

## TB and its sequela chronic pulmonary aspergillosis (CPA)

### Summary

About 1 in 10 patients diagnosed with pulmonary TB, don't have TB but chronic pulmonary aspergillosis (CPA). CPA is a slowly destructive lung infection, with marked systemic features (weight loss, fatigue) and pulmonary features (productive cough, haemoptysis, breathlessness) almost indistinguishable from TB. CPA presents like 'smear negative TB'. It usually follows a pulmonary insult, especially TB, sarcoidosis, pneumothorax and emphysema/COPD). Most patients are not immunocompromised, although HIV infection may be present. Some patients have subtle immune defects including reduced natural killer, T helper and/or B cells and sometimes reduced gamma interferon or interleukin 12 production. Several genetic variants are also associated with CPA. Rates of progression vary, but worsening symptoms and lung destruction or fibrosis occur over many months or years. The key diagnostic features are cavitory lung lesions with pleural thickening on radiology, sometimes containing a fungal ball (aspergilloma) and elevated serum *Aspergillus* antibody. A simple aspergilloma (<10% of cases) is best surgically removed. Antifungal therapy is effective at controlling symptoms and progression in about 60% of patients. Untreated mortality is 75-80% over 5 years, reduced to ~40% with long term antifungal therapy. Estimates suggest a prevalence of ~1.2M CPA cases during or immediately after pulmonary TB with 230,000 deaths in the first year of disease, and probably ~3 million overall.

### Similarity of CPA to TB

There are many similarities between TB and CPA in clinical presentation and radiological appearances (Fig. 1) <sup>1</sup>. Haemoptysis and a cough that persists beyond 3 months is more typical of CPA than TB. Pleural thickening combined with a cavity, with either a fungal ball or para-cavitary fibrosis is also more common with CPA.

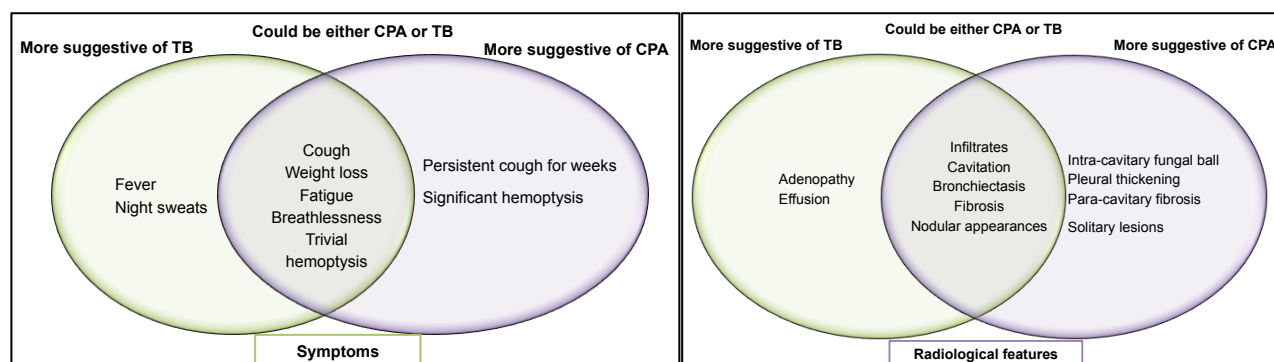


Fig 1. Similarities and differences between CPA and pulmonary TB.

Small and large series of CPA patients have been reported in recent years from China and Hong Kong <sup>2-4</sup>, Taiwan <sup>5</sup>, India <sup>6</sup>, Pakistan <sup>7</sup>, Korea <sup>8,9</sup>, Japan <sup>10-12</sup>, Indonesia <sup>13,14</sup>, Vietnam <sup>15</sup>, Cuba <sup>16</sup>, France <sup>19-19</sup>, Italy <sup>20</sup>, Spain <sup>21,22</sup>, Finland <sup>23</sup> and UK <sup>24-26</sup>, Uganda <sup>27</sup>

and Nigeria <sup>28</sup>, as well as several surgical series from Africa <sup>29</sup>.

