Peer review file
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Reviewer A

Comment 1: Authors have submitted a clear and well written manuscript describing the safety and diagnostic yield of flexible bronchoscopy for pulmonary infections in patients with and without haematological malignancies. Perhaps the addition of data on percentage of patients who required a change in their clinical management as a consequence of results from flexible bronchoscopy will add further weight and significance to their results.

Reply 1: First of all, we were happy to learn that the reviewer judged our manuscript as clear and well written. We agree that changes in the clinical management of patients according to the results of flexible bronchoscopy, e. g. initiation, termination, or any change in the anti-infective therapy, are highly relevant in this context. Hence, we have retrieved data about the clinical management of hematological patients after bronchoscopy from our records showing a change in the therapeutic strategy in 36.9% which is higher compared to an earlier study by Pagano and colleagues (*Annals of Medicine 1997*).

Changes in the text: This data has been added in the revised version of our manuscript (page 8, lines 9-11).

Reviewer B

Comment 1: It will be helpful to know whether results from bronchoscopy change patients' management.

Reply 1: This is a very important point which has also been brought up by reviewer A. We have therefore analyzed the clinical management of patients with hematological malignancies after bronchoscopy and included this information in our revised manuscript. Briefly, bronchoscopy results lead to a change in the therapeutic strategy in 36.9% which is higher compared to an earlier study by Pagano and colleagues (*Annals of Medicine 1997*). This data has been added in the revised version of our manuscript.

Changes in the text: This data has been added in the revised version of our manuscript (page 8, lines 9-11).

Comment 2: The severity of respiratory symptom and coagulation, platelet status will determine complications of bronchoscopy, this factor should be noted and compared.

Reply 2: We highly agree with the reviewer that factors potentially increasing the risk of complications have to be taken into account when performing an invasive procedure such as flexible bronchoscopy. In general, severe complications rarely occurred in our patient population. Interestingly, as already mentioned in our manuscript (page 8, lines 25-26 and page 9 line 1 in the revised manuscript) bleedings rarely occurred even in patients with thrombocytopenia which is in accordance with

the literature (Nandagopal L et al.; *Transfusion 2016*). Unfortunately, there is no standardized work-up of a patient´s respiratory status, e. g. arterial blood gas analysis before bronchoscopy in our institution. Therefore, the decision whether a bronchoscopy can safely be done in an individual patient was made clinically. Interestingly, the rate of AEs or SAEs was only slightly higher in patients with underlying cardiovascular or pulmonary disease (14.1% vs. 18.8%; p=0.1185).
Changes in the text: Nevertheless, we are aware that this is a limitation of our study which is mentioned in the discussion section now (page 12 lines 9-10).

Comment 3: There is no tuberculosis in the yield. Is there a low prevalence of this infection?
Reply 3: Indeed, the prevalence of tuberculosis is low in Germany. However, as this is a highly relevant pathogen, we have added the yield for tuberculosis in table 3.

Comment 4: What are the explanation or hypothesis on the difference yields in these two groups. It seems that state of immunosuppression may look the same.
Reply 4: In our study, the overall diagnostic yield did not differ between patients with and without hematological malignancies. Only when cultures positive for Candida were not considered as clinically relevant a higher diagnostic yield was observed in procedures with hematological patients. As the diagnostic yield in non-hematological patients on immunosuppression was very similar compared to hematological patients, the differences in diagnostic yield between hematological and non-hematological patients are indeed most likely due to the presence of immunosuppression.
Changes in the text: We have clarified this aspect in our revised manuscript now (page 10 line 25 and page 11 lines 1-5).

Comment 5: What is the usual practice in the author's institution regarding bronchoscopy request such as early or late bronchoscopy in this situation.
Reply 5: The usual practice for aplastic hematologic patients in general follows the recommendations of the German Infectious Disease Working Party (AGIHO) of the German Association for Hematology and Oncology (DGHO) according to published guidelines (Ruhnke M et al., *Mycoses 2018, PMID*: 30098069; Ruhnke M et al., *Ann Oncol. 2012, PMID: 21948809*; Maschmeyer J et al., *Ann Oncol. 2015, PMID: 24833776*). This means that CT scans are performed early in the disease process and if these reveal signs of infection/infiltration, bronchoscopy/BAL are performed if the patient's general condition allows so. In patients who are not aplastic (both with and without underlying hematological malignancy) the indication for bronchoscopy is made individually based on the clinical history, laboratory findings and imaging (typically CT scans).
Changes in the text: We have added this information to the M&M part in our revised manuscript (page 4 lines 4-12).
Comment 6: The detail of bronchoscopy and BAL procedure should be

described in detail such as how to select the segment and amount of fluid etc.
Reply 6: We thank the reviewer for this important comment.
Changes in the text: We have added this information in the M&M section of our revised manuscript (page 5 lines 1-7).

