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Reviewer A

This is a review of the outcome of bronchiectasis admissions in Korea focusing on the presence or absence of significant haemoptysis. While of value, there are a number of concerns.

Comment 1. The authors in the title, abstract and discussion need to make clear that the findings are "in Korea". The findings may very well not be generalisable to other countries with different causes of bronchiectasis. Your findings are very much dominated by post-infective (especially TB) bronchiectasis which is a very different pathological process to active ongoing disease such as with NTM.

Reply: We added "in Korea" in the title, abstract, and discussion.

Changes in the text:

Title:

1) Hemoptysis as the presenting manifestation of bronchiectasis-associated hospitalization in Korea

2) Abstract-Methods:

We retrospectively collected the data of patients with bronchiectasis-associated hospitalization at a tertiary referral center in Korea, and classified them into the hemoptysis and infective exacerbation (IE) groups.

3) Abstract-Conclusions:

In Korea, bronchiectasis patients hospitalized with hemoptysis exhibit a distinct phenotype, and are more likely to have previous pulmonary TB, mycetoma, and bronchial artery

hypertrophy.

4) Discussion-first paragraph:

In the present study conducted in Korea, >50% of the patients with bronchiectasis-associated hospitalization were categorized to the hemoptysis group.

5) Discussion, study limitation paragraph:

The findings may very well not be generalizable to other countries with different causes of bronchiectasis.

Comment 2. The definition of haemoptysis is pretty subjective "more blood than sputum". It is more normal to classify it in terms of volume of blood. Lots of previous literature (not cited other than the 1 paper on 100 ml - there are many more suggesting different cut offs from 50 ml up) clearly shows the biggest predictor of outcome with haemoptysis is the volume at presentation.

Reply: We modified the definition of the hemoptysis group to indicate the volume of hemoptysis. We revised sentences in the Abstract and Materials and Methods section.

Changes in the text

1) Abstract-Methods: The presence of hemoptysis was defined as a volume of expectorated blood larger than 10 mL per 24 hours.

2) Second paragraph in the "Materials and Methods-Study design and population":

The patients were categorized into two groups: 1) bronchiectasis patients with more than 10 mL of hemoptysis per 24 hours (hemoptysis group) and 2) those with clinical symptoms of respiratory tract infection, with or without less than 10 mL of hemoptysis per 24 hours (IE group).

Comment 3. My biggest concern is that the comparison is haemoptysis without infection vs infection. In clinical practice, there are 3 groups, haemoptysis without infection, haemoptysis with infection and infection without haemoptysis. We really should see the data divided in this manner.

Reply:

Of the 267 patients in the hemoptysis group, only 10 patients showed evident respiratory infection. Patients with respiratory infection and small amounts of hemoptysis (<10 mL/24 hours) were classified as the infective exacerbation group. We compared the 'hemoptysis without infection' and 'hemoptysis with infection' groups, and the results are as follows. Although the number of patients in the 'hemoptysis with infection' group was too small to obtain definitive conclusions, there was no statistically significant difference in clinical characteristics and outcomes between the two groups. Since the number of patients in "hemoptysis with infection" group was quite small and there were no differences in clinical characteristics from "hemoptysis without infection" group, we integrated these patients and analyzed them as a "hemoptysis" group.

Clinical characteristic of the patients with hemoptysis (n=267)

Characteristics	Hemoptysis without infection (n=257)	Hemoptysis with infection (n=10)	p-value
Age, years	66 (59-73)	66 (62-78)	0.408
Male sex	139 (54.1)	3 (30.0)	0.197
Smoking			
Ever-smoker	91 (35.8)	6 (60.0)	0.179
Pack-years	0 (0-20)	15 (0-25)	0.268
BMI (kg/m^2)	21.4 (19.2-23.9)	19.1 (18.6-22.4)	0.159
Heavy drinker	19 (7.5)	1 (10.0)	0.515
ECOG	1 (1-1)	1 (1-2)	0.202
CCI	0 (0-1)	0 (0-1)	0.712
Antithrombotic drugs	59 (23.0)	1 (10.0)	0.465
Colonization			
Pseudomonas aeruginosa	9 (3.5)	1 (10.0)	0.322
Other pathogens	5 (1.9)	1 (10.0)	0.206
Systolic blood pressure, mmHg	150 (134-167)	147 (128-160)	0.368

