Natural History of Pulmonary Coccidioidomycosis: Further Examination of the VA-Armed Forces Database

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Lay Summary (292 characters):

Coccidioidomycosis (CM), also known as San Joaquin Valley Fever, causes a variety of symptoms including pneumonia. This historical study investigates CM of the lungs in American soldiers with CM in the 1950s, prior to modern antifungals, to better understand the natural history.

ABSTRACT

There are still many limitations related to the understanding of the natural history of differing forms of coccidioidomycosis, including characterizing the spectrum of pulmonary disease. The historical Veterans Administration-Armed Forces database, recorded primarily before the advent of antifungal therapy, presents an opportunity to characterize the natural history of pulmonary CM. We performed a retrospective cohort study of 342 armed forces service members who were diagnosed with pulmonary CM at VA facilities between 1955-1958, followed to 1966, who did not receive antifungal therapy. Patients were grouped by predominant pulmonary finding on chest radiograph. The all-cause mortality was low for all patients (4.6%). Cavities had a median size of 3-3.9cm (IQR: 2-2.9cm – 4-4.9cm), with heterogeneous wall thickness and no fluid level, while nodules had a median size of 1-1.19cm (IQR 1-1.9cm – 2-2.9cm) and sharp borders. The majority of cavities were chronic (85.6%), and just under half were found incidentally. Median complement fixation titers in both the nodular and cavitary groups were negative, with higher titers in the cavitary group overall.

This retrospective cohort study of non-disseminated coccidioidomycosis, the largest to date, sheds light on the natural history, serologic markers, and radiologic characteristics of this understudied disease. These findings have implications for the evaluation and management of CM.

INTRODUCTION

Coccidioidomycosis (CM) refers to the spectrum of disease caused by *Coccidioides immitis*, which is most common in California, while *C. posadasii* predominates elsewhere.[1,2] Up to 60.0% of cases may be asymptomatic. In those with symptomatic infection, the most common clinical presentation is a subacute pulmonary syndrome known colloquially as "San Joaquin Valley Fever," consisting of cough, fever, chills, and fatigue, frequently with rheumatologic and dermatologic features such as erythema nodosum.[3] In endemic areas of the United States, predominantly California's Central Valley and Arizona's Sonoran Desert region, pulmonary coccidioidal infection is common, accounting for roughly 25.0% of community-acquired pneumonia cases.[4,5] Although the pulmonary illness usually resolves after weeks to months of illness, occasionally it is much more severe, even fatal.[6,7] Extrapulmonary dissemination is rarer, occurring in only approximately 1.0% of all infections.[8]

In 2019, California recorded 9,004 and Arizona recorded 10,358 cases of coccidioidomycosis.[9] Nationally, epidemiologic surveillance data shows the incidence of coccidioidomycosis in the U.S. has doubled since a relative nadir in 2014.[10] The actual incidence of CM, however, may be higher, as testing for CM in these regions is low, compounded by a lack of awareness about CM in the general population.[11] Despite causing a significant burden of morbidity and mortality as well as close to $1.5 billion in direct and indirect costs annually in California and Arizona alone,[12,13] CM remains poorly studied.

In the 1950s, a large cohort of armed forces service members receiving medical care at Veterans Administration (VA) facilities within the endemic region, diagnosed with coccidioidomycosis were prospectively enrolled into the Coccidioidomycosis Study Group and

followed for a decade; comprising one of the largest coccidioidomycosis datasets to date (n=699 unduplicated patients).[14,15] As the VA cohort preceded the availability of effective antifungal therapy, these records provide a unique opportunity to better understand the natural history, analytic markers, and non-pharmacologic management of primary pulmonary coccidioidomycosis. Two past publications addressed coccidioidal meningitis and other manifestations of disseminated CM[14,15]; here we extend our analysis to patients with the pulmonary manifestations of CM.

Methods

Of the 699 total patients in the abstracted records of the VA Coccidioidomycosis Study Group, 104 were excluded for lack of complete data. Among the remaining 595 patients, 462 were identified as non-disseminated. Diagnosis of coccidioidomycosis was made through culture, pathology, complement fixation serology, or a combination of these methods. Cases were defined as pulmonary if they had an abnormal chest X-ray and there was no evidence of extrathoracic disease. Of the 462 non-disseminated patients, we identified 376 patients diagnosed with pulmonary coccidioidomycosis without dissemination, diagnosed between January 1, 1955 and December 30, 1958 and followed through 1966. The provenance of this data, from its original abstraction to paper media through its eventual compilation into an online database, has previously been described.[15] In brief, all medical records were reviewed and classified by a pulmonary specialist (D. S.) and a mycologist (M. H.). Data were abstracted onto standardized collection forms, coded on computer cards, transferred onto electronic media, and subsequently transitioned to an online database (REDCap, Vanderbilt University, Nashville, TN) for further analysis. Twenty-seven patients who received amphotericin B deoxycholate therapy, one patient whose amphotericin B status could not be determined, and four patients with inconsistent medical records were excluded from analysis, leaving 342 subjects, of whom 48 were treated surgically.

