The Efficacy of Bronchoscopy versus Computerised Tomography in Initial Identification of Patients with Hemoptysis

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ABSTRACT

The effects of bronchoscopy and chest CT on early evaluation of patients with hemoptysis are still controversial. PubMed, EMBASE, and the Cochrane Library databases were systematically searched. Odds ratio (OR) was applied to assess the utility of bronchoscopy for hemoptysis etiology and site in comparison with CT in the various clinical processes. A total of 23 studies were included (N=4635). The results showed that bronchoscopy implied a lower overall diagnostic accuracy, especially in identifying the etiology of hemoptysis, compared with CT (OR= 0.34, 95% CI: [0.23, 0.51], OR=0.21, 95% CI: [0.14, 0.31], respectively). When the results of radiograph were normal, the effectiveness of bronchoscopy was significantly weaker than that of CT (OR=0.32, 95% CI: [0.22, 0.45]). In the cases of massive hemoptysis, bronchoscopy and CT had no statistical significance for identifying bleeding (OR=0.27, 95% CI: [0.02, 3.18]). The study suggested that bronchoscopy did not show superior diagnostic accuracy than CT for patients with hemoptysis at the first visit.

Key Words: *Hemoptysis, Bronchoscopy, CT, Meta-analysis.*

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INTRODUCTION

Hemoptysis is defined as bleeding originating from the lung alveoli or airways of the lower respiratory tract,[1] which is a common and challenging symptom that accounts for 0.2% of all hospitalised patients.[2] However, there are a wide spectrum and variations in etiology reported according to the time of publication, geographic location, and medical care facility.[3-5] It is crucial to manage patients with hemoptysis depending upon initial identification of the etiology and localisation of the bleeding.

Bronchoscopy is the main procedure of choice, which plays a key role in detecting the etiology and the sites of bleeding. Naidich *et al.* explained that bronchoscopy outlined the exact location and submucosal extension of tumors.[6] Indeed, bronchoscopy could better assess upper airways and endobronchial abnormalities and could provide histopathological and microbiological samples.[7] However, other studies showed that bronchoscopy could not localise the bleeding site and cause as effectively as compared with CT.[8,9]

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Patients with hemoptysis may seek treatment in the Emergency Department or visit general practice or respiratory medicine.[10,11] The strategy for the investigation of patients with hemoptysis remains under discussion. It is important to decide which procedure to adopt first, in assessing hemoptysis.

Therefore, the purpose of this review was to evaluate the optimal timing of bronchoscopy in a series of patients presenting with hemoptysis.

METHODOLOGY

This review was conducted according to the series of patients with hemoptysis visits. Figure 1 shows the patient's initial evaluation flow framework and key questions that guided the review.

KQ1. Should the bronchoscopy be used as routine workup to screen all patients with hemoptysis?
KQ 1a. Should the bronchoscopy be used as a location strategy?
KQ 1b. Should the bronchoscopy be used as a cause strategy?
KQ 2. Should the bronchoscopy be used for all patients with normal radiographs?
KQ 3. How does bronchoscopy contribute to the diagnosis with negative findings on CT?
KQ 4. Should the bronchoscopy be used to routinely investigate massive hemoptysis patients?
KQ 5. Should the bronchoscopy be used to screen all hemoptysis with a high risk of malignancy?

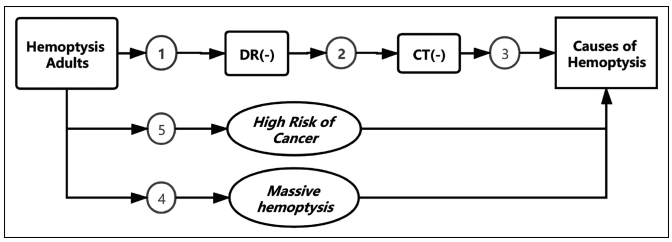

Figure 1: Patient pathway flow framework and key questions (KQs).

