

Clinical Implications of Size of Cavities in Patients With Nontuberculous Mycobacterial Pulmonary Disease: A Single-Center Cohort Study

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Research

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Abstract

Background

The presence of cavities is a poor prognostic factor in patients with nontuberculous mycobacterial pulmonary disease (NTM-PD). However, little is known about the characteristics of such cavities and their impact on clinical outcomes. The aim of this study is to investigate the size of cavities and their implications on treatment outcomes and mortality in patients with NTM-PD.

Methods

We included patients diagnosed with NTM-PD at Seoul National University Hospital between 1 January 2007 and 31 December 2018. We measured the size of cavities on chest computed tomography scans performed at the time of diagnosis, and used multivariable logistic regression and Cox-proportional hazards regression analysis to investigate the impact of these measurements on treatment outcomes and mortality.

Results

The study cohort comprised 421 patients (non-cavitary, n=329; cavitary, n=92) with NTM-PD. During a median follow-up period of 49 months, 118 (35.9%) of the 329 patients with non-cavitary and 64 (69.6%) of the 92 patients with cavitary NTM-PD received antibiotic treatment. Cavities >2 cm were associated with worse treatment outcomes (adjusted odds ratio, 0.38; 95% confidence interval [CI], 0.16–0.86) and higher mortality (adjusted hazard ratio, 2.50; 95% CI, 1.04–6.02), while there was no difference in treatment outcomes and mortality between patients with cavities \leq 2 cm and patients with non-cavitary NTM-PD.

Conclusions

Clinical outcomes are different according to the size of cavities in patients with cavitary NTM-PD; thus the measurement of the size of cavities could help in making clinical decisions.

Background

Nontuberculous mycobacteria (NTM) are ubiquitous micro-organisms that can be isolated from the environment, including soil and water [1]. The most common clinical manifestation of human NTM infection is pulmonary disease (PD) [2]. The burden of NTM-PD is currently increasing globally. Between 2008 and 2016, the annual incidence of NTM infection increased from 6.0 cases/100,000 person-years to 19.0 cases/100,000 person-years in South Korea [3]. Similar increases in incidence have also been reported in Japan [4], the USA [5], and Europe [6].

NTM-PD can be classified into clinical phenotypes according to radiographic presentations: nodular bronchiectatic (NB) and fibrocavitary (FC). NB types can be sub-classified into non-cavitary and cavitary

NB [7, 8]. The presence of cavities is reportedly associated with a worse prognosis [9]. The mortality risk is highest for the FC form, followed by cavitory NB, and non-cavitory NB forms. Similarly, the responses of cavitory NB and FC forms to antibiotic treatment are worse than those of non-cavitory NB forms [7, 8].

Because of their prognostic impact, it is recommended that patients with cavities commence antibiotic treatment, rather than be managed by watchful waiting [2]. Furthermore, more aggressive treatment, including parenteral agents, is also recommended for such patients [10, 11]. The presence of cavities in itself has been considered an important prognostic factor; however, the clinical course may vary according to the radiographic features of such cavities [12]. Nevertheless, the impact on treatment outcomes and mortality of radiographic features such as size of cavities has rarely been reported. In this study, we elucidated the relationships between the size of cavities and treatment outcomes and mortality in patients with NTM-PD.

Methods

Study design and subjects

This retrospective study included patients diagnosed with NTM-PD between 1 January 2007 and 31 December 2018, at Seoul National University Hospital. The diagnostic criteria for NTM-PD were as proposed in the American Thoracic Society/European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases/Infectious Diseases Society of America clinical practice guidelines [2]. Patients who were at least 18 years old and had chest computed tomography (CT) scans at the time of diagnosis were included. Patients who were lost-to-follow-up within a year after NTM-PD diagnosis were excluded from the analysis. Some of the patients were included in a previously reported prospective study that was launched on 1 July 2011 (NCT01616745) [13, 14]. This study was conducted in accordance with the tenets of the amended Declaration of Helsinki; the Institutional Review Board of Seoul National University Hospital approved the study protocol (IRB No. 2001-047-1092).