Reviewer C

The authors conducted a retrospective study at a single institute to evaluate the role of bronchoscopy with BAL in the diagnosis of lung infection, and concluded with similar results between patients with and without hematological malignancy. The manuscript was well written, but there were some major issues need to be addressed. The following comments were provided.
Comment 1: The role of bronchoscopy in the diagnosis of pulmonary infiltrates in immunocompromised patients remains controversial. In addition to the wide variation in the diagnostic yield, the safety issue is another concern as the authors mentioned (reference 4) and excluded critically ill patients in the study.
Reply 1: We absolutely agree with the author that the indication for bronchoscopy for the diagnostic work-up of pulmonary infiltrates in immunocompromised patients is still a matter of debate. Open questions could only be answered by randomized trials, though the conception of such a trial would be challenging in this highly heterogenous patient population. Therefore, most evidence in this context is drawn from retrospective studies which - in spite of all limitations - can still provide useful information.
Changes in the text: We have tried to make these aspects clearer in the discussion of our revised manuscript (page 12 lines 13-18).

Comment 2: What is the implication from the study results in the daily clinical practice?
Reply 2: Though our study did not prospectively assess diagnostic yield and safety of flexible bronchoscopy for the diagnosis of pulmonary infections it can still provide useful information. As neutropenic hematological patients are a highly vulnerable patient population, the benefits of an invasive procedure such as flexible bronchoscopy must be weight against the risks. One implication which can be drawn from the study results could be that additional diagnostic information which are of clinical relevance (see point 5.) can be provided by bronchoscopy with a good safety profile when national recommendations for the indication are followed and when the patient's general condition allows so (see point 3.).

Comment 3: The indication of bronchoscopy is not mentioned. Was it done on the lung infiltrates persisted on broad-spectrum antibiotics?
Reply 3: This is an important point which has also been raised by reviewer B. The usual practice for aplastic hematologic patients in general follows the recommendations of the German Infectious Disease Working Party (AGIHO) of the

German Association for Hematology and Oncology (DGHO) according to published guidelines (Ruhnke M et al., *Mycoses 2018, PMID*: 30098069; Ruhnke M et al., *Ann Oncol. 2012, PMID: 21948809*; Maschmeyer J et al., *Ann Oncol. 2015, PMID: 24833776*). This means that CT scans are performed early in the disease process and if these reveal signs of infection/infiltration, bronchoscopy/BAL are performed if the patient's general condition allows so. In patients who are not aplastic the indication for bronchoscopy is made individually based on the clinical history, laboratory findings and imaging (typically CT scans).
Changes in the text: We have added this information to the M&M part in our revised manuscript (page 4 lines 4-12).

Comment 4: Is the microorganism, bacteria, virus, or fungus isolated from the BAL pathogenic? How to define it as the pathogen of lung infiltrates?
Reply 4: We thank the reviewer for bringing up this important issue. Indeed, not all microorganisms which are isolated in samples from the lungs are clinically relevant. Therefore, we have also calculated diagnostic yield omitting cultures positive for Candida as pneumonia related to Candida is extremely rare (Meerseman W et al., *Intensive Care Med 2009*). Nevertheless, microorganisms apart from Candida detected in respiratory samples might as well be clinically irrelevant. This is supported by the finding that bronchoscopy results lead to a change in the clinical management of hematological patients in 36.9% whereas the microbiological yield (without Candida) was 62.7%.
Changes in the text: This aspect has now been included in the discussion section of our revised manuscript (page 10 lines 20-23)