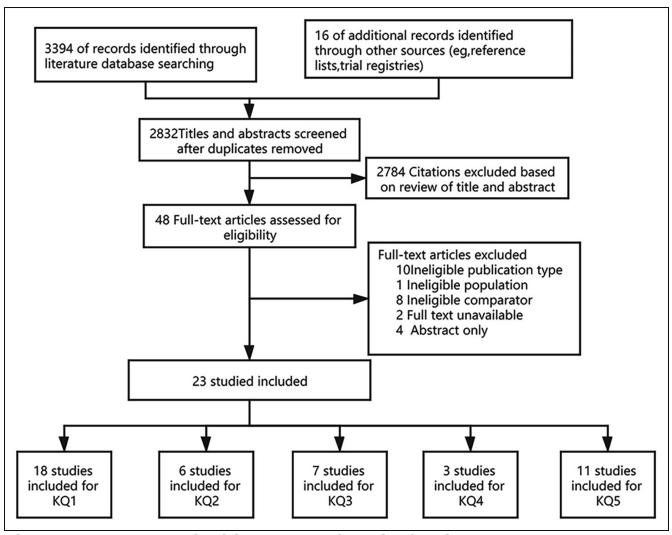

Figure 2: Summary of evidence search and selection.

A systematic and comprehensive search was conducted in these databases: Embase, PubMed and Cochrane Library to December 1, 2020. The search terms included "hemoptysis" OR "airway bleeding" OR "pulmonary bleeding", "bronchoscope" OR "bronchoscopy" OR "fiberoptic bronchoscopy" OR "FOB"; and "tomography, X-ray computed" OR "computed tomography" OR "CT". ClinicalTrials.gov and Cochrane databases were also searched for unpublished literature. All the reference lists of the included articles and review articles about hemoptysis were also selected and evaluated. The last surveillance was conducted on December 12, 2020.

Two investigators (HDX and HKS) independently conducted the reviews of the titles, abstracts, and full-text articles to determine eligibility, using a common set of criteria for each key question (KQ). The divergence in opinions was resolved through discussion or with the help of a third reviewer (HD). The review included studies that included: patients presenting with hemoptysis older than 16 years, and both CT and bronchoscopy were compared. The following exclusion criteria were used: Studies including patients with previous known diagnosis of disease relative to hemoptysis; incomplete or duplicated data; letters, case reports or review articles.

For massive hemoptysis, the cutoff value ranged from 100 to 600 ml of blood produced in 24 hours.[12,13] Physicians only estimate the volume and do not know the real volume. For this review, the definitions of massive hemoptysis that the included studies used, were accepted.

To avoid overlapping patient populations, the data were compared *via* recruitment years and data sources. If a patient population was found to overlap, only the article with the most comprehensive population was included. This resulted in the exclusion of one article from this systematic review.[14] For each included study, one investigator (HDX) extracted the information about the first author; publication year; designs of the studies; characteristics and demographics, sample size, duration of research and follow-up; causes of hemoptysis; and comparators and outcomes. The second investigator (HKS) checked the results for completeness and accuracy.

Two independent investigators (HDX and HD) assessed the quality of each included study, using the Newcastle-Ottawa Scale (NOS). The cross-sectional study, as a modified version of the case–control study criteria, got a maximum score of 7. Scores ≤5 were considered low quality. Disagreements were resolved by discussion and consensus.

Findings for each question were summarised in tabular and narrative form. For the meta-analysis, odds ratios (ORs) with 95% confidence intervals (95% CIs) by forest plot for dichotomous comparisons across all studies were pooled. Heterogeneity between studies was assessed using Cochran's Q test and Higgins I^2 statistics. $P < 0.1$ or $I^2 \geq 50\%$ was defined as high heterogeneity; then, the effect size by means of random or fixed models for heterogeneous or homogeneous studies were estimated, respectively. A subgroup analysis was also performed to determine whether the study design affected the results of this study. A sensitivity analysis was performed by removing the data of each individual study in turn each time. Potential publication bias was evaluated by the Begg funnel plot. Statistical analysis was performed using Review Manager (version 5.4). Statistical significance was rendered as $p < 0.05$.

RESULTS

The literature search yielded 3,394 articles and 22 articles through the references; of which, 23 studies[3-5,7-9,15-30] met the inclusion criteria for the overall systematic review of the comparison of bronchoscopy and chest CT imaging (Figure 2).

The 23 eligible studies were published between 1990 and 2020 and included a total of 4,635 participants from 13 countries (Table I). The majority of participants were males (52.6%-91%) and current or former smokers (24-91%). The main causes included malignancy (0.4-41.1%), bronchiectasis (2-57.1%), pneumonia or airway infection (3.2-69%), and tuberculosis (0.6-50.9%). Cryptogenic hemoptysis account for 5.4-83.8%.

Meta-analysis was performed to evaluate the effectiveness of bronchoscopy for hemoptysis etiology and bleeding site detection in comparison with CT, and the main results for each key question are summarised below (Table II).

In general, compared with CT, bronchoscopy implied an initial overall effectiveness, especially regarding identification of the etiology of hemoptysis (OR=0.34, 0.21, respectively). No significant difference in finding the location of hemorrhage was noted for bronchoscopy and CT (OR=0.00, Figure 3).