Baseline and follow-up data collection

The clinical and laboratory data at the time of NTM-PD diagnosis, including age, sex, body mass index (BMI), smoking history, comorbidities (chronic obstructive pulmonary disease, diabetes mellitus, and malignancy), sputum smear results, and the species of causative organisms, were collected for all patients. The species were identified by 16S rRNA and *rpoB* gene sequencing analysis [15–17]. Radiographic findings (presence of cavities and their size) were interpreted by three reviewers (one chest radiologist and two pulmonologists). The presence of a cavity was defined as a gas-filled space presenting as a lucent or as low-attenuated space within pulmonary consolidation [18]. Cavity size was determined by measuring the longest diameter on axial images. Three measurement was made and the average values used for analysis. Any discrepancies between the reviewers were resolved by discussion. The patients were classified according to the presence and size of cavities.

After diagnosis with NTM-PD, the patients were followed up every 3–6 months. At each follow-up visit, the patient submitted a sputum specimen for an acid-fast bacilli smear test and mycobacterial culture. Chest CT scans were usually performed at intervals of 2 years in patients being managed by watchful waiting and intervals of 6 months for patients on antibiotic treatment. Timing of initiation of anti-mycobacterial treatment was decided at the discretion of the on-duty physician on the basis of symptoms and radiographic changes. After initiation of treatment, the patients were followed up every 4–8 weeks.

Clinical outcomes

Clinical outcomes were assessed according to the criteria suggested by an NTM-NET consensus statement [19]. Culture conversion was defined as at least three consecutive negative mycobacterial cultures from sputum samples collected at least 4 weeks apart. Microbiological cure was defined as maintenance of multiple consecutive negative cultures of respiratory samples from after culture conversion until the end of anti-mycobacterial treatment. Patient death was confirmed using the database of the Ministry of the Interior and Safety, South Korea.

Statistical analysis

Data are presented as median values with interquartile ranges (IQRs) for continuous variables and as proportions for categorical variables. Wilcoxon's rank-sum test, Kruskal–Wallis test, and Fisher's exact test were used to compare continuous and categorical variables. Multivariate logistic regression analysis was used to identify factors associated with the presence of cavities in patients with NTM-PD. Kaplan–Meier analysis with log-rank test and Cox-proportional hazards regression were performed to analyse survival data. Variables with a P-value < 0.2 in univariate analysis were used in the multivariate analysis. A P-value < 0.05 was considered to denote statistical significance. All statistical analyses were performed with STATA 13.1 (College Station, TX, USA).

Results

Baseline characteristics of patients with NTM-PD

The study cohort comprised 421 patients with NTM-PD. Their median age was 64 years (IQR, 57–73 years) and 271 (64.4%) were women. Non-cavitary NTM-PD was diagnosed in 329 patients, the remaining 92 having at least one cavity at the time of diagnosis. The distribution of mycobacterial species did not differ significantly between non-cavitary NTM-PD (*M. avium* complex [MAC] 72.0%, *M. abscessus* complex 18.2% and others 9.8%) and cavitary NTM-PD (MAC 67.4%, *M. abscessus* complex 23.9% and others 8.7%) ($P = 0.464$). The median diameter of the cavities was 1.8 cm (IQR, 1.2–2.8 cm) and 53 patients (57.6%) had a single cavity. Median size (2 cm- rounded up) was used for further analysis, as described below.

A higher proportion of patients with cavitary NTM-PD (51.1%) than with non-cavitary NTM-PD (36.2%) had a history of previous pulmonary tuberculosis (TB). Positive sputum smears were also more prevalent

in patients with cavitory NTM-PD (29.4% versus 17.3%, $P = 0.017$). Patients with cavitory NTM-PD were younger ($P = 0.045$) and their BMI was lower ($P = 0.003$) than those of patients without cavitory NTM-PD. Further, the distribution of comorbidities and NTM species did not differ between these two groups (Table 1).