Pulse rate, /min	90 (80-102)	99 (93-114)	0.042
Respiratory rate, /min	20 (18-21)	20 (18-24)	0.249
Symptoms at presentation			0.111
Duration of symptom, days	1 (1-3)	3 (2-3)	0.069
Cough	188 (73.2)	10 (100)	0.068
Sputum production	135 (52.5)	9 (90.0)	0.023
Dyspnea	95 (37.0)	6 (60.0)	0.185
Fever	13 (5.1)	9 (90.0)	<0.001
Altered mental status	2 (0.8)	1 (10.0)	0.109
Chest pain	6 (2.3)	1 (10.0)	0.237
Massive hemoptysis	83 (32.3)	4 (40.0)	0.733
Bronchial artery embolization	73 (28.4)	4 (40.0)	0.481
Mechanical ventilation	3 (1.2)	0 (0.0)	>0.999
Vasopressor infusion	3 (1.2)	0 (0.0)	>0.999
Systemic corticosteroids	72 (28.0)	3 (30.0)	>0.999
30-day mortality	4 (1.6)	0 (0.0)	>0.999
In-hospital mortality	3 (1.2)	0 (0.0)	>0.999
Length of hospital stay, days	6 (4-8)	7 (6-9)	0.081
Etiology			
Idiopathic	88 (34.2)	2 (20.0)	0.503
Previous pulmonary TB	120 (46.7)	5 (50.0)	>0.999
Previous NTM pulmonary disease	13 (5.1)	0 (0.0)	>0.999
Post-infectious			
Measles	18 (7.0)	2 (20.0)	0.167
Pertussis	8 (3.1)	1 (10.0)	0.295
Unclassified RTI	4 (1.6)	0 (0.0)	>0.999
COPD	5 (1.9)	0 (0.0)	>0.999

Data are presented as median (interquartile range) or n (%). BMI, body mass index; CCI, Charlson comorbidity index; TB, tuberculosis; NTM, nontuberculous mycobacterial; RTI, respiratory tract infection; COPD, chronic obstructive pulmonary disease.

Computed tomography findings

CT findings	Hemoptysis without infection (n=257)	Hemoptysis with infection (n=10)	p-value
Cystic bronchiectasis	90 (35.0)	4 (40.0)	0.745
Number of involved lobes	2 (1-3)	3 (2-4)	0.099
Involved lobes ≥ 3	125 (48.6)	8 (80.0)	0.060
Modified Reiff score	3 (2-6)	5 (4-7)	0.104
Fungus ball	39 (15.2)	0 (0.0)	0.366
Tuberculosis-destroyed lung	25 (9.7)	1 (10.0)	>0.999
Emphysema	51 (19.8)	3 (30.0)	0.428
Bronchial anthracofibrosis	29 (11.3)	2 (20.0)	0.327
Bronchial artery hypertrophy on enhanced CT	113 (45.4)	5 (62.5)	0.476

Data are presented as n (%).

CT, computed tomography.

Comment 4. I am not convinced the statistical analysis is valid. To answer the question of "is haemoptysis a good or bad prognostic indicator" then you really need to do a matched case-control study to minimise the huge differences you report in key factors like age, sex, ECOG status etc. Alternatively, you could do propensity matching, but I would suggest a specialist statistical review. Trying to compare the outcome of patients who have some bleeding without any sepsis, with patients who have sepsis and a much higher rate of mechanical ventilation does not seem like a valid comparison clinically.

Reply:

We consulted a statistician regarding the statistical analysis. As you mentioned, age, sex, and ECOG status can act as confounding variables in the comparison of short-term mortality between the hemoptysis and IE groups. Therefore, the odds ratio (OR) for 30-day mortality of "no or minimal hemoptysis" was estimated after propensity matching using age, sex, and ECOG, and OR (95% confidence interval) was 1.70 (0.40-7.26, p = 0.477). When propensity matching was performed using age and sex, OR (95% CI) of 'no or minimal hemoptysis' was 2.89 (0.90-9.29, p = 0.075). It is described in the Discussion section that the characteristics of the IE group, such as the poor performance status, may be related to the higher risk of short-term mortality.

Usually, to estimate effect sizes after controlling for confounding variables, we can either do propensity score matching on the confounding variables or utilize a regression model to estimate adjusted OR controlled for them. Propensity score matching can reduce the sample size relative to the original sample size, causing selection bias. In this study, the number of mortality cases was small, which limits the use of the propensity score matching method. Therefore, adjusted OR values were presented using the multiple logistic regression. The

analysis result of this study that the mortality of the IE group was high cannot be said to be incorrect because the direction of the OR value did not change when using the propensity score matching method or using the model.

Changes in the text: 5th paragraph

"Although the characteristics of the IE group, such as poor performance status, may be related to the higher risk of short-term mortality, 'no or minimal hemoptysis' in multiple logistic regression analysis was an independent predictor of 30-day mortality."

Comment 5. Given the overwhelming data on volume of blood as a predictor, this needs to be included in the model, possibly using different cutoff values to establish if there is a key threshold.

Reply:

The following Table shows the amount of hemoptysis of patients in the hemoptysis group.