CPA may:

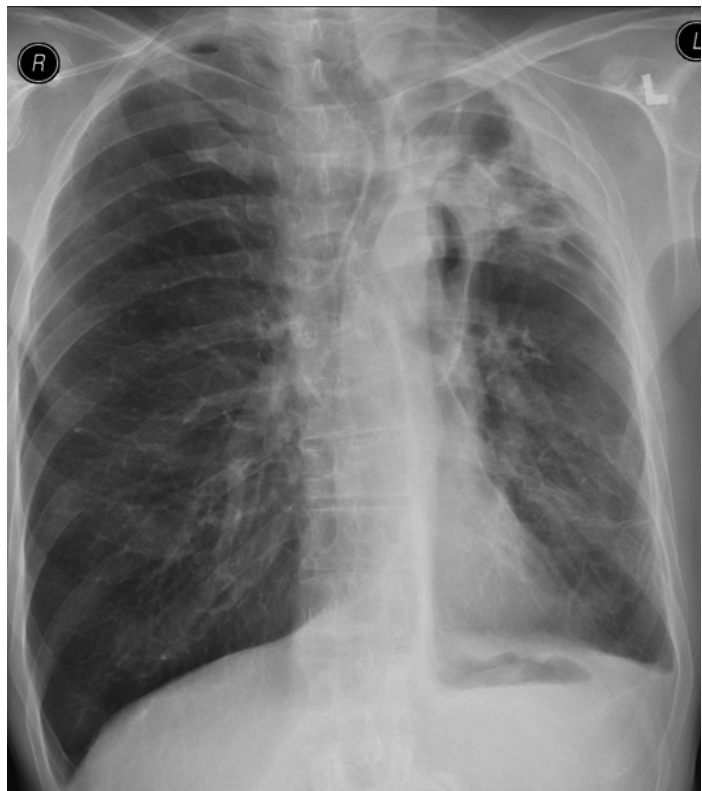
1) **mimic TB**: especially manifest as 'smear negative' TB. Probably CPA comprises 20-30% of this clinically diagnosed TB group, based on data from Nigeria in HIV+ and HIV- patients <sup>28</sup> and Benin. The WHO reports that ~45% of those with pulmonary TB are unproven (i.e. smear and/or GeneXpert/PCR negative). Only 20-40% of these patients would be culture positive, if tested. The remainder probably don't have TB, but are treated as if they do. Several other underlying lung disorders can be complicated by CPA, i.e. pneumothorax, COPD, sarcoidosis and asthma <sup>7,26</sup>.

2) **occur during TB treatment**: *Aspergillus* can co-infect alongside TB, documented in 8-13% of patients in Indonesia and Pakistan <sup>7,13,14</sup>.

3) **follow TB**: mostly in those left with cavities. In MRC studies in the UK in the 1960's, this was documented in 22% of those with a residual cavity 1-3 years after completion of TB <sup>30,31</sup>, in Uganda in 6.5% annually, 2-7 years after TB, and only 0.2% in those without a cavity <sup>27</sup>, and in Taiwan one active TB patient (0.2%) and four old TB patients (2.1%) developed CPA over 2.5 years after TB <sup>5</sup>. In Vietnam, 54% and in India 57% of patients with recurrent symptoms after TB treatment completion had CPA<sup>15,32</sup>.

### Prevalence

The prevalence of CPA is not known with confidence. In the late 1960s, one year after completion of anti-TB treatment in the UK, 25% of 544 patients with a residual cavity had *Aspergillus* antibodies and at least 14% CPA (aspergilloma) on chest Xray <sup>30</sup>. On resurvey three years later, 34% of all patients had developed *Aspergillus* antibodies, >20% had CPA and 42% of these were coughing up blood <sup>31</sup>. Overall 63% of patients with *Aspergillus* antibodies developed CPA with an aspergilloma within 3 years.