Table 1

Baseline characteristics of 421 patients with nontuberculous mycobacterial pulmonary disease according to the presence of a cavity

	Patients without cavities (n = 329)	Patients with cavities (n = 92)	P-value
Age, years, median (IQR)	65 (58–73)	63 (55–72)	0.045
Sex, female (%)	216 (65.7)	55 (59.8)	0.325
BMI, kg/m ² , median (IQR)	21.1 (19.6–22.6)	20.1 (18.6–21.9)	0.003
Former or current smoker, n (%)	79 (24.0)	22 (23.9)	0.984
History of pulmonary tuberculosis	119 (36.2)	47 (51.1)	0.011
Comorbidities, n (%)			
Diabetes mellitus	21 (6.4)	11 (12.0)	0.116
COPD	24 (7.3)	10 (10.9)	0.281
Malignancy	18 (5.5)	6 (6.5)	0.799
Sputum smear positivity, n (%)	57 (17.3)	27 (29.4)	0.017
Causative organism, n (%)			0.464
<i>M. avium</i> complex	237 (72.0)	62 (67.4)	
<i>M. abscessus</i> complex	60 (18.2)	22 (23.9)	
Others	32 (9.8)	8 (8.7)	
Abbreviations: IQR, interquartile range; BMI, body mass index; COPD, chronic obstructive pulmonary disease.			

Table 2
Clinical outcomes of 421 patients with nontuberculous mycobacterial pulmonary disease

	Patients without cavity (n = 329)	Patients with \leq 2 cm sized cavities (n = 48)	Patients with > 2 cm sized cavities (n = 44)	P-value
Follow-up duration, month, median (IQR)	49 (31–71)	41 (24–62)	51 (34–76)	0.212
Observed without treatment, n (%)	211 (64.1)	17 (35.4)	11 (25.0)	< 0.001
Spontaneous conversion in patients without treatment, n (%) [*]	66 (31.3)	8 (47.1)	4 (36.4)	0.396
Treated with antibiotics, n (%)	118 (35.9)	31 (64.6)	33 (75.0)	< 0.001
Microbiological cure, n (%) [†]	71 (60.2)	15 (48.4)	12 (36.4)	0.045
The denominators were patients who were observed without treatment [*] and patients who were treated with antibiotics [†] , respectively.				

Clinical course of NTM-PD according to the size of cavities

During a median follow-up of 49 months (IQR, 31–70 months), 239 patients (211 with non-cavitary and 28 with cavitary NTM-PD) were managed by watchful waiting and required no treatment. Of these patients, a higher proportion had non-cavitary (64.1%) than cavitary NTM-PD (30.4%) ($P < 0.001$). Sixty-six of the 211 (31.3%) patients with non-cavitary NTM-PD being managed by watchful waiting achieved culture conversion without treatment, as did 12 of the 28 (42.9%) patients with cavitary NTM-PD (8 patients with cavities \leq 2 cm and 4 patients with cavities $>$ 2 cm) ($P = 0.396$).

During the study period, 118 (35.9%) of the 329 patients with non-cavitary NTM-PD and 64 (69.6%) of the 92 with cavitary NTM-PD received antibiotic treatment. When patients were classified according to cavity size, those with cavities $>$ 2 cm (75.0%) were the most likely to require antibiotic treatment, followed by patients with cavities \leq 2 cm (64.6%), and patients without cavities (35.9%) ($P < 0.001$).

The proportion of patients who achieved microbiological cure was the lowest among patients with cavities $>$ 2 cm (36.4%), followed by those with cavities \leq 2 cm (48.4%), and those without cavities (60.2%) ($P = 0.045$). Finally, cavities $>$ 2 cm (adjusted odds ratio, 0.38; 95% confidence interval [CI], 0.16–0.86) were inversely associated with microbiological cure according to multivariable logistic regression. However, small cavities (\leq 2 cm) ($P = 0.207$) did not affect treatment outcomes (Table 3).

Table 3

Factors associated with microbiological cure in patients with nontuberculous mycobacterial pulmonary disease

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age, years	0.98 (0.95-1.00)	0.162	0.97 (0.94–1.01)	0.112
Sex, male	0.76 (0.41–1.41)	0.380		
BMI, kg/m ²	1.08 (0.96–1.21)	0.204		
History of pulmonary tuberculosis	1.09 (0.74–1.60)	0.676		
Comorbidities, n (%)				
Diabetes mellitus	1.00 (0.32–3.10)	0.999		
COPD	0.66 (0.25–1.75)	0.402		
Malignancy	1.30 (0.36–4.79)	0.689		
Causative organism, n (%)				
<i>M. avium</i> complex	Reference			
<i>M. abscessus</i> complex	1.35 (0.65–2.81)	0.415		
Sputum smear positivity	0.43 (0.22–0.85))	0.014	0.47 (0.24–0.93)	0.031
Size of cavity				
absence of cavity	Reference			
≤ 2 cm sized	0.62 (0.28–1.37)	0.240	0.59 (0.26–1.33)	0.207
> 2 cm sized	0.38 (0.17–0.84)	0.017	0.38 (0.16–0.86)	0.021

