Original Article

# Extent of Lung Involvement and Serum Cryptococcal Antigen Test in Non-Human Immunodeficiency Virus Adult Patients with Pulmonary Cryptococcosis

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## Abstract

**Background:** Serum cryptococcal antigen (CrAg) test is the most used noninvasive method to detect cryptococcal infection. However, false-negative CrAg test is not uncommon in clinical practice. Then, the aim of this study was to investigate the factors associated with false-negative CrAg test among non-human immunodeficiency virus (HIV) adult patients with pulmonary cryptococcosis and its clinical features.

**Methods:** One hundred and fourteen non-HIV adult patients with pulmonary cryptococcosis, proven by biopsy, were retrospectively reviewed. Finally, 85 patients were enrolled; 56 were CrAg positive (CrAg+ group) and 29 were negative (CrAg− group). It was a cross-sectional study. Then, baseline characteristics, underlying diseases, clinical symptoms, laboratory findings, and chest radiological findings were reviewed and analyzed. Chi-square test was used to analyze categorical variable. Odds ratio (*OR*) was used to measure correlation. Student's *t*-test was obtained to analyze continuous variable.

**Results:** No difference in baseline characteristics, underlying diseases, clinical symptoms, and laboratory findings were found between two groups ($P > 0.05$ in all). Nevertheless, diffuse extent lesion was 82.1% in CrAg+ group and 10.3% in CrAg− group ($\chi^2 = 40.34$, $P < 0.001$; $OR = 39.87$).

**Conclusions:** Among patients with limited pulmonary involvement, a negative serum CrAg does not preclude the diagnosis of pulmonary cryptococcosis. However, among patients with extensive pulmonary involvement, serum CrAg is a useful diagnostic tool for pulmonary cryptococcosis. Furthermore, we also noticed that the untypical and mild presentations with extensive pulmonary lesion might be the features of pulmonary cryptococcosis, which needs further investigation.

**Key words:** Chest Radiological Findings; Cryptococcal Antigen; Extensive Pulmonary Lesion; Pulmonary Cryptococcosis

## Introduction

*Cryptococcus neoformans-Cryptococcus gattii* species complex is a nonmycelial, budding encapsulated yeast-like fungus, which can lead to significant infections, ranging from asymptomatic pulmonary colonization to lethal meningoencephalitis.[1,2] Although cryptococcosis is a typical systemic opportunistic pathogen in immunocompromised hosts such as human immunodeficiency virus (HIV) infection, pulmonary cryptococcosis is not rare in patients without recognized immunologic defect.[3,4] Some studies showed that the most common radiological presentations of pulmonary cryptococcosis were lung nodules and

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masses that required differentiation from lung cancer.[5,6] Several studies demonstrated that symptoms of pulmonary cryptococcosis are often untypical and can emulate those of lung cancer including cough and expectoration.[7,8] Biopsy of suspected pulmonary cryptococcosis from lung nodule or mass can be challenging. At present, serum cryptococcal antigen (CrAg) test is the most used noninvasive method to detect cryptococcal infection. However, in clinical practices, having negative serum CrAg is common among patients with pulmonary cryptococcosis. The purpose of the current study was to explore the factors associated with positive serum CrAg test among non-HIV adult patients with biopsy-proven pulmonary cryptococcosis.

## Methods

### Ethical approval

This cross-sectional study was approved by the Research Ethics Committees of the Zhujiang Hospital of Southern Medical University (No. 2016-HXNK-007) and was conducted according to the *Declaration of Helsinki*. The clinical information, records, and data involved in this study were analyzed anonymously without intervention. Thus, informed consent was waived.