Table I: Main characteristics of studies included.

Study	Type	Location	Research time	Follow-up	Patients (n)	Men,n (%)	Age (years)	Smokers n (%)	Amount	Malignancy,n(%)	Bronchiectasis, n(%)	Infection,n(%)	TB,n(%)	Cryptogenic, n(%)	Quality assessment (NOS)
Naidich-1990[15]	Retro	USA	1988.4-1989.7		58	50□86□	56	NA	NA	24(41.4)	10(17.2)	NA	NA	NA	**6**
Patricia-1993[16]	Pros	England	1991.3-1992.12		91	64□70□	63.14	79(87)	Mild-moderate	35(38.4)	14(15.4)	3(3.2)	NA	NA	6
McGuinness-1994[17]	Pros	USA	1991.7 -1992.4		57	47(82)	59(26-74)	49(86)	Mild-moderate	7(12)	14(25)	4(7)	9(16)	11(19)	6
Hirshberg-1997[18]	Retro	Israel	1980.1- 1995.8		208	127□61□	58±17	110(53)	ALL	39(19)	41(20)	70(34)	3(1.4)	17(8□	6
Tak-1999[3]	Pros	India	NA		50	33(66)	37.2(15-68)	12(24)	Mild-moderate	3(6)	12(24)	1(2)	1(2)	33(66)	7
Hsiao-2001[19]	Retro	USA	1988-2000		28	19(68)	54.6□16-91)	NA	Massive	4(14.3)	16(57.1)	0	2(7.1)	2(7.1)	6
Abal-2001[20]	Pros	Kuwait	1998.1-1998.11	1y	52	42(81)	42.4(16-86)	31(60)	ALL	5(9.6)	11(21.2)	3(5.8)	17(32.7)	13(25)	7
Fidan-2002[4]	Retro	Turkey	2000.1-2000.12		108	79(75)	51.74±17.51	65(60)	ALL	37(34.3)	27(25)	11(10.2)	19(17.6)	9(8.3)	6
Revel-2002[21]	Retro	USA	1995.1- 1999.6		80	57(71)	58□20-93)	NA	Massive	9(11)	25(31)	8(10)	15(19)	8(10)	7
Tsoumakidou-2006[22]	Pros	Greece	2001.1 - 2003.11	2-4y	168	137(81)	NA	145(86)	ALL	24(13)	48(26.1)	35(19)	8(4.3)	10(5.4)	7
Khalil-2007[8]	Retro	France	2year-period		80	67(84)	56(28-86)	NA	ALL	4(5)	23(28.7)	1(1.25)	19(23.7)	27(33.7)	6
Thirumaran-2009[23]	Retro	UK	2001.3-2005.12		270	162(60%)	60	246(91)	NA	26(9.6)	20(7.3)	16(69)	4(1.5)	16(5.8)	7
Uzun-2010[7]	Pros	Turkey	2003.11-2006.9		178	136(76%)	54.3±16	119(66.9)	ALL	53(29.7)	23(12.9)	14(7.8)	11(6.2)	10(5.6)	7
Lee-2012[24]	Retro	Korea	2003.1-2009.10	2.1y	228	120(52.6)	51.6	98(43.0)	NA	1(0.4)	NA	9(3.9)	NA	191(83.8)	7
Mohammad-2015[25]	Retro	Iran	NA		40	22(55)	44(22-77)	NA	NA	2(5%)	11(27.5)	3(7.5)	6(15)	8□20□	5
Bønløkke-2015[9]	Retro	Denmark	2000 2010	2y	269	159(59.0)	55.4±15.3	NA	Mild-moderate	16□6.0%□	63□23.4□	NA	NA	NA	6
Seon-2016[26]	Retro	South Korea	2005.1-2009.7		161	94 (58)	57(48-68)	NA	ALL	4(2.5%)	36(22.4)	11(6.8)	31(19.3)	36(22.4)	7
Nielsen-2016[27]	Retro	Italy,Denmark	2009.1-2014.11		326	206 (63)	60.5□15.3	262(80)	mild-moderate	13(4.0%)	19(5.8)	53(16.3)	2(0.6)	171(52.5)	6
muhammad-2017[28]	Retro	India	1 year		175	160(91)	57.31±13.57	NA	ALL	54(33.72%)	NA	NA	84(50.9)	NA	6
Arooj-2018(1)[5]	Retro	Ireland	2011–2012		155	82(53)	59±12.2	NA	NA	24(16%)	3(2)	73(47)	NA	25(16)	6
Arooj-2018(2)[5]	Pros	Ireland	2013-2016	6m	182	116(64)	61±10.2	NA	NA	33(18%)	17(9)	91(50)	NA	35(19)	7
Mondoni-2019[29]	Retro	italy	2013.7_2015.9		486	336(69)	67□53-76□	327 (54)	ALL	NA	NA	NA	NA	NA	6
christian-2020[30]	Retro	Denmark	2006.1-2016.11		1185	726(61)	57.5±14.55	871□74□	NA	0	26(2.2)	149(12.6)	NA	989(83.5)	6