Since then, a cross-sectional study of TB patients in Nigeria, found both HIV positive and negative patients had CPA (8.7%), with the highest proportion (19%) in smear and GeneXpert negative, HIV negative patients <sup>28</sup>. In Uganda, a 2 year prospective study in 285 patients who had had TB 2-7 years earlier, found CPA present in 14 (4.9%, 95% CI 2.8–7.9%)<sup>27</sup>. CPA was significantly more common in those with chest radiography cavitation (26% versus 0.8%;  $p < 0.001$ ), but possibly less frequent in HIV co-infected patients (3% versus 6.7%;  $p = 0.177$ ). The annual rate of new CPA development between surveys was 6.5% in those with chest

radiography cavitation and 0.2% in those without ( $p < 0.001$ ).

Current modelling estimates for pulmonary TB patients are as follows:

- Co-infection of TB (confirmed) with CPA = 3% (Indonesia <sup>14</sup>)
- CPA proportion among clinical diagnosed TB HIV- = 20% (Nigeria <sup>28</sup>)
- CPA proportion among clinical diagnosed TB HIV+ = 10% (Nigeria <sup>28</sup>)
- CPA proportion at end of TB therapy = 10% (Indonesia <sup>13</sup>)
- 12-35% have with a cavity at the end of TB therapy
- 6.5% annual rate of CPA for years 2-7 if cavity present after TB therapy (Uganda <sup>27</sup>)
- 0.2% annual rate of CPA for years 2-7 if no cavity present after TB therapy (Uganda <sup>27</sup>)
- 50% mortality of TB and CPA co-infection (Indonesia <sup>14</sup> (few data))
- 7-35% year 1 CPA mortality, ~10% per year from year 2-5 (Japan, USA, UK, South Korea, France <sup>20,26,33-35</sup>).

Using these data, the global CPA incidence would be 995,523 (16.9%) among 5.89 million newly presenting pulmonary TB cases (as per WHO 2019 data). Among these patients, 228,260 die (15.7% of all TB deaths) within the year of CPA alone or CPA and TB. Calculation of the 5 year period prevalence lies at the upper end of the range estimated in 2011 using 2007 TB data ie > 1.25 million (range 0.8-1.37 million)<sup>8</sup>. These estimates do not include CPA presenting as 'recurrent or relapsing TB' or CPA complicating other underlying conditions.

In countries with a high pulmonary TB incidence, TB is the dominant underlying disease accounting for up to 80% of cases <sup>25</sup>. When pulmonary TB is less frequent, other pulmonary disorders are more important, notably COPD and non-tuberculous mycobacterial infection, and prior TB was present in <20% of cases <sup>25</sup>. Overall therefore, a provisional prevalence estimate of 3 million CPA patients was made <sup>37</sup>.

### Clinical presentation

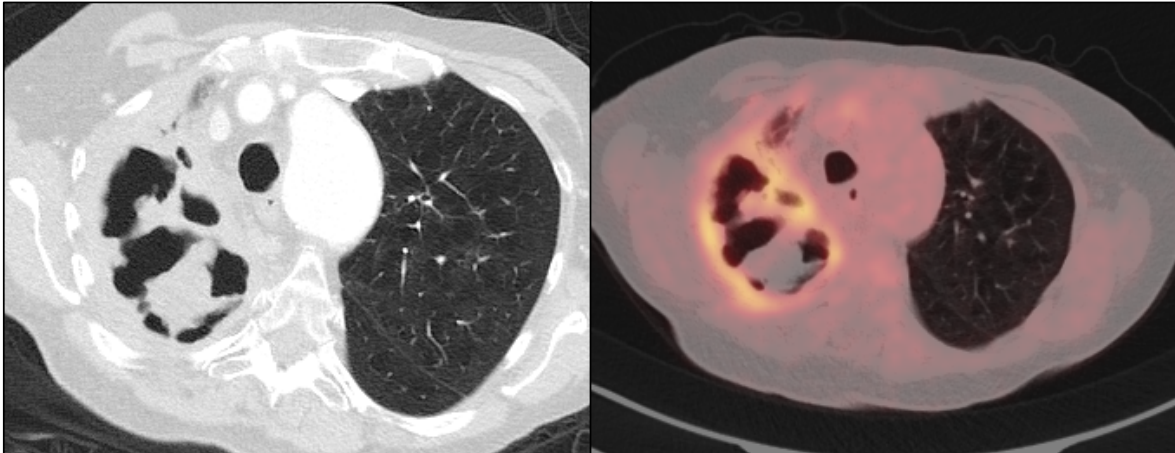
Patients with CPA present most commonly with weight loss, chronic productive cough, hemoptysis of variable severity, significant fatigue, and/or shortness of breath <sup>1,33,34,38,39</sup>. Fever, night sweats and chest discomfort occur occasionally. The systemic symptoms of chronic cavitary pulmonary aspergillosis are an important point of distinction from a simple aspergilloma, in which these do not occur <sup>40</sup>.