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Factors associated with mortality in patients with NTM-PD

During the study period, 32 of 421 (7.6%) patients died, comprising 21 of 329 (6.4%) with non-cavitary and 11 of 92 (12.0%) with cavitary NTM-PD. According to the log-rank test, there was a significant difference in mortality between patients with cavities > 2 cm and patients with non-cavitary NTM-PD ($P = 0.003$). However, there was no difference in mortality between patients with cavities ≤ 2 cm and patients with non-cavitary NTM-PD ($P = 0.897$) (Fig. 1). According to multivariable Cox-proportional hazards regression analysis, patients with cavities > 2 cm had a higher risk of death (adjusted hazard ratio, 2.50; 95% CI, 1.04–6.02) than did patients with non-cavitary NTM-PD (Table 4).

Table 4
Factors associated with mortality in patients with nontuberculous mycobacterial pulmonary disease

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, year	1.06 (1.02–1.10)	0.001	1.05 (1.01–1.09)	0.031
Sex, male	3.91 (1.80–8.47)	0.001	3.83 (1.59–9.26)	0.003
BMI, kg/m ²	0.86 (0.75–0.99)	0.030	0.83 (0.71–0.96)	0.013
History of pulmonary tuberculosis	1.44 (0.72–2.88)	0.305		
Diabetes mellitus	4.23 (1.89–9.44)	< 0.001	4.08 (1.55–10.8)	0.004
COPD	2.87 (1.33–6.17)	0.007	0.82 (0.32–2.09)	0.669
Malignancy	2.50 (0.96–6.52)	0.062	5.44 (1.81–16.3)	0.003
Causative organism				
<i>M. avium</i> complex	reference			
<i>M. abscessus</i> complex	1.67 (0.75–3.72)	0.210		
Sputum smear positivity	1.82 (0.84–3.94)	0.128	2.34 (0.98–5.62)	0.056
Size of cavity				
absence of cavity	Reference			
≤ 2 cm sized	0.89 (0.21–3.81)	0.879	0.89 (1.89–4.19)	0.882
> 2 cm sized	3.09 (1.40–6.79)	0.005	2.50 (1.04–6.02)	0.041
Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; COPD, chronic obstructive pulmonary disease.				

Discussion

In this study, we analysed the clinical course of 421 patients with NTM-PD according to the size of cavities at the time of diagnosis. We found that patients with cavities > 2 cm had worse treatment outcomes than did patients with non-cavitary NTM-PD. In contrast, patients with cavities ≤ 2 cm had treatment outcomes that were comparable to those of patients with non-cavitary NTM-PD. Our results support the need for planning treatment according to the radiographic features of cavities in patients with NTM-PD.

The presence of cavities in patients with NTM-PD has been recognised as an indicator of poor prognosis [9]. Cavities are associated with unfavourable treatment outcomes, including higher mortality [20, 21]. Cavity formation has been found more commonly in patients who do not respond to treatment than in

those with culture conversion [21]. Additionally, the presence of a cavity increases the risk of all-cause mortality in patients with *Mycobacterium avium* complex pulmonary disease (MAC-PD) [20]. Moreover, large cavities are strongly associated with disease progression [12]. However, the impact of detailed differentiation based on radiographic findings has not been reported.

NTM-PD has been classified into NB and FC types [11]. However, it is sometimes difficult to clearly differentiate between these types. Bronchiectasis co-exists with cavities in most patients with NTM-PD [22]. Pathologic findings on examination of specimens from patients with NTM-PD has suggested that peri-bronchial nodules evolve into cavities [22]. Another cohort study found that cavities develop over time, even in the NB form of MAC-PD [23]. If we assume that bronchiectasis and cavities are on the same disease spectrum, NTM-PD could be differentiated initially by the presence of one or more cavities and the extent of those cavities. In our study, we classified NTM-PD according to the presence and size of cavities.