Table II: Summary of evidence for evaluation of hemoptysis.

Key question and topic	No. of studies	No. of participants	Summary of main findings
KQ1: Initial evaluation	18	3472	OR=0.34, 95% CI: [0.23, 0.51, p<0.001, I^2 = 90%
KQ1a: Bleeding site	6	847	OR=0.00, 95% CI: [-0.04, 0.05], p=0.47, I^2 = 0%
KQ1b: Bleeding cause	13	1374	OR=0.21, 95% CI: [0.14, 0.31], p<0.001, I^2 = 75%
KQ2: DR negative	6	401	OR=0.32, 95% CI: [0.22, 0.45], p=0.23, I^2 = 27%
KQ3: CT negative	7	738	Only 4 meaningful positive cases
KQ4: Massive hemoptysis	3	123	OR=0.27, 95% CI: [0.02, 3.18], p=0.001, I^2 = 87%
KQ5: High risk of cancer	11	175	OR=0.12, 95% CI: [0.05, 0.28], p=0.76, I^2 = 0%

When the radiograph was normal, the effectiveness of bronchoscopy was significantly weaker than that of CT (OR = 0.32, Figure 4).

Among the 738 patients with a negative CT, bronchoscopy only selected 4 tumor patients. Hirshberg *et al*.[18] from Jerusalem, Israel reported that CT alone failed to locate three lung cancers that were successfully found by bronchoscopy. Lee *et al*. showed that only one in 228 patients was diagnosed with malignancy by initial bronchoscopy.[24]

In massive hemoptysis, no statistical significance was noted between bronchoscopy and CT (OR =0.27, 95% CI: [0.02, 3.18], supplementary Figure 5).

In the screening of hemoptysis with a high risk of lung cancer, bronchoscopy was dramatically weaker than CT (OR=0.12, supplementary Figure 6).

Significant heterogeneity was noted between the studies in this analysis, and the authors conducted a sensitivity analysis to confirm robustness. After excluding NOS score <6,[25] the OR remained 0.34 *vs*. 0.36. In a second subgroup analysis, the authors calculated a pooled OR for studies with retrospective case recruitment (n=10) and prospective studies (n=8). The retrospective group had an OR of 0.32 (95% CI, 0.18-0.56), and the prospective group had an OR of 0.36 (95% CI, 0.22-0.59). Finally, the authors excluded individual study estimates one at a time to examine the influence of each study on the overall OR. The omission of any one study did not appreciably change the pooled OR (OR=0.32-0.36).

No potential publication bias was evident for the studies that evaluated bronchoscopy for patients with hemoptysis. The site of bleeding, massive hemoptysis, and publication bias could not be analysed due to the low number of studies.