Demographic data, comorbidities, radiologic features, complement fixation serologies, skin test results, and surgical management and sequelae were assessed. Survival analysis for death due to coccidioidomycosis was completed for the patients characterized as having pneumonia, nodular disease, or cavitary disease (n=328) excluding 5 patients that had data entry errors. Due to very limited numbers, patients with unknown disease (n=1), pleural disease (n=2), fibrocavitary disease (n=8) were excluded from formal survival analysis. Survival was analyzed with Kaplan-Meier curves and the log rank test using SAS® software version 9.4 for Windows® (SAS Institute Inc., Cary, NC).

Results

Patient Demographics

The demographics of this cohort, being a sample of patients receiving care at Veterans Administration facilities, reflects the make-up of the mid-twentieth century American armed forces: predominantly male (97.4%, n=335) and white (77.3%, n=289), with a median age of 34 years at the time of enrollment (Table 1). Most patients had no diagnosed pulmonary comorbidity (80.5%, n=277), with the most common concurrent pulmonary diagnoses being tuberculosis (10.2%, n=35) and emphysema (0.5%, n=12) (Table 1) based on listed patient comorbidities. A small number of individuals had co-occurring diagnoses of silicosis (0.9%), asthma (1.2%), or lung cancer, unspecified type (1.2%). Of the short list of extrapulmonary comorbidities assessed at baseline (diabetes mellitus, peptic ulcer disease, or "other"), the vast majority (86.6%, n=298) had none, while 7.8% (n=15) carried a diagnosis of diabetes of unspecified type.

Radiographic Findings

All patients underwent chest X-ray. Most cases were either nodular (37.8%, n=130) or cavitary (45.8%, n=154), with 49 cases (14.2%) that were characterized as predominantly

pneumonic (Table 2). Cavitary and nodular lesions were not found to be mutually exclusive, and the majority of patients (59.3%, *n*=204), including many patients classified as predominantly cavitary in presentation, were identified as having at least one nodule. There were 8 patients (2.3%) who had underlying cavities with associated pulmonary fibrosis.

Of patients found to have evidence of disease on chest x-ray (*n*=325), isolated right-sided disease (*n*=173; 53.2%) was found to be more common than left-sided (*n*=127; 39.1%) or bilateral (*n*=25; 7.7%) (Table 5). In both lungs, isolated upper lobe involvement was much more prevalent (R: 54.5%; L: 52.0%) than lower lobe involvement (R:23.2%; L: 32.9%). Findings were also more common in the right middle lobe (10.6%) than the lingula (5.9%). A similar proportion of patients had multiple left lobes involved compared to multiple right lobes (11.6% vs. 9.2%, respectively). Mediastinal lymphadenopathy was seen in 13.5% of patients and absent in 85.7% with 0.9% having unknown mediastinal lymphadenopathy. When present, it occurred with initial infection 100.0% of the time and was only calcified in 2.2% of cases. *Characterization of Pulmonary Nodules*

Among all patients with nodules, the median number of nodules was 1 (Table 2) with a median size of 1-1.9 cm (IQR: 1-1.9 cm - 2-2.9 cm) (Figure 1). Nodules were more likely to have a sharp border (69.6%, *n*=142) than hazy border (0.5%, *n*=1). Nodules were calcified approximately 10.0% of the time. It was very rare for nodules to resolve on their own, with only 2.9% disappearing over the period of follow-up, a maximum of 11 years.

Characterization of Pulmonary Cavities

The prevalence of cavities in this cohort was found to be slightly lower (54.7%) than that of nodules, with the same median count of 1 (Table 2) and a slightly larger median size of 3-3.9cm (IQR: 2-2.9cm - 4-4.9cm) (Figure 1). Most cavities were not fluid-filled (60.1%, *n*=113), and of

those that contained fluid, completely filled (blockage) was more common than partial filling (18.6% vs 11.7%). Cavity walls were more likely to be thin (46.8%, *n*=88) than thick (31.4%, *n*=59) or variable (17.0%, *n*=32). Satellite lesions were approximately equally likely to be present or absent (45.7% vs 47.8%, respectively).

The majority of cavities were chronic (85.6%, *n*=161), with time to appearance not documented consistently enough for quantification. Just under half (48.9%, *n*=92) were discovered incidentally during work-up for an unspecified non-pulmonary syndrome, while 25.0% were diagnosed during the initial acute presentation of pulmonary CM. A small subset of cavities (6.9%, *n*=13) evolved from a pre-existing nodule. Cavities were more likely to remain unchanged (30.1%) than to evolve in any consistent manner. In those that did change during follow-up, no clear pattern predominated: 16.5% (*n*=30) closed, 2.7% (*n*=5) ruptured, and 5.3% (*n*=10) disappeared. A decrease in size was notably rare (1.6%, *n*=3).