### Study subjects

From January 2012 to December 2016, HIV-negative adult patients (more than 18 years old) with pulmonary cryptococcosis from Zhujiang Hospital of Southern Medical University, Second Affiliated Hospital of Chongqing Medical University, and First Affiliated Hospital of Chengdu Medical College were enrolled in our study. Pulmonary cryptococcosis was diagnosed by percutaneous transthoracic needle biopsy (PTNB) or postoperative biopsy with hematoxylin and eosin, periodic acid–Schiff, and methenamine silver staining. Meanwhile, the patients combined with extrapulmonary cryptococcosis, such as cerebral cryptococcosis, were excluded from our investigation. According to the criteria, 114 non-HIV adult patients with pulmonary cryptococcosis, proven by biopsy, were retrospectively reviewed. Finally, 85 patients were enrolled; 56 were CrAg positive (CrAg+ group) and 29 were negative (CrAg− group) [Figure 1].

### Data and information collection

The data and information were collected without intervention, including age, gender, symptoms, chest radiological findings, underlying diseases, concentrations of hemoglobin (Hb), platelet counts (PLT), white blood cell (WBC) counts, neutrophils counts, and plasma procalcitonin (PCT) level. Then, serum CrAg was detected by lateral flow assay (IMMY, Norman, OK, USA). Symptom scores, the number of symptoms a patient presented, were calculated. Chest radiological findings were reviewed. We divided the radiological findings into two conditions, diffuse extent lesion and limited extent lesion. Then, we defined diffuse extent lesion as lesions in multiple lobes, multiple lesions in a single lobe, or the lesion diameter >3 cm in a single lobe. The limited extent lesion was defined as the lesion (the diameter <3 cm) in a single lobe.

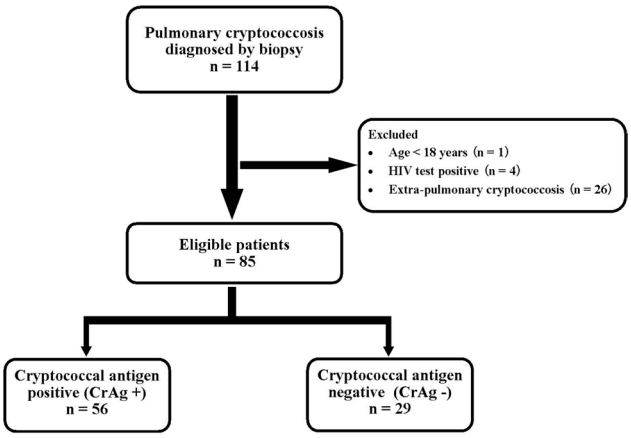


**Figure 1:** Flow diagram of the study patient selection. Two HIV-positive patients combined with extrapulmonary cryptococcosis. Two HIV-positive patients combined with pulmonary cryptococcosis. One pulmonary cryptococcosis patient was under 18 years old. HIV: Human immunodeficiency virus.

### Data analysis

Statistical analyses were performed with SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA). Chi-square test was used to analyze categorical variable. Odds ratio (*OR*) was used to measure correlation. Student's *t*-test (mean ± standard deviation) was obtained to analyze continuous variable. $P < 0.05$ indicated a significant difference.

## Results

### Patients' characteristics

One hundred and fourteen patients were diagnosed with pulmonary cryptococcosis by PTNB or postoperative biopsy between January 2012 and December 2016 from Zhujiang Hospital of Southern Medical University, Second Affiliated Hospital of Chongqing Medical University, and First Affiliated Hospital of Chengdu Medical College. Moreover, 29 patients were excluded by excluding criteria. Finally, 50 males and 35 females were enrolled in our study. The serum CrAg test was positive in 56 participants and was negative in 29 participants [Figure 1 and Table 1].

### Underlying diseases

Fifteen cases (17.6%) complicated with underlying diseases. Among them, type 2 diabetes mellitus (T2DM) (7.1%) and kidney transplantation (4.7%) were the two most common underlying diseases. Moreover, one case was diagnosed as kidney transplantation combined with T2DM. Then, other underlying diseases included systemic lupus erythematosus (1.2%), astrocytoma (1.2%), nephrotic syndrome (1.2%), nasopharyngeal cancer (2.4%), and Langerhans cell histiocytosis (1.2%). Then, no significant difference in rates of underlying diseases was observed between two groups.