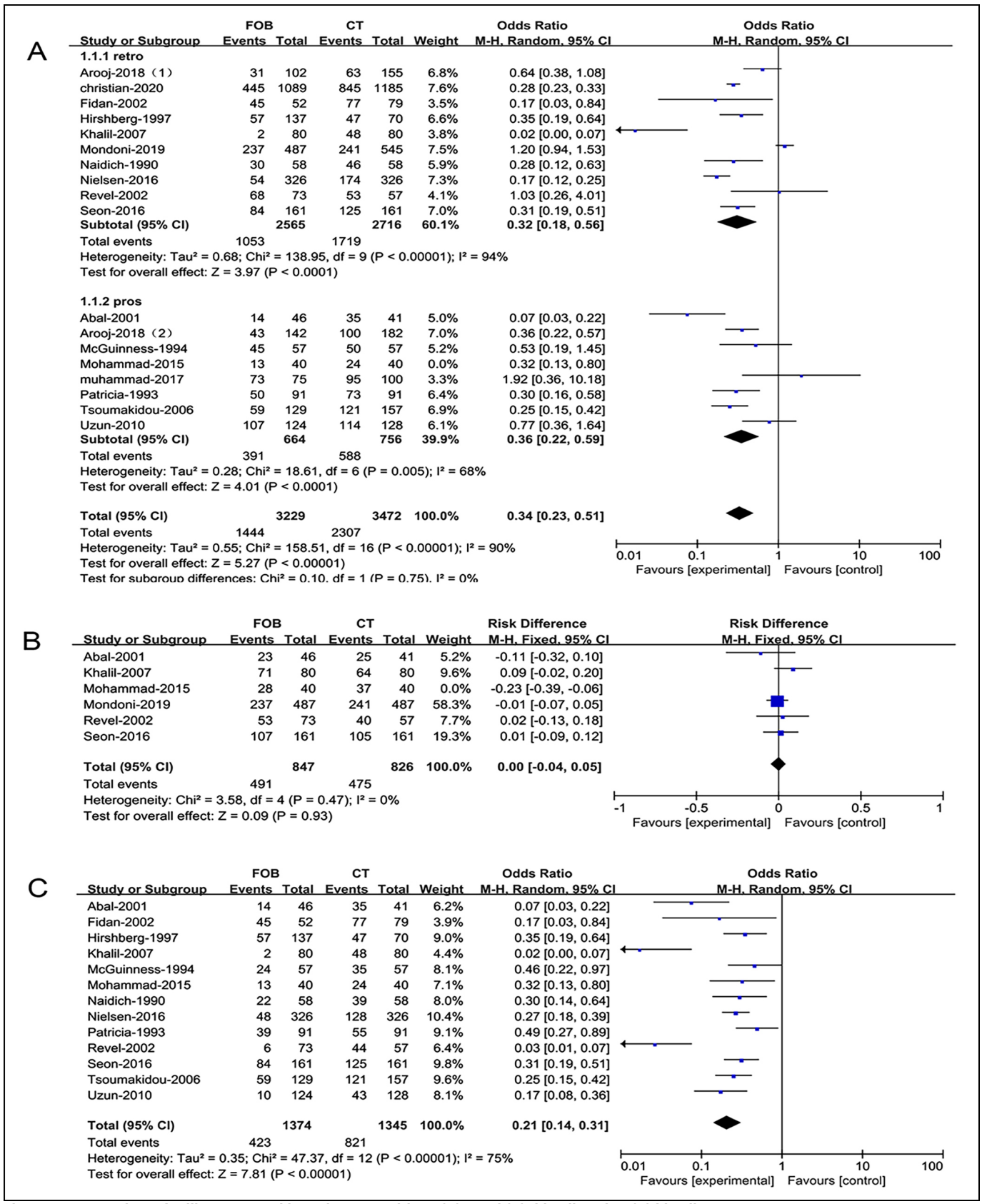

Figure 3: Forest plots of utility compared bronchoscopy with CT (A), total (B), bleeding site, (C) bleeding cause.

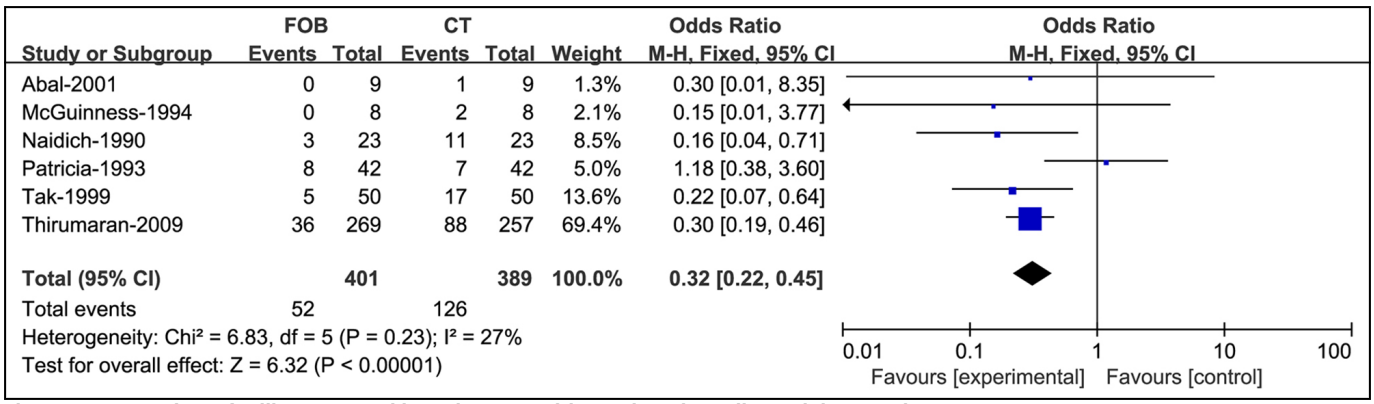

Figure 4: Forest plots of utility compared bronchoscopy with CT when the radiograph is normal.