Impact of Diabetes

Due to the association between diabetes and chronic pulmonary coccidioidomycosis, a small sub-group analysis of the 15 patients with diabetes was done. The size of pulmonary nodules was similar in the diabetes group with both having a median of 1-1.9 cm in size (Figure 3A). The size of pulmonary cavities was also similar in the diabetes group with a median size of 3-3.9cm (Figure 3B). None of the patients with diabetes died secondary to coccidioidomycosis. All-cause mortality for those with diabetes was higher at 14.3% (2/14), however, no information was available regarding glycemic control.

Laboratory Data

Complement fixation studies were performed for all patients. Those with cavitary-predominant and nodular-predominant disease were both found to have a negative median titer,

albeit with slightly different interquartile ranges (0-1:8 vs. 0-1:2) (Figure 2). Eighty-five percent of patients also received a coccidioidal antigen skin test (coccidioidin at dilutions of either 1:100 or 1:10), the results of which were recorded as either positive or negative rather than as diameter of induration. Seventy-four percent of skin tests were positive, with 26.0% negative.

Surgical Outcomes

Forty-eight patients (14.0%) underwent pulmonary resection during the period of follow-up. Indications for surgery included the need to differentiate from malignancy or mycobacterial infection (77.1%), hemoptysis (6.3%), or increased cavity size (6.3%). Patients receiving surgery were equally likely to have nodular or cavitary-predominant disease (50.0% each). Median lesion size in this subset of patients was similar to that of patients who did not receive surgery (2-2.9 cm, IQR: 1-1.9 cm - 3-3.9 cm). Left/right laterality in surgical patients were approximately equal (L: 45.8%; R: 54.2%), while upper lobe resection was more common than middle, lower, or multiple lobe involvement (56.3%, 2.1%, 31.3%, and 8.3%, respectively). The vast majority of resections were successful in removing all disease (87.5%).

Fourteen patients experienced complications, including surgical site infection, empyema, hemothorax, bronchopleural fistula, and air leak. The most common complication was air leak (n=3). Unfortunately, only limited data were recorded on the treatment and outcomes of these complications.

Clinical Outcomes

Excluding patients with fibrocavitary, unknown, or pleural disease, 4.6% (15/328) had a recorded death during the follow-up time (313 censored), which went to a maximum of 23 years for this study. In the cavity group, 6.5% died (10 out of 153, 143 censored) compared to 3.9% (5 out of 127, 122 censored) for the nodule group. For the pneumonia group, 0% (0 out of 48, 48

censored) of participants died. There were no significant differences in mortality (p=0.4086) when comparing pneumonic (0%), nodular (3.9%), or cavitary (6.5%) disease (Figure 3). Mortality attributed to coccidioidomycosis was even less frequent, with an overall mortality of 0.9%: 0% for those with pneumonic, 0.8% for nodular, and 1.3% for cavitary disease. Mean survival times in years were 12.17 (SE=0.28) for cavity patients, 6.82 (SE=0.10) years for nodule patients. Mean survival time was not estimable for pneumonia patients due to no observed events. Only 8.2% (n=27) of patients had documented need for ongoing medical care related to coccidioidomycosis at the end of the study period. Considering the primitive radiographic technology of the period, the lack of triazole antifungal agents, and the limited surgical techniques available, overall and mortality were low.

DISCUSSION

This large historical cohort of patients with non-disseminated coccidioidomycosis provides essential insights into the radiologic features and natural history of CM prior to the widespread use of amphotericin B or triazole antifungals. In our retrospective analysis, two general trends emerged in the chest radiographs of adult male patients with pulmonary CM. The first is that most nodules were small (median size = 1-1.9cm) and sharply demarcated. Since is it unusual for pulmonary lesions smaller than 3cm to be malignant,[16] this suggests that large pulmonary nodules are unlikely to be secondary to CM regardless of a patient's history of CM or serologic status. Second, cavities were found to be larger than nodules and non-fluid filled, and of variable wall thickness. Although coccidioidal cavities are often thin-walled on imaging, our findings demonstrate that this not uniformly the case.[17]

This longitudinal cohort study has the advantage of following patients for several years to better understand the trajectory of chronic nodules and cavities. Only 2.9% of nodules resolved

without specific intervention. This is helpful when considering the differential diagnosis of a pulmonary nodule in patients residing in coccidioidomycosis endemic regions with non-resolving nodules. This is consistent with current guidelines suggesting definitive evaluation of pulmonary nodules to differentiate malignancy from residual coccidioidal nodules.[8] While the dataset did not investigate if nodules increased in size, we have longitudinal data on cavities with the caveat of having limited data regarding the timing of initial cavity development. Cavities were very unlikely to disappear (5.3%) or decrease in size (1.6%). Interestingly, with regard to antifungal therapy in asymptomatic patients, there has not been compelling evidence that treatment improves the rate of cavity disappearance or decrease in size, leading to the recommendation to not treat those with asymptomatic cavitary coccidioidomycosis.[8] The cavity natural history was otherwise varied with 30.9% staying the same size and 19.1% increasing in size (Table 2). The feared complication of ruptured cavities was very rare, despite lack of treatment, only occurring in 2.7% of patients with cavities. In comparison to tuberculosis, another chronic pulmonary infection known to form cavities, the pathogenesis for cavity development appears similar with both diseases relying on caseous necrosis for cavity development.[18,19] However, whereas tuberculosis cavities propagate further disease, this is not seen in coccidioidomycosis.[18]