Amount of hemoptysis (mL/24 hours)	n=267	30-day mortality (n=4)
10-30	71 (26.6)	1
30-300	163 (61.0)	3
>300	33 (12.4)	0

Since the small number of non-survivors based on 30-day mortality in the hemoptysis group (n=4), it is considered difficult to conduct an analysis on the predictors of short-term mortality according to the amount of hemoptysis. Further research on large population is needed to analyze the amount of hemoptysis as a predictor of short-term mortality in bronchiectasis-associated hospitalization.

Reviewer B

Major Comments

Comment 1. This is an interesting analysis of hemoptysis in bronchiectasis patients, with results that are likely what many experts wouldn't have expected, specifically that hemoptysis was not predictive of mortality. Given the evidence that hemoptysis patients overall were less likely to have the various markers of "severe" bronchiectasis, the authors have shown us why these results were seen. I think that this is an important message from these results, that the authors should give a little more attention to in the Discussion. Specifically, I think most experts would predict that hemoptysis would be more common in patients with more severe bronchiectasis, while the results suggest that this is not the case; hemoptysis is not clearly associated with severity of bronchiectasis, rather it is associated with specific underlying characteristics not necessarily related to severity, eg. history of TB, smoking.

Reply:

We revised the fourth paragraph of the "Discussion" as follows.

Changes in the text:

This study demonstrated that in bronchiectasis-associated hospitalization, patients with hemoptysis had less severe bronchiectasis than those with IE. Our study suggests that hemoptysis phenotype is not associated with severe bronchiectasis, but with specific etiology and radiological findings. In the present study, previous pulmonary TB, mycetoma, and bronchial artery hypertrophy were factors independently associated with the hemoptysis group.

Comment 2. The authors have provided evidence that the mechanism/phenotype of patients with hemoptysis vs IE are different, yet in the analyses presented in Table 4, they combine

both groups when presenting predictors of mortality. Would perform these analyses for each individual group---hemoptysis and IE. I suspect that different predictors might be found in the 2 groups.

Reply:

Due to small number of non-survivors based on 30-day mortality in the hemoptysis group (n=4), it is considered difficult to obtain meaningful results when logistic analysis is performed to find factors predicting 30-day mortality in the hemoptysis group. Further research on large population is needed to find factors in predicting short-term mortality of patients with hemoptysis.

Minor Comments

Comment 1. Abstract/Discussion---It seems incorrect to say that hemoptysis could be protective. I don't think hemoptysis saves lives. Rather, it makes more sense to say that an infective exacerbation may be more dangerous than an exacerbation characterized by hemoptysis, or probably even more accurate to say that patients with IE are at higher risk based on their underlying characteristics.

Reply:

We revised sentences in the abstract and "Discussion" section.

Changes in the text

1) Abstract-Conclusions:

Hemoptysis is associated with a lower risk of short-term mortality compared to IE in bronchiectasis-associated hospitalization.

2) Discussion-fifth paragraph:

The present study suggests that patients with IE have a higher risk of 30-day mortality than those with hemoptysis in bronchiectasis-associated hospitalization.

Based on these findings, it can be assumed that the long-term mortality of the hemoptysis group might be lower than that of the IE group.

3) Discussion-last paragraph:

Hemoptysis is associated with a lower risk of short-term mortality compared to IE in bronchiectasis-associated hospitalization.

Comment 2. Table 1-Change "heavy drinker" to "Excessive alcohol use" or something similar

Reply:

We changed "heavy drinker" to "excessive alcohol use", as recommended.

Comment 3. Table 1—The outcomes (30-day mortality, In-hospital mortality, Length of hospital stay) are interspersed in between the patient characteristics. Would change the order, putting all the patient characteristics first and the outcomes at the bottom.

Reply: We changed the order as recommended.

Comment 4. In the results, would describe patient characteristics of the 2 groups first and then describe the outcomes.

Reply:

We revised the second paragraph of the "Results-Baseline and clinical characteristics".

Changes in the text:

In the hemoptysis group, 89 (33.3%) patients experienced massive hemoptysis and 79 (29.6%) patients underwent bronchial artery embolization. Compared with the IE group, the hemoptysis group was significantly younger and had lower proportions of males and ever-smokers, lower ECOG-PS and CCI, and a lower frequency of P. aeruginosa colonization (Table 1). Regarding etiology, previous pulmonary TB was significantly more common in the hemoptysis group than in the IE group. The hemoptysis group had a significantly higher percent predicted FEV1 and significantly lower disease severity scores, such as FACED and BSI than the IE group. In terms of the treatment outcome, the hemoptysis group had a significantly lower 30-day mortality (4 [1.5%] vs. 20 [9.0%], $p < 0.001$) and in-hospital mortality (3 [1.1%] vs. 16 [7.2%], $p = 0.001$), as well as a significantly shorter length of stay (6 days [4-8 days] vs. 10 days [7-13 days], $p < 0.001$) than the IE group.

Comment 5. Would refer to mycetoma, not "fungus ball"

Reply: We changed "fungus ball" to "mycetoma" in the manuscript.