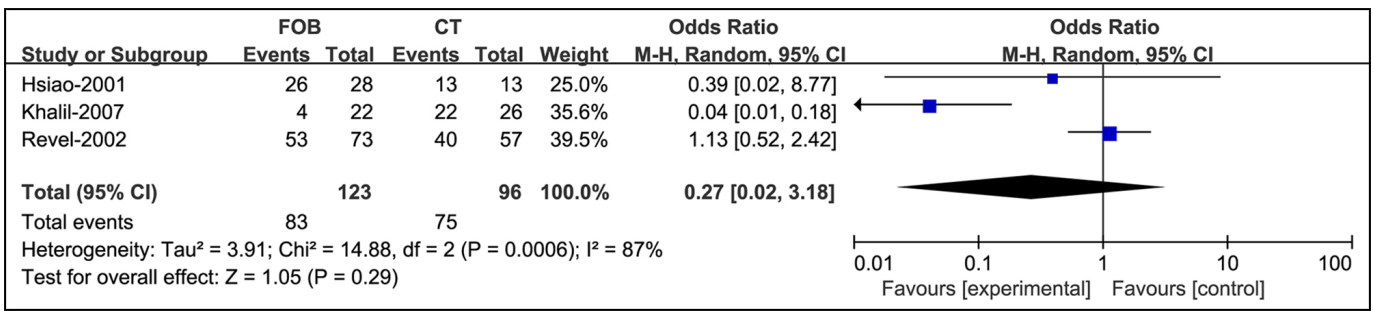

Figure 5: Forest plots of utility compared bronchoscopy with CT in massive hemoptysis.

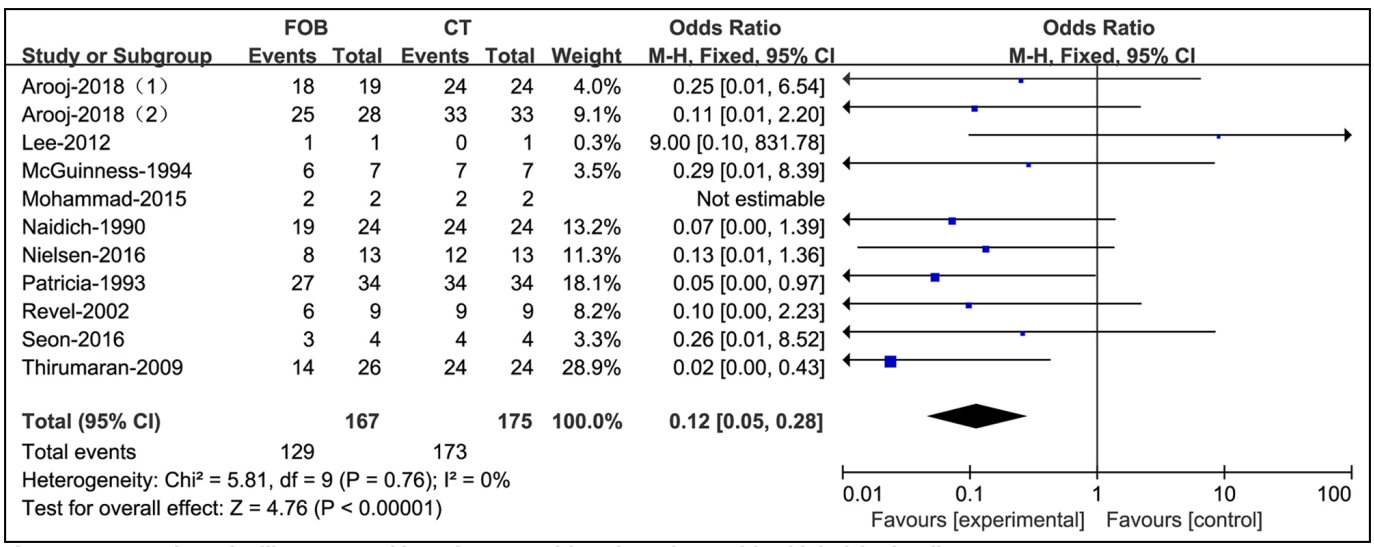

Figure 6: Forest plots of utility compared bronchoscopy with CT in patients with a high risk of malignancy.