**Table 1: Baseline characteristics of non-HIV adult patients with pulmonary cryptococcosis**

| Characteristics | CrAg+ | CrAg− | Statistical values | *P* |
|---|---|---|---|---|
| *n* | 56 | 29 | | |
| Male gender, *n* (%) | 34 (60.7) | 16 (55.2) | 0.242* | 0.623 |
| Age (years) | 45.8 ± 10.0 | 49.9 ± 12.5 | −1.646† | 0.103 |
| Weight (kg) | 64.84 ± 14.00 | 62.37 ± 11.10 | 0.821† | 0.414 |
| Symptoms | | | | |
| Cough, *n* (%) | 44 (78.6) | 18 (62.1) | 2.636* | 0.104 |
| Expectoration, *n* (%) | 31 (55.4) | 13 (44.8) | 0.848* | 0.357 |
| Chest tightness, *n* (%) | 11 (19.6) | 6 (20.7) | 0.013* | 0.909 |
| Hemoptysis, *n* (%) | 5 (8.9) | 1 (3.4) | 0.875* | 0.350 |
| The numbers of symptoms (symptom scores) | 1.52 ± 0.95 | 1.31 ± 0.98 | 0.947† | 0.347 |
| Underlying diseases, *n* (%) | 10 (17.9) | 5 (17.2) | 0.005* | 0.944 |
| T2DM, *n* | 4 | 2 | | |
| Kidney transplantation, *n* | 2 | 2 | | |
| SLE, *n* | 1 | 0 | | |
| Astrocytoma, *n* | 1 | 0 | | |
| Nephrotic syndrome, *n* | 1 | 0 | | |
| Nasopharyngeal cancer, *n* | 1 | 1 | | |
| Langerhans cell histiocytosis, *n* | 0 | 1 | | |
| Hb (g/L) | 132.85 ± 18.27 | 133.24 ± 17.07 | −0.094† | 0.925 |
| Platelet ($10^9$/L) | 266.98 ± 59.28 | 262.86 ± 76.13 | −1.060† | 0.292 |
| WBC ($10^9$/L) | 6.98 ± 1.69 | 7.04 ± 2.42 | −0.133† | 0.895 |
| Neutrophils ($10^9$/L) | 4.82 ± 1.40 | 4.89 ± 1.83 | −0.171† | 0.865 |
| Plasma procalcitonin level (ng/ml) | 0.11 ± 0.16 | 0.14 ± 0.24 | −0.799† | 0.427 |

*Chi-square test; †*t*-test. T2DM: Type 2 diabetes mellitus; SLE: Systemic lupus erythematosus; Hb: Hemoglobin; HIV: Human immunodeficiency virus; CrAg: Cryptococcal antigen; WBC: White blood cell.

### Clinical symptoms

As shown in Table 1, cough (72.9%) and expectoration (51.8%) were the most common symptoms in patients with pulmonary cryptococcosis. Other common symptoms included chest tightness (20.0%) and hemoptysis (7.1%). Then, no significant difference in types of symptoms and symptom scores (1.52 ± 0.95 vs. 1.31 ± 0.98, $P = 0.944$) was observed between two groups.

### Laboratory findings

There was no significant difference in Hb (132.85 ± 18.27 vs. 133.24 ± 17.07, $P = 0.925$), PLT (266.98 ± 59.28 vs. 262.86 ± 76.13, $P = 0.292$), WBC (6.98 ± 1.69 vs. 7.04 ± 2.42, $P = 0.895$), neutrophils (4.82 ± 1.40 vs. 4.89 ± 1.83, $P = 0.865$), and plasma PCT level (0.11 ± 0.16 vs. 0.14 ± 0.24, $P = 0.427$) between two groups [Table 1].

### Chest radiological findings

Table 2 figured out that diffuse extent lesion was 82.1% in CrAg+ group and 10.3% in CrAg− group ($\chi^2 = 40.34$, $P < 0.001$). Moreover, *OR* was 39.87. Chest radiological findings and biopsy results in patients with pulmonary cryptococcosis were shown in Figure 2.