### Radiology

Radiographic examination usually reveals one or more cavities, typically within the upper lobes, which may or may not contain fungus balls <sup>39,41</sup>. Pleural thickening is common.

A simple aspergilloma is a fungus ball in a single pulmonary cavity with limited surrounding inflammation, pleural thickening, or fibrosis, and few symptoms <sup>40</sup>. Chronic cavitary pulmonary aspergillosis usually begins as ill-defined regions of consolidation that progress to form clearly defined cavities <sup>1,38,39</sup>. Cavities may contain fungus balls, debris, or fluid. There are often multiple cavities of different sizes. The interior of the cavity may show marked irregularity, representing fungal growth on the cavity wall. Cavities may be thick- or thin-walled. Pleural thickening is common but not universal. New cavity formation or expansion of one or more existing cavities

over time is highly characteristic, and typically occurs over months in the absence of treatment.



Matching CT and PET scan from a woman with CPA showing remarkable inflammatory response in the pleura and multiple cavities with an irregular inside surface

Some patients get *Aspergillus* nodules – which may be single or multiple, and occasionally cavitate <sup>42</sup>. Some are asymptomatic, others are associated with many pulmonary symptoms and haemoptysis.

Chronic fibrosing pulmonary aspergillosis <sup>38,43</sup>, otherwise known as ‘destroyed lung’, is a late stage of disease and characterized by the same radiographic findings that occur with chronic cavitary pulmonary aspergillosis in combination with significant fibrosis.

### Diagnosis

The key test for CPA is a positive *Aspergillus* antibody test (precipitins) in serum <sup>39,41,44</sup>. The best tests have >90% sensitivity and a 85% specificity <sup>2,45,41,44</sup>. An affordable new lateral flow device with excellent performance characteristics has recently been commercialized <sup>45-47</sup>. The presence of antibody alone is not enough to diagnose CPA but the frequency of these antibodies gives an indication of the proportion of such patients in a given population. In Japan 20% of treated TB patients had antibodies to *Aspergillus* <sup>48</sup>. Two surveys in India showed *Aspergillus* antibodies in 23% and 25% of patients with “chronic lung diseases”, 90% of whom had had prior TB <sup>49,50</sup>. In Brazil 65% patients at a tertiary chest clinic with positive *Aspergillus* antibodies had an aspergilloma <sup>51</sup>. Almost all patients with ‘recurrent TB’ in Iran had *Aspergillus* antibody detectable <sup>52</sup>.