Comment 5: The percentage of change of the antibiotic strategies or other treatment after BAL, followed by improved outcome need to be addressed, as it is the most important thing to support the procedure.
Reply 5: This is a very important point which has also been brought up by reviewers A and B. We have therefore analyzed the clinical management of patients with hematological malignancies after bronchoscopy and included this information in our revised manuscript. Briefly, bronchoscopy results lead to a change in the therapeutic strategy in 36.9% which is higher compared to an earlier study by Pagano and colleagues (*Annals of Medicine 1997*). However, whether the altered clinical management due to the results of the bronchoscopy is associated with better clinical outcome cannot be determined by retrospective data analysis which is definitively a limitation of our study. Such a question could only be answered by a randomized trial which would be very challenging to design (see point 1.).
Changes in the text: The mentioned aspects have been added to the revised version of our manuscript (page 8, lines 9-11 and page 12 lines 14-18).

Comment 6: The immunocompromised patients in the group without hematological

malignancy were various, which may affect the results.
Reply 6: We thank the reviewer for this helpful comment and have included this point in the discussion section now (page 10 line 25 and page 11 lines 1-3).

Comment 7: What is the implication of the line 180-182 in the daily clinical practice?
Reply 7: Our data showed that diagnostic yield in immunocompromised patients not suffering from a hematologic malignancy did not differ from hematological patients and was therefore higher compared to immunocompetent patients. Though the heterogeneity of immunocompromised patients in clinical practice and the limitations of our study must be taken into account our data still support the use of flexible bronchoscopy for the diagnosis of pulmonary infections especially in the context of immunosuppression.
Changes in the text: We have now mentioned this aspect in our manuscript (page 11 lines 1-5).

Comment 8: Bronchoscopy performed in a patient with platelet count less than 50/ nl ran the risk of massive hemoptysis.
Reply 8: We absolutely agree that pulmonary bleeding is a serious complication of fiberoptic bronchoscopy. In our study most bleedings were considered as minor even in patients with a low platelet count. The only severe bleeding occurred after a transbronchial biopsy in a patient with a platelet count of more than 50/nl. In contrast, severe bleedings are rare events when performing bronchoscopy with broncho-alveolar lavage only (Nandagopal L et al., *Transfusion 2016*). Therefore, in our institution we perform bronchoscopy with BAL with a platelet count of more than 20/nl in accordance with different guidelines (Du Rand IA et al., *Thorax 2013*; Mohan A, *Lung India 2019*).

Comment 9: The line 95-97 have grammar problem.
Reply 9: We have corrected this in the revised version of our manuscript.

Reviewer D
Comment 1: The comparison between the two patient populations is an interesting goal. About methods it's necessary defined how BAL was performed.
Reply 1: We thank the reviewer for this important comment. We have added this information in the M&M section of our revised manuscript (page 5 lines 1-7).

Comment 2: About exclusion criteria it's necessary clarify when the patient with respiratory failure is excluded (for example with paO2 criteria, P/F criteria and so on).
Reply 2: This very important issue has also been noticed by reviewer B. Unfortunately, there is no standardized work-up of a patient´s respiratory status, e. g. arterial blood gas analysis before bronchoscopy in our institution. Therefore, the

decision whether a bronchoscopy can safely be done in an individual patient was made clinically. Interestingly, the rate of AEs or SAEs was only slightly higher in patients with underlying cardiovascular or pulmonary disease (14.1% vs. 18.8%; p=0.1185).

Changes in the text: Nevertheless, we are aware that this is a limitation of our study which is mentioned in the discussion section now (page 12 lines 9-10).

Comment 3: About bleeding there is no definition of mild and severe bleeding, it's necessary clarify.

Reply 3: We thank the reviewer for bringing up this important issue. Bleedings requiring endotracheal intubation, or the placement of a bronchus blocker were categorized as severe. Any other bleedings which resolved by the end of the procedure (spontaneously or after endobronchial instillation of vasoconstrictors) were considered as mild.

Changes in the text: We have added the information in the M&M section of our revised manuscript (page 5 line 26 and page 6 line 1).

Comment 4: Finally, it may be interesting to know transient respiratory failure is linked to the type of sedation.

Reply 4: We thank the reviewer for bringing up this interesting aspect. We have therefore compared the 3 sedation regimes mostly used in our study in the whole population: The incidence of transient respiratory failure during the procedure was 8.1% under combined sedation with midazolam/fentanyl/propofol, 5.0% with midazolam/fentanyl and 7.0% with midazolam/propofol (p=0.4943).