Patients with cavitary NTM-PD more frequently received antibiotic treatment than those without cavities. When the cavity was > 2 cm in diameter, the treatment outcome was unfavourable. The mortality rate was also higher in patients with cavities > 2 cm. However, the cavities ≤ 2 cm did not affect the clinical outcomes. In our study, cavities only had an impact on the prognosis of patients with NTM-PD when they were > 2 cm.

Cavitation in the lung results from a number of pathological processes, including suppurative, caseous, and ischemic necrosis [24]. In NTM-PD, cavitation occurs in patients with more extensive disease and the cavities contain numerous organisms [24, 25]. Drugs penetrate cavities poorly and sub-therapeutic drug concentrations in these lesions can lead to acquired drug resistance [26]. These factors explain the worse outcomes of patients with NTM-PD with cavities > 2 cm.

Interestingly, in our study, a small cavity (< 2 cm) was not associated with poor prognosis. Large cavities were more prevalent in progressive cavitary NTM-PD [12]. Thus, the favourable outcomes of small cavities in patients with NTM-PD may be attributable to slow disease progression. Another possible explanation is that, once such cavities have been detected, more careful monitoring and aggressive treatment are adopted, resulting in favourable outcomes given that such patients respond better to treatment than do those with larger cavities.

Our findings suggest the need for more detailed planning of treatment for cavitary NTM-PD according to the characteristics of the cavities. Recent guidelines recommend initiation of antibiotic treatment for NTM-PD rather than watchful waiting, especially when sputum smears are positive for acid-fast bacilli or when there is evidence of cavitary lung disease [2]. Parenteral agents are recommended for cavitary disease in patients with MAC-PD, [2, 10]. Our results suggest a more complex treatment strategy for patients with cavitary NTM-PD. In patients with > 2 cm, immediate and intensive treatment is indicated. If the cavity size is ≤ 2 cm, whether or not to treat should be decided on the basis of the overall clinical situation, under the premise that watchful follow-up is guaranteed.

Retrospective studies from South Korea have shown that the condition of about 40% of patients with non-cavitary NB NTM-PD remains stable when they are observed without treatment [27, 28]. Spontaneous culture conversion occurs in 35–50% of untreated patients [27, 28]. In our study, spontaneous conversion was achieved in 12 of 28 patients (42.9%) with cavitary NTM-PD who had been undergoing regular monitoring without initiation of treatment. Thus, when an immediate initiation of treatment is not available, watchful waiting might be a valid management option for patients with small cavities, once close monitoring is ensured.

This study has some limitations. First, the causes of the cavities could not be determined. Although the cavities were suggested to be the manifestation of NTM-PD, we could not completely exclude the possibility of combined fungal infection or other chronic infection [29, 30]. Second, we did not use the classical classification of NB or FC forms in our analysis. In fact, cavities frequently co-exist with bronchiectasis and some of cavities develop from bronchiectatic changes [22]. It is difficult to distinguish between non-cavitary NB, cavitary NB, and FC types in some patients. In contrast, a classification based on size may be easier to use.

Conclusions

In conclusion, the clinical outcomes of patients with cavitary NTM-PD differ according to the size of cavities. A cavity > 2 cm in size in patients with NTM-PD is associated with unfavourable treatment outcomes and higher mortality, whereas cavities \leq 2 cm do not affect the prognosis. The radiographic features of cavities could help clinicians to decide whether to initiate treatment or not.

Abbreviations

aOR = adjusted odds ratio

BMI = body mass index

CT = computed tomography

FC = fibrocavitary

IQR = interquartile range

NB = nodular bronchiectatic

NTM = nontuberculous mycobacteria

PD = pulmonary disease

Declarations

Ethics declarations

Ethics approval and consent to participate

Ethics approval was obtained, and consent was waived by the Institutional Review Board of Seoul National University Hospital approved the study protocol (IRB No. 2001-047-1092).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflict of interest to declare.