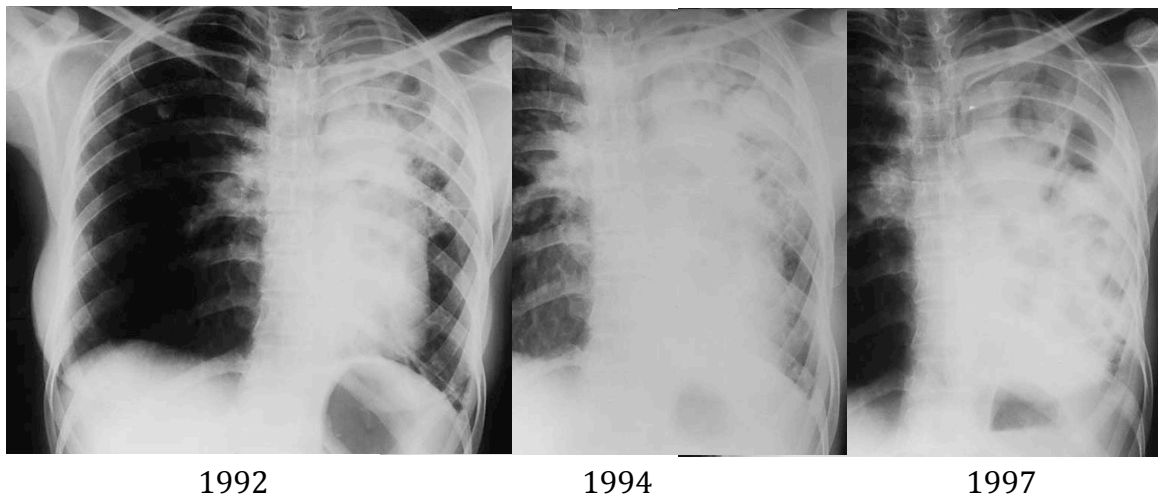
Raised inflammatory markers (CRP, plasma viscosity or ESR) are seen in about 50% of patients <sup>38</sup>, often linked to anaemia and low albumin. *Aspergillus* antigen is sometimes detectable in serum, but usually in bronchoalveolar lavage <sup>6,53</sup>, and in sputum but the cut-off is much higher <sup>54</sup>. Cultures are positive for *Aspergillus* spp. in ~25% of patients (usually *A. fumigatus*) <sup>39</sup> but the yield is much higher if high volume cultures are done <sup>55</sup>. *Aspergillus* PCR is more often positive (~80%) <sup>54-57</sup>. Guidelines on diagnosis,

including radiological features, are published <sup>39</sup>, and for low resource settings an algorithm is now available for diagnosis <sup>41</sup>.

Many patients have some degree of impaired immunity. Low T helper, B cell and/or natural killer cells are frequent <sup>58</sup>. Low pneumococcal and *Haemophilus* antibodies are frequent and usually partially responsive to conjugate vaccine <sup>59</sup>. Poor production of gamma interferon or interleukin 12 (which is required to produce gamma interferon) is common in the more complex patients, and gamma interferon replacement has a beneficial effect in reducing hospitalization <sup>60</sup>. Multiple genetic variants are also described, but their frequency in different ethnicities is not known.

#### Typical untreated example

An example of a Gujarati woman who had had TB and developed CPA was diagnosed in 1992 <sup>38</sup>. Without treatment, she lost the function of her whole left lung (chronic fibrosing pulmonary aspergillosis) over 5 years and subsequently died. In contrast other patients have remained well on treatment for 20+ years.



#### Management

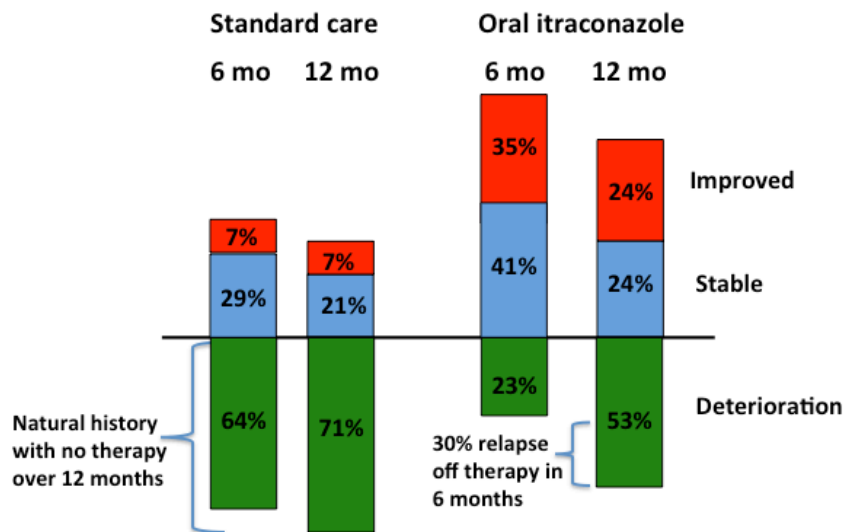
Simple aspergilloma should be resected, usually requiring a lobectomy <sup>36</sup>. Survival rates after such surgery are excellent, if patients are carefully selected <sup>23,30,61-64</sup>. About 5% of patients with CPA are immediately suitable for resection surgery. Recurrence does occur in >25% of cases <sup>64,65</sup>. Surgery in patients with multicavity disease who are systemically unwell, has a considerable mortality and morbidity, and is rarely curative. Antifungal therapy before and during resection surgery reduces the rate of recurrence over the following years <sup>65</sup>.

