mycobacterium avium complex	10	2	1	9	8
Mycobacterium kansasii	1	0	0	1	1
Total mycobacteria	**11**	**2**	**2**	**10**	**9**
Fungal					
Pneumocystis jiroveci	10	8	1	9	2
β-D-glucan	20	19	18	2	1
Aspergillus species	2	2	1	1	0
Aspergillus galactomannan	7	0	0	7	7
Scedosporium apiospermum	1	0	0	1	1
Total fungal	**40**	**29**	**20**	**20**	**11**
Noninfectious					
Diffuse alveolar hemorrhage	**7**	**na**	**0**	**7**	**7**
Total	**210**	**174**	**83**	**127**	**36**

uniquely detected with noninvasive testing. Unique diagnoses established noninvasively commonly included bacterial and viral infections. Gram-positive organisms, such as Staphylococcus species, were prevalent in the peri-engraftment period, HHV6 and CMV infections common in the post-engraftment period (up to 3 months post-transplant), and Mycobacteria and Pneumocystis infections prevalent late (i.e., after 3 months) from transplant. The spectrum and timing of pathogens seen in this study are representative of what has been reported previously among hematologic transplant [13, 14].

Over the past two decades, there have been several reviews that attempt to quantify the yield of bronchoscopy with BAL among the immunocompromised as well as the capacity of this test to affect management. In an early study, Raño et al. [6] reviewed 200 non-HIV immunocompromised patients who underwent both noninvasive testing and bronchoscopy to evaluate pulmonary infiltrates. One-quarter of these patients had undergone HSCT; the rest had a variety of other non-HIV immunocompromised conditions, and almost half were ill enough before bronchoscopy to require mechanical ventilation. The yield of noninvasive testing alone was 41%. Our patient population differed from Raño's because fewer patients were critically ill, and all had undergone HSCT. Nonetheless, the major conclusions are the same – that many patients ultimately undergoing bronchoscopy could have been diagnosed by noninvasive means.

Many other studies, however, imply that BAL continues to be helpful. In a prospective study, 148 cancer patients with respiratory failure were randomized to noninvasive testing versus BAL. One-third of these patients had undergone HSCT. While patients in the noninvasive testing arm had a higher diagnostic yield, no difference in intubation rates or 30-day mortality was observed between study groups [15]. A more recent study by Bauer et al. [9] found a 27% unique diagnostic yield with BAL among 618 cancer patients with acute respiratory failure, 40% of whom had hematologic malignancy. Bauer et al [9] found that bronchoscopy with BAL combined with noninvasive testing had a higher diagnostic yield than noninvasive testing alone, but bronchoscopy was also associated with worsening respiratory status, as well as a higher ICU and hospital mortality.

Inferences regarding these previously published studies – particularly those involving HSCT patients – are limited because many do not account for some important advances in diagnostic techniques, such as *Aspergillus galactomannan*, β-D-glucan, and PCR for *Pneumocystis jiroveci*, which offer the opportunity to diagnose respiratory disorders noninvasively. Reports involving hematologic malignancy patients, but not exclusively HSCT recipients, have concluded that measuring galactomannan in both serum and BAL is helpful to maximize the diagnostic yield of Aspergillus [16, 17]. Other studies have noted a higher yield by including more advanced methods of diagnosing Aspergillus, not employed in our studies, such as combining serum and BAL antigen with Aspergillus PCR [18]. Further studies on the usefulness of Aspergillus PCR are needed to better define its sensitivity and specificity in different specimens, such as sputum and BAL. Using PCR for the detection of *Pneumocystis jiroveci* in BAL exclusively or combined with serum β-D-glucan has been shown to have excellent yield [19, 20]. Moreover, not all these studies consider the yield of *Pneumocystis jiroveci* PCR from sputum. Several studies have shown that PCR of sputum samples has comparable sensitivity and specificity for *Pneumocystis jiroveci* to BAL [21, 22]. While the small number of *Pneumocystis jiroveci* patients in our population precludes similar conclusions, it may be that sputum PCR alone is a viable diagnostic alternative for this infection and that BAL might be best reserved for those who are thought to have *Pneumocystis jiroveci* combined with other infections. Nevertheless, despite the heterogeneity of the patient populations and significant variations in patients' clinical status and management outcomes compared to our study, these studies cumulatively imply that bronchoscopy with BAL remains a helpful diagnostic tool, albeit with a very wide range of diagnostic yields [16, 23, 24].