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Authors' contribution

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, were fully responsible for all content, and were involved at all stages of manuscript development. HRK and NK designed the study and protocol. HRK, EJH and NK did the data analysis. HRK, JJY and NK wrote the initial draft of the manuscript and all authors were involved at all stages of critical revision of manuscript. All the authors read and approved the final manuscript.

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Figures

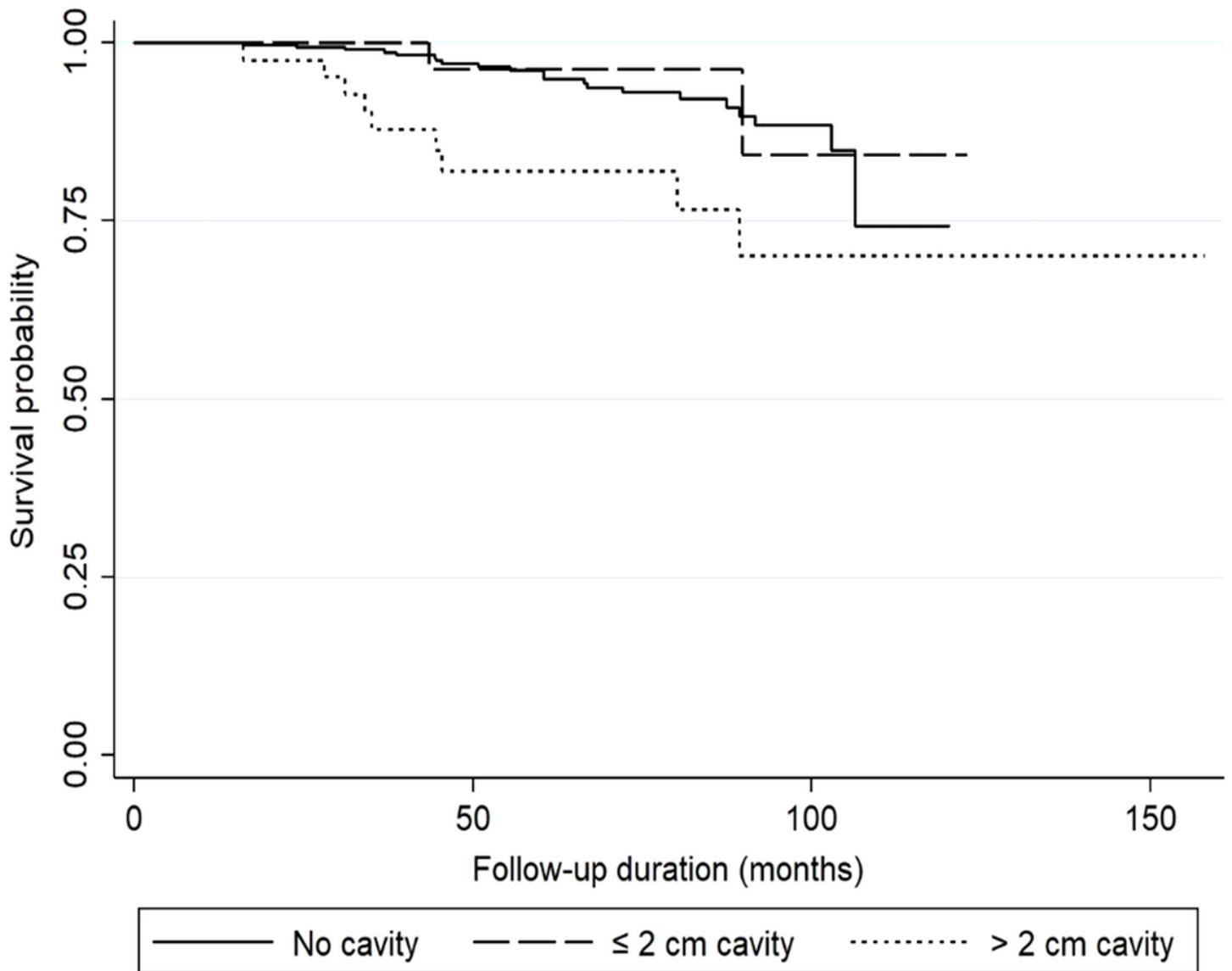


Figure 1

Kaplan–Meier curve according to the presence and size of cavities.