Our primary points of comparison here are two recent retrospective studies that have examined surgical approaches and outcomes in pulmonary coccidioidomycosis.[20,21] These two studies, which examine sequential cohorts at the same academic center in the American southwest, differ significantly from the present one. The Jaroszewski[20] and Ashfaq[21] cohorts include only surgical patients and are thus relatively small (*n*=86 and 58). They are less homogeneous than the mid-20th century VA demographically, drawing from a modern, mixed metropolitan and urban civilian population; they are more gender diverse (56% and 55% women, respectively, vs. 2.6%

in our series) and older (median age 58 and 52, respectively, vs. 34 in our series). In the Jaroszewski cohort, 12.0% of patients were immunosuppressed due to having received organ transplantation (vs. none in our study), and another 12.0% carried a diagnosis of diabetes mellitus a known risk factor for progression of CM, vs 4.4% in ours. The Jaroszewski participants also had a much higher baseline burden of cancer of unspecified type (40.0% vs. 1.2%). A sizeable portion of both these modern cohorts (32.0% and 41.0%, respectively) underwent antifungal therapy ranging in duration from 1 week to three years prior to surgical intervention, in contrast to the uniformly treatment-naïve population we examined. Finally, radiographic diagnostics improved dramatically between the 1950s and 2000s, increasing the likelihood of detecting pulmonary lesions in the more recent studies.

Both nodules and cavities were more prevalent in our dataset than in the other sets described above (59.3% vs 24.0% and 54.7% vs 11.0%, respectively). This may be explained by the fact that all patients in our cohort were initially hospitalized and subsequently followed longitudinally, allowing more opportunities for serial imaging, which increased the likelihood of detecting a radiographic abnormality. It is also likely that our cohort of hospitalized patients had more advanced or severe disease, on average, than the mix of ambulatory and in-patients reported by Jaroszewski and colleagues. While our study is not applicable to all patients that develop CM, it does suggest that those that develop symptomatic infection are likely to develop pulmonary sequalae of disease (e.g., nodule or cavity).

Our findings differ from those evaluating chronic forms of coccidioidomycosis, which have found higher median complement fixation titers, even as high as 1:64 in non-disseminated patients in other historical studies.[22] This was adduced as evidence that elevated titers could not be correlated with dissemination. To the contrary, our findings of consistently low titers in non-

disseminated patients support the use of elevated titers (greater than 1:16) as a marker of occult dissemination, consistent with other research from the period.[23,24] It should be noted that bias was potentially introduced into this dataset by excluding the small number of patients who received amphotericin B as presumably these patients had more significant symptoms.

A higher percentage of patients in this cohort underwent surgery for coccidioidomycosis (14.0%) as compared to 6.0% and 2.7%, respectively, in the Jaroszewki and Ashfaq cohorts. This is likely due to diagnostic innovations such as bronchoscopy, computed tomography imaging, and validated scoring systems[25] introduced in the past several decades that decrease the need for surgery in resolving diagnostic dilemmas. At the same time, the utility of surgery for workup of suspected coccidioidomycosis persists, as just over two-thirds of the surgical patients in the Jaroszewski cohort underwent surgery in order to differentiate CM from malignancy or other diagnoses.

Surgery was quite successful in this group, removing all infection in 87.5% of cases, with 14 patients (29.0%) experiencing at least one complication. These findings are similar to the Jaroszewki and Ashfaq cohorts, reporting complication rates of 21.0% and 19.0%, respectively,[20,21] and underscore that surgery for workup of suspected coccidioidomycosis is safe in most cases. It is worth noting that 34.0% and 95.0% of cases in these studies, respectively, received video-assisted thoracic surgery (VATS), a less invasive technique that was not available to the patients in our mid-century VA cohort. Overall, the list of surgical complications as well as their management, resembles those of the aforementioned modern cohorts. One major exception to this similarity is the use of thoracoplasty, a disfiguring technique that was commonly employed in the 1950s but is today primarily considered a salvage therapy.[26] This supports the use of surgical management in severe pulmonary coccidioidomycosis, particularly cavitary, as discussed in the

current guidelines[8]. These data demonstrate low mortality in those with pulmonary coccidioidomycosis especially when compared to patients in the same dataset, but with disseminated disease (all-cause mortality of 29.55% in non-central nervous system (CNS) disseminated patients and 96% in CNS disseminated patients).[15] Given that these patients did not receive any antifungal therapy and still had favorable outcomes related to mortality, this data supports the guideline recommendations related to monitoring patients off antifungal therapy for uncomplicated primary pulmonary coccidioidomycosis in those that are immunocompetent and otherwise young and healthy as those in this cohort.[8] While there were not significant differences in mortality when comparing patients with pneumonia, cavities, or nodules, visually there were trends for increased mortality in those with cavities and nodules compared to pneumonia. These data are limited by having only 8 patients (2.3%) with fibrocavitary disease, preventing meaningful analysis of this group. The mortality analysis was further limited by the duration of follow up. As seen in Figure 4, most deaths occur after over 50% of the patients have already been censored due to lack of follow up. This affects the survival probability over time as the at-risk population has decreased by the time deaths are occurring. There may have been a significant difference in mortality between pneumonia and either nodular or cavitary disease if there was longer follow-up for each group, but we were not able to see that in this analysis.