DISCUSSION

In this review, a meta-analysis of 4,635 subjects in 23 studies from PubMed, Embase, and the Cochrane Library was conducted to compare the utility of bronchoscopy and CT to determine the site and cause of hemoptysis along with the initial evaluation flow. It was found that bronchoscopy plays a less effective role in identifying the causes of hemoptysis than CT in any circumstance.

The strengths of the study include a comprehensive, systematic review of the literature and that the incidence and mortality of patients with hemoptysis was analysed and pooled accurately with appropriate epidemiologic methods. Jones reported that the annual incidence was approximately 0.1%.[2,11] Among those patients, those with massive hemoptysis account for about 5-15%[21,31] and often come the emergency department at first.[10] Therefore, the conclusion of this study could be useful in clinical practice.

Several diagnostic techniques are prescribed to assess hemoptysis. Chest radiography, bronchoscopy, and CT were the most frequently employed tools. For centuries, bronchoscopy has been considered the gold standard to detect bleeding sites.[6]

However, according to the findings and recent studies, chest

CT and bronchoscopy may have similar utility in identifying the bleeding site (OR=0.00, 95% CI: [-0.04, 0.05]). A study by Revel *et al.* demonstrated equivalence between bronchoscopy and CT to localise the source of bleeding (73% *vs*. 70%, respectively).[21] Indeed, given the development of highly sensitive imaging techniques[1] combining the most ground-glass attenuation (GGA) with specific lesions,[31] CT demonstrated a remarkably higher ability to detect the exact location of bleeding than bronchoscopy both in early ([130/252 (51.6%) *vs*. 73/190 (38.4%), p=0.006)] and delayed examinations [(111/293 (37.9%) *vs*. 65/261 (24.9%)].[29] In a word, bronchoscopy did not show significant advantages than CT in identifying the source of hemoptysis.

Hemoptysis can be a sign of many different diseases varying from infections to malignancy. Effective evaluation flow is needed to identify the underlying pathogenesis so that the appropriate treatment can be employed. All the studies included in the review demonstrated that CT, rather than bronchoscopy, should be applied to determine the types and causes of hemoptysis, including tumor, bronchiectasis, pneumonia, *etc.* Bronchoscopy is better used to identify the pathogen in infectious diseases, if the CT could not identify them accurately.

First, it is unnecessary to use bronchoscopy to screen each patient with hemoptysis (KQ1); second, when chest radiography is interpreted as normal, it is suggested that CT is superior to bronchoscopy (KQ 2). Nielsen *et al.* reported that the sensitivity on CT was 0.92 (p<0.05), and the combination of FOB and computed tomography (CT) did not increase accuracy of diagnosis of malignant or nonmalignant causes in hemoptysis patients (0.97, p=0.58).[32]

The only issue is the third key question (KQ 3); should bronchoscopy be used for patients with negative findings on CT. Indeed, there were many cryptogenic hemoptysis events, accounting for 5.4-83.8% of all hemoptysis events in the included studies and other published studies. This review showed that in 738 negative CT scans, only 4 cancers were detected by bronchoscopy based on two studies in 1997 and 2012.[18,24] In contrast, Petersen *et al.* retrospectively reviewed 1,185 patients in Denmark, with no malignancy suspected on computed tomography and no malignant disease by initial bronchoscopy.[30] In 609 patients, lung cancer developed in 1.5% of patients (n=9) in the following five years.[14] In addition, bronchoscopists may need to intervene in iatrogenic bleeding since they perform procedures, such as transbronchial biopsies, which are associated with significant bleeding in 5.1-10.6% of cases.[33,34] Bronchoscopy is only provided to limited patients due to limited medical resources. Therefore, patients without evidence of hemoptysis would likely benefit from an initial evaluation of bronchoscopy.

Additionally, it is recommended that in patients with hemoptysis, whose chest CT was negative for the cause of hemoptysis, a thorough, careful history and full examination were essential parts to distinguish from pseudohemoptysis.[35] Among the 228 patients with hemoptysis and no identified cause on chest CT, Lee *et al.* found 43 cases that were not real hemoptysis.[24] Savale *et al*. found anticoagulant and antiplatelet treatments predisposing patients to hemorrhage in 24% of their patients.[36]

Massive hemoptysis represents one of the most challenging conditions in clinical practice. Severe hemoptysis accounts for only 10-15% of all hemoptysis cases,[18] but is associated with a significant mortality rate as high as 80% without timely and effective management. There is no consensus on a uniform cutoff value for hemoptysis to be considered massive; the present inclusive studies reported 200, 300 and 400 ml per 24 hours.