There have been different findings in some studies regarding the relationship between BAL timing and outcomes. Shannon et al. [8] studied a transplant population and found a significant difference in outcome when the BAL was done within 4 days of admission. While we did not find any such relationship, we nonetheless feel a reasonable strategy is to pursue noninvasive testing while planning for a bronchoscopy to be performed within 24–48 h. If noninvasive testing negates the need for BAL, there is usually time to avoid the latter procedure.

What can be concluded about the respective role of noninvasive testing and BAL in the evaluation of HSCT patients with respiratory complications? While both modalities achieved at least one diagnostic result among a substantial proportion of patients in our study, each appeared to detect some disorders more easily than others. Noninvasive testing appeared more useful for bacterial and viral infections; bronchoscopy with BAL appeared more useful for atypical mycobacterial isolates, detecting galactomannan, and was the only test capable of finding

diffuse alveolar hemorrhage – a significant cause of mortality among HSCT patients [25]. Pursuing both modalities, as others have found, allows one to combine tests, such as serum β-D-glucan with BAL PCR for *Pneumocystis jiroveci*, which may increase overall yield, emphasizing the complementary role that noninvasive testing can have together with BAL [20]. The data described herein, and other studies, cumulatively imply that the utility of noninvasive testing performed together with BAL might be more effective than either strategy performed separately and that they can complement each other in the evaluation of HSCT recipients with pulmonary complications.

It is worth noting that the inherent heterogeneity of our patient sample limits making any general conclusions regarding the benefits of testing in every circumstance. For instance, 35% of patients were within 30 days of transplant, a period characterized by profound immunosuppression, cytopenia, and susceptibility to bacterial, Aspergillus, and some viral infections. Nearly two-thirds of patients were more than 90 days from transplant, a period characterized by susceptibility to Mycobacteria, *Pneumocystis jiroveci*, other viral infections, and GVHD. As viral infections, such as CMV and HHV6 were found through noninvasive means alone commonly, it is conceivable that a sample of patients studied in the immediate post-transplant period, near engraftment, may find noninvasive more sensitive relative to BAL. Ideally, more studies are needed with patients stratified by time from transplant and clinical severity of respiratory illness to better understand the relative benefits of these modalities.

Strengths of this study include the fact it exclusively studied HSCT recipients, rather than immunocompromised patients in general, and therefore, the results may be easier to extrapolate toward this unique group of patients. It is also one of the few such studies to address noninvasive testing, including viral PCR and fungal molecular markers, in addition to bronchoscopy with BAL. Shannon et al. [8] studied exclusively HSCT patients but did not explore the yield of noninvasive testing.

Limitations include a targeted population derived from a single urban cancer center, where patients may be managed differently than elsewhere. It is somewhat heterogenous, representing different times from transplant and different severities of respiratory illness. The study is susceptible to problems inherent to its retrospective design, including confounding by indication. These limitations, when taken together, may limit the generalizability of results to the population at large or populations with different inherent characteristics.

We found both bronchoscopy with BAL and noninvasive tests to be valuable tools in evaluating pulmonary disorders among HSCT recipients. However, their relative sensitivity varies depending on the underlying diagnosis. They should be considered complementary strategies in diagnosing respiratory disease among HSCT recipients.

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Statement of Ethics

Research described herein was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors listed herein fulfilled the 4 criteria of authorship, as stated by the International Committee of Medical Journal Editors, including (1) substantial contribution to study design and data acquisition, (2) drafting of the manuscript, (3) final approval of the manuscript to be published, and (4) agreement of the accuracy and integrity of the data.

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