The limitations of the VA-Armed Forces data set are largely related to its historical nature and different pharmacotherapeutic context, have recently been described by Bays *et al.*[15] Nevertheless, this large dataset offers key clinical insights and a fruitful foundation for additional research. Moving forward, it would be helpful to recreate this study with large, diverse populations at the level of health systems, providing insight into the disease course in patients with a higher base rate of comorbidities, especially diabetes mellitus.[27] Though a rare comorbidity in our dataset,

diabetes mellitus is thought to exacerbate pulmonary coccidioidal lesions, requiring prolonged courses of antifungal therapy.[27,28] More data on diagnosis and management of coccidioidomycosis in this and other higher-risk populations are badly needed.

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Figure Legend:

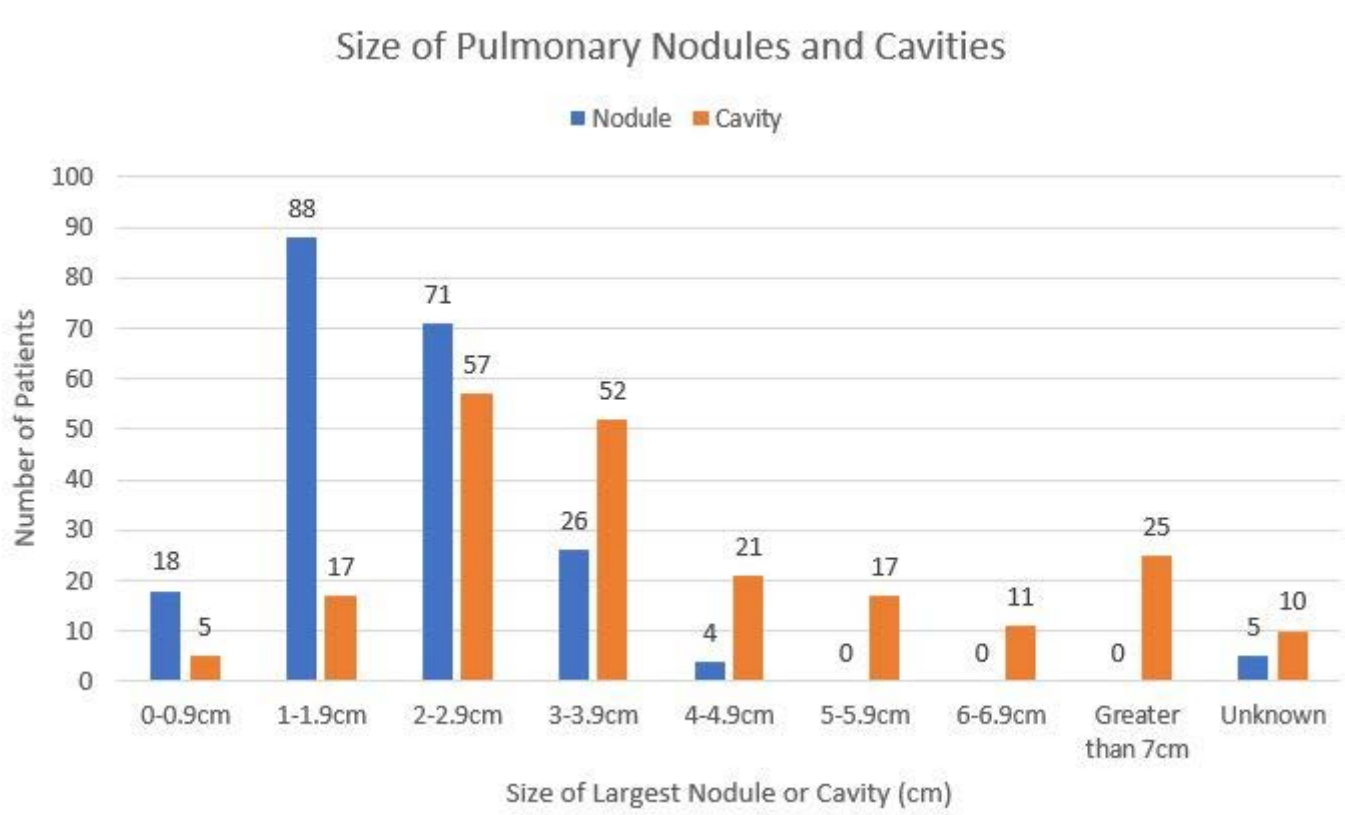
Figure 1. Size of Pulmonary Nodules and Cavities