Antifungal therapy with oral itraconazole is about 60-70% effective in improving or stabilising symptoms and arresting progression <sup>10,24,39,66</sup>. Response and deterioration rates documented in an RCT comparing oral itraconazole (400mg daily) with standard care over 6 months, followed by 6 months of follow up <sup>66</sup> is shown in the figure below. Of those on standard care, 61% deteriorated at 6 months and 71% at 12 months. In contrast, 76% of patients improved or stabilized on itraconazole. Discontinuation of itraconazole lead to a 30% relapse rate 6 months later. Voriconazole therapy is



probably slightly superior <sup>21,25,39,68</sup> and a reduced rate of azole resistance emergence <sup>25</sup>, especially in those with large fungal balls, but tolerability can be an issue.

Response can be assessed by symptom reduction, weight gain, reduced fatigue, falling inflammatory markers and *Aspergillus* IgG antibody titre <sup>25,39</sup>, and reduction in pleural thickening on CT scanning or chest radiograph <sup>18</sup>.



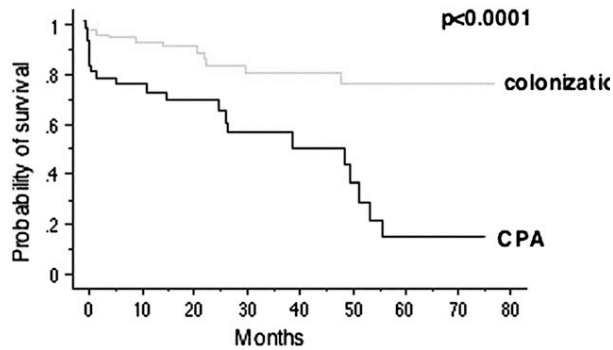
Similar response rates are seen with IV amphotericin B (short term), IV micafungin (short term), IV caspofungin (short term), oral voriconazole, oral posaconazole and oral isavuconazole <sup>39,70</sup>. Therapy needs to be long term (>6 months) <sup>25</sup>. Longer durations of therapy improve outcomes <sup>69</sup>, but some patients cannot tolerate current oral therapies <sup>72</sup>. Drug interactions are problematic, especially rifampicin, anticonvulsants, some anti-retroviral agents and cardiac drugs. Itraconazole and pan-azole resistance in *A. fumigatus* occurs in some patients, and this is difficult to treat <sup>25,39,72</sup>.

### Outcome

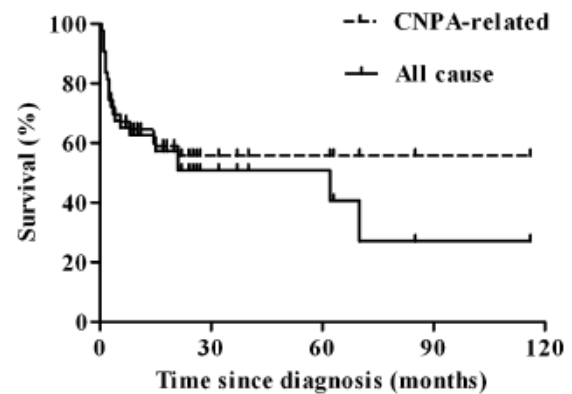
Recent series indicate a steep mortality shortly after presentation, with stabilization over time <sup>20,27,33-35</sup>, probably because of antifungal therapy and a less severe phenotype (slower progressors). Certain features are associated with a worse outcome: male sex, older age, bilateral disease, presence of an aspergilloma, concurrent mycobacterial infection and a low albumin.