**Table 2: Chest radiological findings of non-HIV adult patients with pulmonary cryptococcosis**

| Chest radiological characteristics | CrAg+ (*n* = 56) | CrAg− (*n* = 29) | $\chi^2$ | *P* |
|---|---|---|---|---|
| Diffuse extent lesion, *n* (%) | 46 (82.1) | 3 (10.3) | 40.34 | <0.001 |
| Limited extent lesion, *n* (%) | 10 (17.9) | 26 (89.7) | | |

HIV: Human immunodeficiency virus; CrAg: Cryptococcal antigen.

## Discussion

In the present study, our data showed that, among patients with suspected pulmonary cryptococcosis, in context of extensive pulmonary involvement, a negative serum CrAg is highly suggestive of an alternate diagnosis. In addition, among patients with limited pulmonary involvement, a negative serum CrAg does not preclude the diagnosis of pulmonary cryptococcosis. Furthermore, our results also suggest that, among patients with the extensive pulmonary lesion, serum CrAg is a useful diagnostic tool for pulmonary cryptococcosis.

Cryptococcosis has been considered a disease of opportunistic infection, mainly, in immunocompromised patients with HIV/AIDS, cancers, and immunosuppressive treatment.[9,10] Moreover, *C. neoformans* was the predominant etiological agent of cryptococcosis.[11] It has been found that $CD4^+$ T-cell plays a critical role on immune responses to *C. neoformans*.[12,13] Th1 cytokines, such as interleukin (IL)-2, IL-12, interferon-γ, and tumor necrosis factor-α, orchestrate neutrophils and dendritic cells and activate macrophages to promote clearance of the pathogen.[14] Some studies figured out that cryptococcal meningoencephalitis is one of the most common disseminated fungal infections in HIV patients and the third most common invasive fungal infection in patients with organ transplants.[8,15,16] Otherwise, mounting