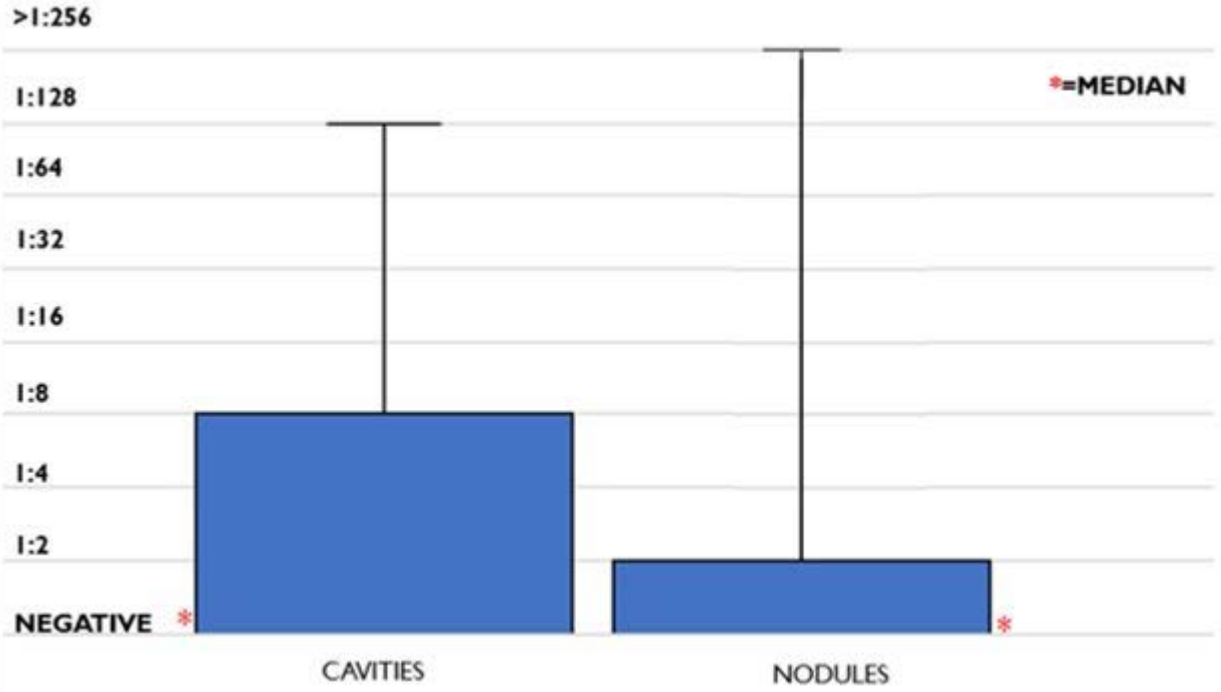
Figure 2. Complement Fixation Serologies of patients with pulmonary cavities and nodules

Figure 3A. Size of Pulmonary Nodules in Patients With and Without Diabetes

Figure 3B. Size of Pulmonary Cavities in Patients With and Without Diabetes

Figure 4. Kaplan-Meier Survival Estimates by Clinical Status with 95% Hall-Wellner Bands