CPA co-infection with non-tuberculous *Mycobacteria* has a worse outcome than NTM infection alone <sup>27,73</sup>. Outcomes are improved if CPA is treated early. The same is likely to be true of concurrent pulmonary TB and CPA, but the optimal management of dual infection has yet to be studied. The profound interaction of rifampicin and azole therapy is highly problematic.

Japanese mortality data <sup>33</sup>

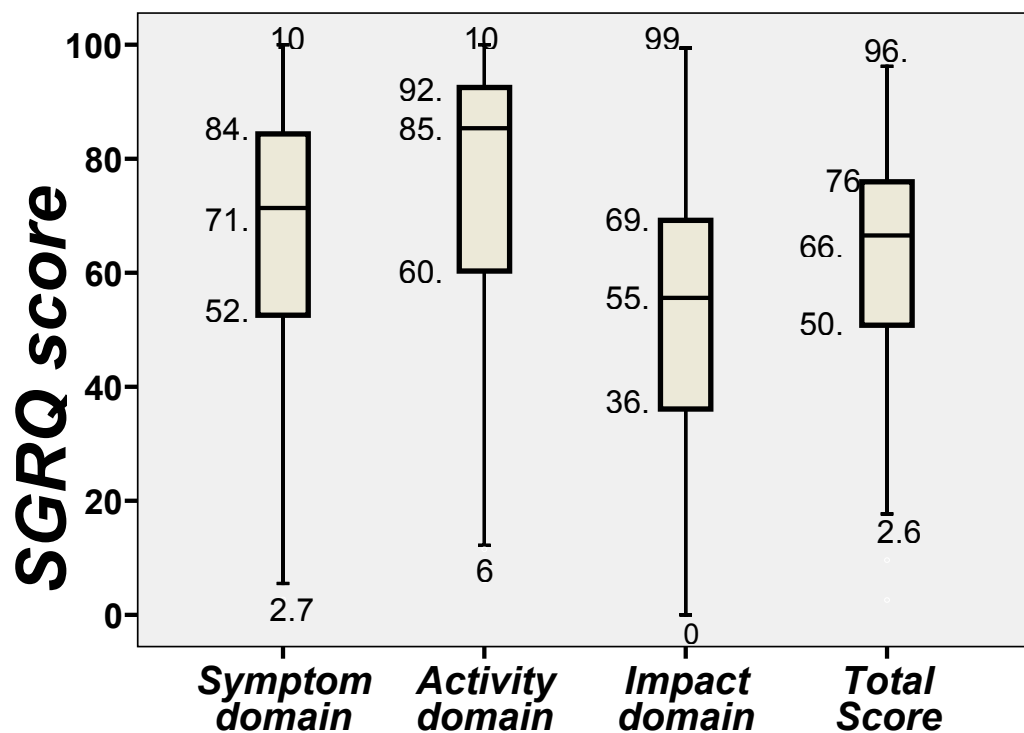


Korean mortality data <sup>34</sup>



### Morbidity impact

The impact of CPA on quality of life is can be measured with the St George's Respiratory Score which ranges from 1 (excellent health) to 100 (extremely ill). The spread of scores is shown in this prospectively collected data from a large cohort of UK patients (n=88) <sup>67</sup>. Responders get good improvements in their quality of life <sup>25</sup>.



### Key questions and observations:

- CPA is a global disease but prevalence data show some variability in frequency, depending in part on local pulmonary TB incidence and probably COPD prevalence. More prevalence studies are required.
- The impact of HIV infection on prevalence and diagnosis is not well studied.

- Substantial numbers of smear negative TB cases don't have TB but have CPA; some have dual infection.
- Dual mycobacterial (TB and NTM) infections are difficult to manage and need more study and new non-interacting antifungal agents. Outcomes are worse
- A new lateral flow assay for *Aspergillus* IgG antibody is now available and could transform diagnosis.
- Oral antifungal therapy is partially successful (~60%), but both antifungal tolerance and azole resistance occur in a minority of patients, but are problematic to manage.
- Antifungal therapy before and during resection surgery reduces the chance of relapse.
- Progression rates vary and some patients need intensive therapy, others are stable for long periods.

David Denning  
The University of Manchester and GAFFI  
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