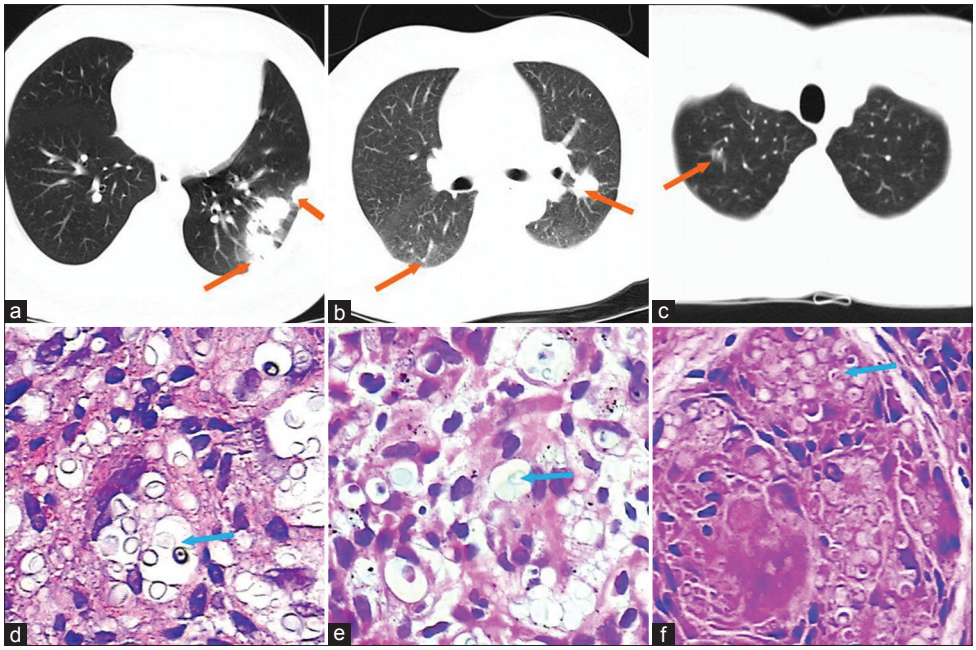


**Figure 2:** The chest radiological findings and biopsy results in patients with pulmonary cryptococcosis. The figures were obtained from three different individuals ([a and d] from case 1, [b and e] from case 2, and [c and f] from case 3). Cases 1 and 2 from CrAg+ group were diagnosed by PTNB and Case 3 from CrAg− group was diagnosed by postoperative biopsy (frozen biopsy). Chest radiological findings (a-c): (a) Multiple lesions in a single lobe and the lesion diameter >3 cm in a single lobe (diffuse extent lesion); (b) lesions in multiple lobes (diffuse extent lesion); (c) lesion (the diameter <3 cm) in a single lobe (limited extent lesion). Biopsy results (d-f): The figures (H and E staining) demonstrates a representative view (×400). Lesion (orange arrows); *Cryptococcus sp.* yeasts (blue arrows). PTNB: Percutaneous transthoracic needle biopsy; H and E: Hematoxylin and eosin.

evidence showed that the prevalence of cryptococcosis in immunocompetent hosts is increasing.[15,16] Then, pulmonary cryptococcosis is the leading type of cryptococcosis in non-HIV patients.[6,8,17] Baddley *et al*. found that, among 166 HIV-negative patients with pulmonary cryptococcosis, 122 had pulmonary infection only and 44 had pulmonary plus extrapulmonary infection.[17] Some studies showed that patients with pulmonary cryptococcosis were frequently symptomless or with mild symptoms.[6,8,9] Then, it is also wildly regarded that the diagnosis of pulmonary cryptococcosis is challenging. At present, serum CrAg screening has become a useful tool in cryptococcosis diagnosis.[18-20] High serum CrAg titer was considered to be associated with the load of fungi.[21] Meanwhile, serum CrAg also was used to monitor the recrudescence.[21] Nevertheless, we noticed that having negative serum CrAg is not rare among patients with pulmonary cryptococcosis, which was proven by biopsy later, in our clinical practices. Therefore, the characteristics of patients with and without serum CrAg test positive were worthy to be evaluated. In our study, 114 patients with pulmonary cryptococcosis, proven by PTNB or postoperative biopsy, were screened and 85 patients were enrolled, 56 in CrAg+ group and 29 in CrAg− group. According to our results, we found that male (60.7% in CrAg+ group and 55.2% in CrAg− group) was slightly more than female and cough and expectoration were two most common symptoms [Table 1]. Interestingly, we also noticed that fever was rare in these patients, indicating that fever probably would be used as a symptom for exclusive diagnosis. Moreover, clubbing finger was not observed in our study, which is an important and typical sign of lung cancer, chronic tuberculosis, and other lung diseases. Kohno *et al.* also showed that only 3% (2 in 67) of non-HIV patients with pulmonary cryptococcosis had fever.[6] Since immunological status and underlying conditions are critical in fungal infection, the underlying status of patients was analyzed in our study. We found that only 17.9% in CrAg+ group and 17.2% in CrAg− group were complicated with underlying diseases. Meanwhile, our data showed that T2DM and kidney transplantation were more common than other diseases [Table 1]. In our study, laboratory findings, including Hb, PLT, WBC, neutrophils, and plasma PCT level, were analyzed. According to our data, no special change was observed between two groups, indicating that no severe systematical inflammatory response was stimulated in immunological systems. Moreover, these can partially explain the reason of symptomless or mild symptoms in pulmonary cryptococcosis. Therefore, further studies should be carried out to elucidate the underlying mechanism of the immune escape in pulmonary cryptococcosis. Then, these results suggested that pulmonary cryptococcosis showed untypical symptoms and laboratory findings, particularly without apparently infection features, in clinical practices. Moreover, most non-HIV adult patients with pulmonary cryptococcosis were not combined with underlying diseases. Therefore, we presumed that underlying diseases play a limited role in the pathogenesis of pulmonary cryptococcosis in non-HIV adult patients.