It is better to use the magnitude-of-effect definition,[12,13] which rates the ability to clear tracheobronchial blood and impair lung function.[1] Therefore, in this review, the author's definition was accepted.

Promptly identifying the location and cause of bleeding would vary depending on the condition of the patient. However, in this review, bronchoscopy used in patients with massive hemoptysis was not significantly different from CT (95% CI: [0.02, 3.18]) in general. Revel *et al.* reported that CT was comparable for identifying the bleeding site (70% *vs*. 73%) and much superior in determining the cause of bleeding (77% *vs.* 8%).[21] Similar results were reported in Khalil's studies (site: 80 *vs*. 88.8%, cause: 60% *vs.* 2.5%).[8] Indeed, the clinical focus on patients with massive hemoptysis is the rescue process rather than diagnosis. If the patient is relatively stable, bronchial artery embolisation (BAE) has been proven to be more effective in severe hemoptysis with reported immediate termination of bleeding rates from 70% to 99%.[37-39] CT with IV contrast has been used with the intention of procedural planning for BAE, which was not discussed in our review. However, in unstable situations, it is preferable to secure the patient's airway before transfer to the operating room. Bronchoscopy could be performed at the bedside with an experienced bronchoscopic team and adequate equipment. Bronchoscopy may help clear the airways by aspirating or isolating the involved airway by selective endobronchial intubation and controlling the hemorrhage by using vasoconstrictive substances, or glue.[40,41] Whether and when bronchoscopy should be determined according to the condition of the individual, but the only use for diagnosis is not needed.

Malignancy was one of the most frequent causes of hemoptysis with an incidence of 0.4-41.4%, according to this review. A recent European observational study showed that malignancies were the most frequent etiology,[42] and the majority of neoplasms were lung cancers (106/116, 91.3%) with endobronchial lesions (84/116, 72.4%). Hemoptysis may be an early symptom of lung cancer, and a thorough investigation of patients with this symptom may lead to early diagnosis.[43] The Danish Lung Cancer Group (DLCG) recommended in their guidelines that CT and bronchoscopy should be performed in patients who are smokers and 40 years of age or older.

However, in this review, all the studies suggested that the application of initial bronchoscopy was futile in the detection of lung cancer compared to CT (OR=0.12). Petersen *et al.* reported that all cryptogenic patients with hemoptysis (n=989) had no malignant disease by a prompt investigation, and lung cancer developed in 1.5% of patients in the following five years.[30] This finding is comparable to results from previous studies. Tsoumakidou *et al*. found no new lung cancers in 189 hemoptysis patients during an average follow-up of 2.7 years.[22] Bønløkke *et al*. studied 78 patients with no pathology on CT and found no malignancy within two years of initial referral.[9] Additionally, Nielsen *et al.* reported that the sensitivity of detecting lung cancer by CT was 0.92. Combining CT and bronchoscopy in these cases would not provide a better diagnostic yield given that the sensitivity was 0.97, and the difference was insignificant (p=0.58). Bronchoscopy did not identify any malignant etiologies not already diagnosed by CT.[32]

Considering the possible complications and limited benefits of the procedure, it is reasonable that there is no need to perform direct bronchoscopy in all patients with hemoptysis. Moreover, due to likely underlying malignancies, there is a need for a dedicated follow-up of hemoptysis patients.

There are also certain limitations to this study. First, significant heterogeneity existed among the studies in this analysis. This finding is predictable given the presence of interstudy differences in study design (prospective and retrospective), enrolled populations with a wide spectrum of etiologies, and variations in the reported prevalence among different geographic locations. The heterogeneity among the studies remained despite the extraction of low-quality records, usage of a random-effects model and subgroup analyses. Finally, the quantitative meta-analysis was performed based on secondary data, which may lead to inaccurate results.

CONCLUSION

This study suggested that bronchoscopy did not show superior diagnostic accuracy than CT for patients with hemoptysis at the first visit, particularly for those with normal radiography results. It is recommended that CT is firstly used rather than bronchoscopy at this circumstance. However, bronchoscopy could be used to further determine the pathology and pathogen cause. Each case with massive hemoptysis needs to be individually approached according to the patient's condition and team's abilities. Bronchoscopy should not be used exclusively for diagnosis.

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CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
DH, KH, DH: Conceived the study idea, designed the study and wrote the initial draft, collected the data and performed the statistical analyses.
ZL: Supervised the statistical analyses and writing.
All authors critically revised the manuscript for intellectual content and approved the final version.

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