Size of Pulmonary Nodules and Cavities
Nodule
Cavity
Number of Patients
100
90
80
70
60
50
40
30
20
10
0
18
5
88
17
71
57
26
52
4
21
0
17
0
11
0
25
5
10
0-0.9cm
1-1.9cm
2-2.9cm
3-3.9cm
4-4.9cm
5-5.9cm
6-6.9cm
Greater than 7cm
Unknown
Size of Largest Nodule or Cavity (cm)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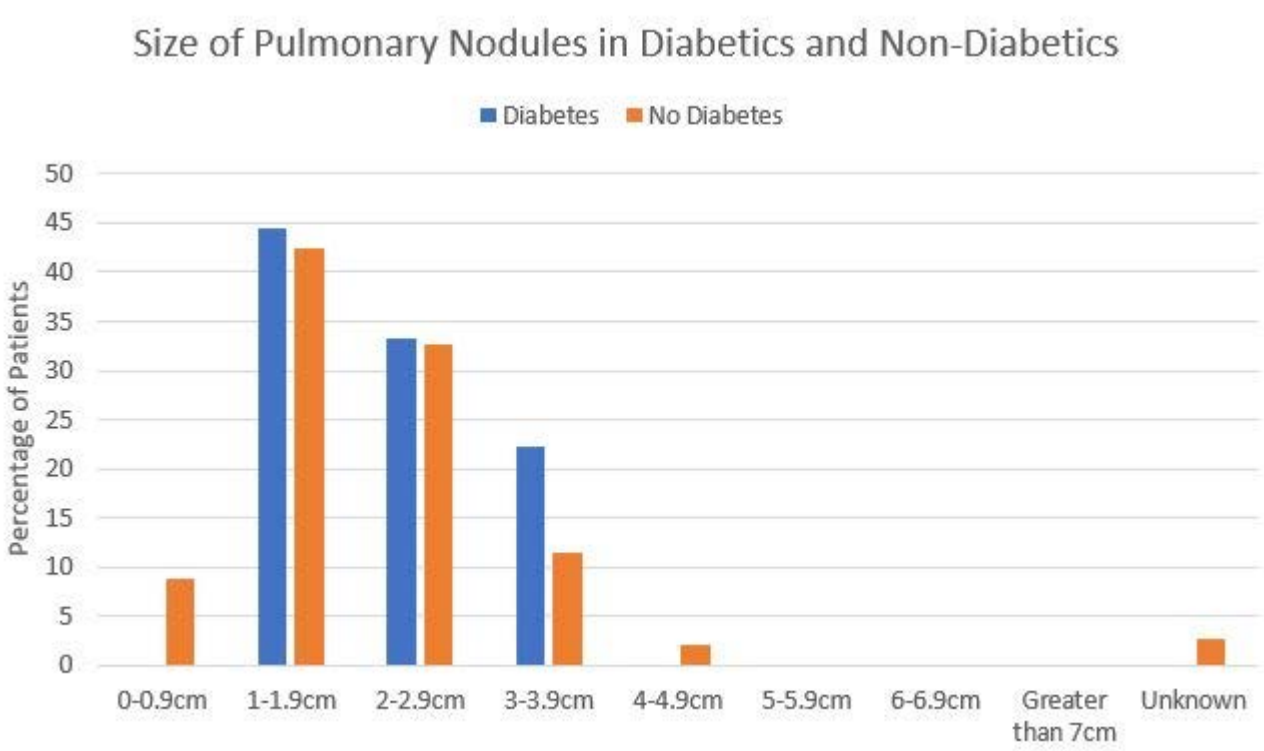
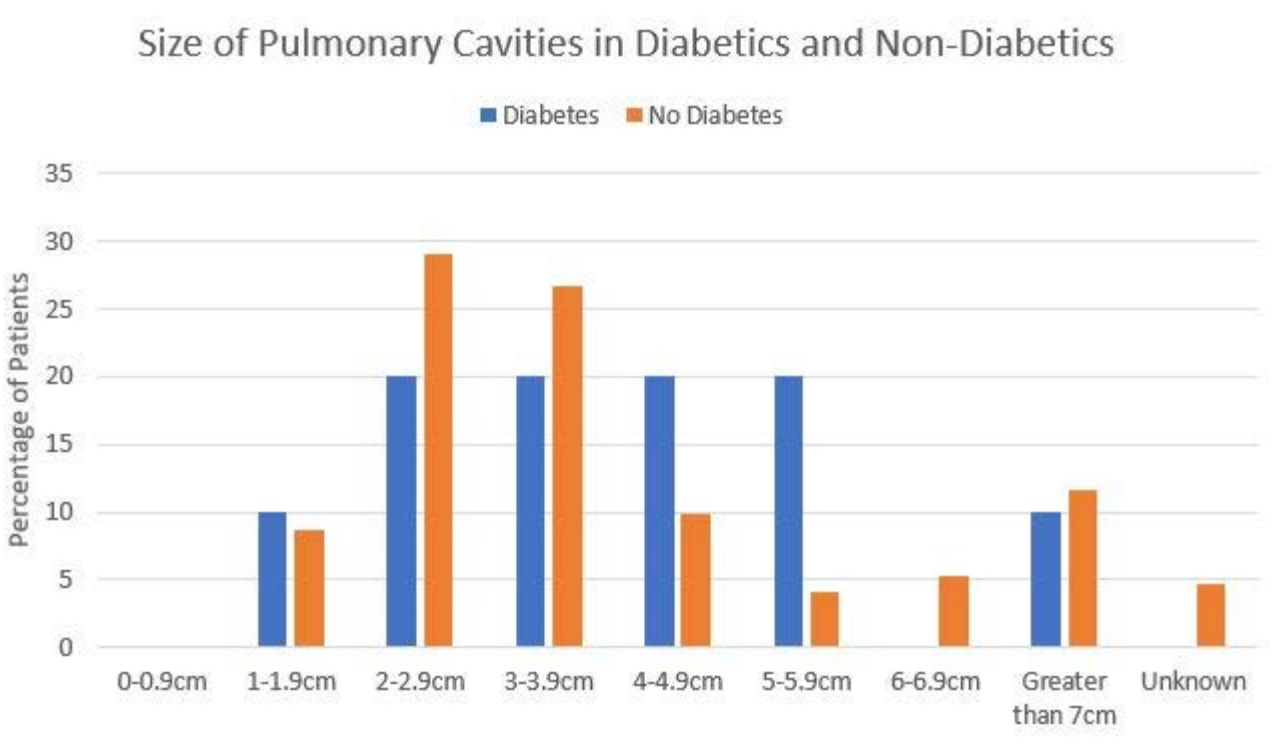
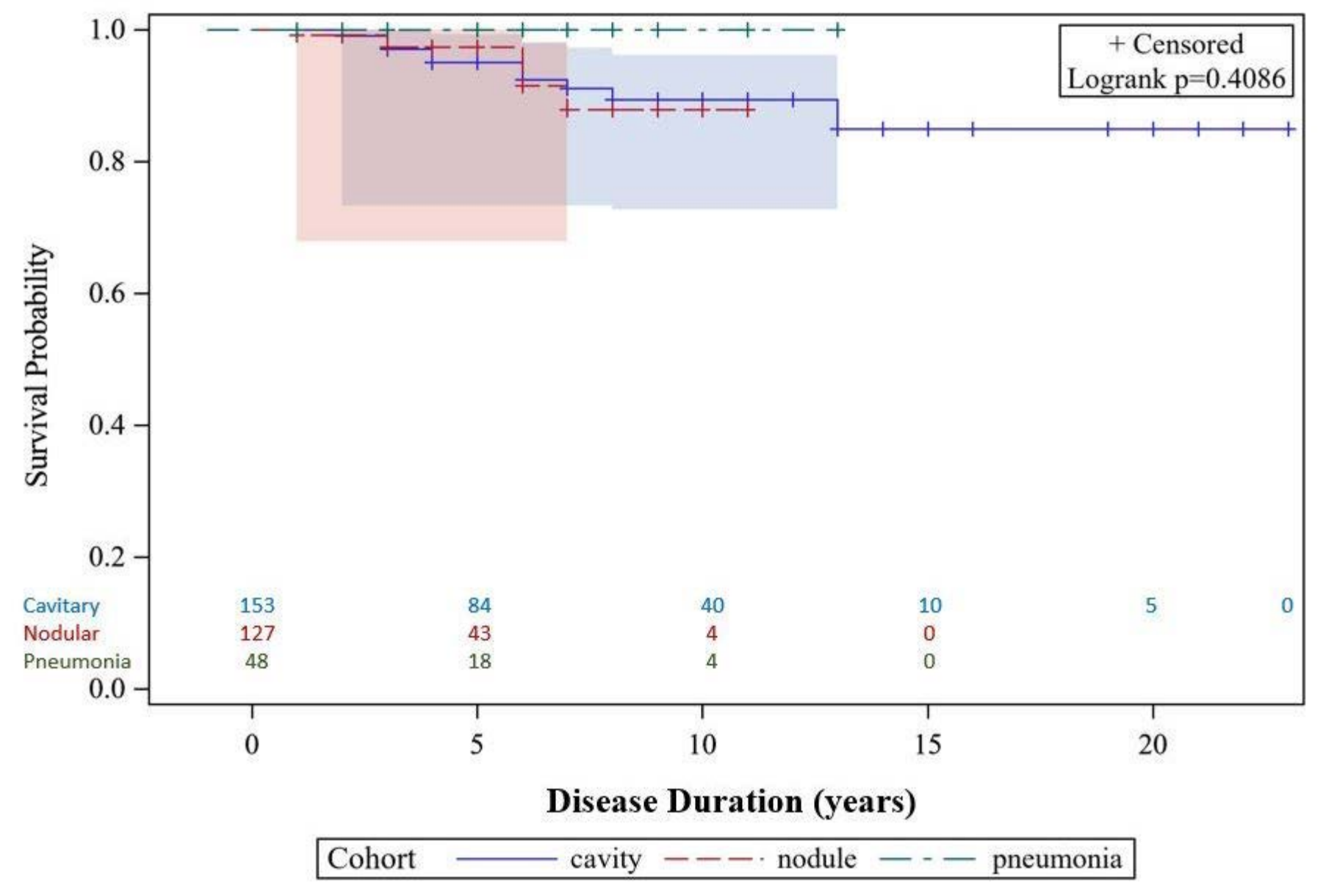
1:128
1:64
1:32
1:16
1:8
1:4
1:2
NEGATIVE
*=MEDIAN
CAVITIES
NODULES


Size of Pulmonary Nodules in Diabetics and Non-Diabetics
Diabetes
No Diabetes
Percentage of Patients
50
45
40
35
30
25
20
15
10
5
0
0-0.9cm
1-1.9cm
2-2.9cm
3-3.9cm
4-4.9cm
5-5.9cm
6-6.9cm
Greater than 7cm
Unknown


Size of Pulmonary Cavities in Diabetics and Non-Diabetics
Diabetes
No Diabetes
Percentage of Patients
35
30
25
20
15
10
5
0
0-0.9cm
1-1.9cm
2-2.9cm
3-3.9cm
4-4.9cm
5-5.9cm
6-6.9cm
Greater than 7cm
Unknown


+ Censored
Logrank p=0.4086
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Cavitary 153 84 40 10 5 0
Nodular 127 43 4 0
Pneumonia 48 18 4 0
0
5
10
15
20
Disease Duration (years)
Cohort cavity nodule pneumonia