In light of most of the pulmonary cryptococcosis patients without symptom or with mild respiratory symptoms, they were accidentally found by routine chest X-ray check.[6-9] In radiography, some studies reported that chest radiological findings of pulmonary cryptococcosis were untypical and varied.[6,22,23] Many studies found that pulmonary nodules and mass were more common.[6,8,24] Lindell *et al.* found that the most common findings of computed tomography (CT) scan were multiple, small, well-defined, and smoothly marinated pulmonary nodules in immunocompetent patients with pulmonary cryptococcosis.[24] According to our data, we figured out that single or multiple nodules and mass were most common chest radiological findings. Meanwhile, ground-glass attenuation, infiltration, and consolidation were not rare. However, we also noticed that cavity, pleural effusion, and interstitial changes were seldom. Then, in the current study, we divided the CT findings into two conditions, diffuse extent lesion and limited extent lesion. Lesions in multiple lobes, multiple lesions in a single lobe, and the lesion diameter >3 cm in a single lobe were defined as diffuse extent lesion. Moreover, the lesion (the diameter <3 cm) in a single lobe was defined as limited extent lesion. Our data showed that diffuse extent lesion was more common in CrAg+ group and limited extent lesion was more frequently observed in CrAg− group. Then, we speculated that there should be a positive association between the extent lesion and the pathogen loads in the lung. Therefore, our results indicated that serum CrAg was valuable for extensive extent lesion in non-HIV adult patients with pulmonary cryptococcosis, whereas serum CrAg negative with limited extent lesion would not preclude the diagnosis of pulmonary cryptococcosis.

In addition, according to our data, we showed that pulmonary cryptococcosis was more common than cryptococcal meningoencephalitis and disseminated cryptococcosis in adult patients without HIV infection. However, due to our limited sample size and study centers, more data should be collected in future.

In conclusion, in the current study, our data indicated that, among patients with suspected pulmonary cryptococcosis, extensive pulmonary lesion combined with a negative serum CrAg is highly suggestive of an alternate diagnosis, whereas, among patients with limited pulmonary lesion combined with a negative serum, CrAg does not preclude the diagnosis of pulmonary cryptococcosis.


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## Conflicts of interest

There are no conflicts of interest.

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# 成年非HIV感染的肺隐球菌病患者血隐球菌抗原水平与肺部病变范围的相关性研究


## 摘要

**背景：**血隐球菌抗原(CrAg)检测是临床上最常用的隐球菌病非有创性检查手段。但该方法在临床应用中假阴性结果并不少见。因此，本研究的目的是探讨在成年非HIV感染的肺隐球菌病患者出现血隐球菌抗原检测假阴性结果的原因，及成年非HIV感染的肺隐球菌病的临床特征。

**方法：**在该回顾性横断面研究中我们共收集了114例成年非HIV感染的肺隐球菌病病例。根据入选标准和排除标准，最后纳入患者85例，其中血隐球菌抗原阳性组(CrAg+组) 56例，血隐球菌抗原阴性组(CrAg-组) 29例。并对患者基线特征、基础疾病、临床症状评分、实验室检查和胸部影像学结果进行记录和分析。卡方检验用于分类变量分析。优势比(OR)用于关联强度分析。t检验用于连续变量分析。

**结果：**两组患者的基线特征、基础疾病、临床症状评分和实验室检查结果均无明显统计学差异($P$均>0.05)。但弥漫性病灶发生率在CrAg+组为82.1%，CrAg-组为10.3% ($\chi^2 = 40.34$, $P < 0.001$)。OR为39.87。

**结论：**若患者胸部影像学为局限性病灶，患者血CrAg检测阴性时仍不能排除肺隐球菌病的可能。对于弥漫性病灶的患者，血CrAg检测意义较大。同时我们的研究还发现肺部存在广泛病灶但临床症状不明显可能是肺隐球菌病的临床特征，但仍需进一步临床研究证实。