The four-drug fixed-dose combination reduced the loss to follow up from TB treatment in Brazil: additional evidence comparing two prospective cohorts at the same health centers

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Abstract

Background: Loss to follow up (*LTFU*) is an obstacle to improving tuberculosis (TB) indicators. The aim of this study was to evaluate the incidence of and risk factors for *LTFU* from TB treatment by comparison of two prospective cohorts enrolled at the same health centers in southern Brazil: patients who used RH-FDC + Z regimen (2007-2010) and 4-FDC regimen (2018-2019).

Methods: Predictors of *LTFU* were investigated using univariate and multivariate multilevel Cox regression models.

Results: Of the 296 cases included, 247 (83.5%) and 49 (16.5%) had *cure* and *LTFU* as outcomes, respectively. Patients treated in first period (RH-FDC + Z regimen) and those with substance abuse (drug addicts, alcoholism, and smokers) had a higher risk for *LTFU* from TB treatment ($p < 0.05$). Accordingly, the cases treated with RH-FDC + Z regimen showed a HR of 2.25 (95% CI: 1.03 - 4.94, $p = 0.042$).

Conclusions: The main result of this research was the significant reduction in the *LTFU* from TB treatment after the consolidation of the 4-FDC in Brazil, strengthening the premise that the presentation of drugs in this way improves treatment adherence. Also, substance abuse should be investigated more carefully in TB patients and systematically recorded as risk factors for *LTFU*, to contribute to better outcomes. Although the TB treatment 4-FDC regimen analyzed is already in use, these new regimens should be implemented with simultaneous pharmacovigilance studies and pragmatic cohort or trial designs to simulate real-world clinical practice, as done by this study.

Background

Non-adherence to drug treatment and consequent loss to follow up (*LTFU*) are identified as majores obstacles to the improvement of tuberculosis (TB) indicators [1, 2], which is among the top deadly infectious diseases worldwide [3]. This is curable when diagnosed and treated correctly, otherwise, when treatment is interrupted or irregular there is an increased transmission time [1, 4], which can also lead to the emergence of drug-resistant cases [5].

To reduce the incidence of TB, the World Health Organization (WHO) recommends that countries keep the treatment success rate above 85% and *LTFU* below 5%. Worldwide, for new cases and relapses that started treatment in 2018, the *LTFU* rate was approximately 5% [3], and in Brazil, among new cases, this indicator was of 11.6% [6].

According to WHO recommendations worldwide, in Brazil, from December 2009 onwards the basic regimen for TB treatment, based on rifampicin and isoniazid in fixed-dose combination (FDC), plus pyrazinamide (RH-FDC + Z), was replaced by the four-drug in FDC regimen (4-FDC), which added ethambutol to the three medications already used, in addition to adjusting the medication doses [5,7].

This regimen consists of two months of intensive phase with the 4-FDC and four months of maintenance with RH, also in FDC [5, 8]. Thus, it was expected that the presentation in 4-FDC would increase the effectiveness of TB treatment, by reducing *LTFU* from TB treatment due to the smaller number of pills to be swallowed, and due to possible better tolerance to the medicines [5, 7, 8].

Despite the expected advantages of FDC anti-TB regimens, questions about their effectiveness have not been completely answered. Many randomized controlled clinical trials (RCT) and observational studies have been conducted to assess the effectiveness of FDC regimens to improve TB treatment outcomes. Due to the more intuitive advantages, FDC formulations are recommended for the treatment of TB by WHO, but further studies are still needed, especially to assess its impacts on adherence [8].

Thus, the main aim of this study was to evaluate the *LTFU* time of TB treatment before and after changing to the 4-FDC regimen. In the present study, this influence of the therapeutic regimen on *LTFU* was controlled for clinical and sociodemographic variables. Our main hypothesis is that the 4-FDC regimen would reduce the risk of *LTFU.*

Methods

Study design

This is a prospective cohort study, which recruited adult patients who started treatment for TB at three referral centers in the city of Juiz de Fora, Minas Gerais, Brazil, which comprised more than 50% of all treatments performed in this municipality according to the database of the Brazilian Notifiable Diseases Information System (NDIS).

Two follow-ups were performed: the first, with patients who started treatment from November 2007 to March 2010 (RH-FDC + Z), and the second from July 2018 to November 2019 (4-FDC). The cases were monitored from the first day of medication use until the end of treatment.

Study setting and population

Juiz de Fora has the highest incidence of TB in the state of Minas Gerais, reaching 41.8 cases per 100 000 inhabitants in 2018, being considered a priority for TB prevention and care in Brazil. Primary health care diagnosed less than a third of TB cases in the same year in the municipality, while the three centers involved in this study, secondary and tertiary care providers, remained the main treatment units. The Directly Observed Treatment Short-course (DOTS) strategy, recommended worldwide to strengthen adherence to TB treatment, covered only 9.5% of cases [9].

Centers 1 and 2 are of secondary complexity and attend general TB patients and HIV/aids patients, respectively; center 3 is a hospital unit.

This research included only new TB cases to avoid including patients with longer treatment regimens, and to better compare the two cohorts focusing on only changing in the first-line drugs for TB treatment. Other inclusion criteria were patients aged 18 years or older, with a diagnosis confirmed by bacteriological tests (smear or positive culture), molecular biology (rapid molecular test for positive TB) or histopathology suggestive of TB (presence of granuloma with caseous necrosis).

Patients were provided with adherence counselling and TB health education by health care workers at the start of TB treatment and on recurrent visits.

Data collection

The data were collected through a semi-structured questionnaire for interviewing patients and a form to verify additional information in medical records and in the NDIS. The data collection instrument used was previously validated in a Brazilian study [10].

The patients were approached at the treatment centers and invited to participate in the research, by signing the informed consent form. In the interview, sociodemographic, economic, behavioral, and clinical information was collected.

Variables

The outcome of interest was defined as the time of occurrence of *LTFU* from TB treatment, as classified by the Ministry of Health of Brazil: “a patient who used medication for 30 days or more and interrupted treatment for 30 consecutive days or more”, or “a patient who used medication for less than 30 days and interrupted 30 consecutive days or more, or when the diagnosed patient does not start treatment” [5].

The time variable was defined in days between the treatment start date and the occurrence of *LTFU*, or the cure (censorship).

The explanatory variables were grouped into three hierarchical levels:

i. distal (socio-demographic and economic variables).
ii. middle (health care variables).
iii. proximal (individual and behavioral variables).

While in the treatment period 1, RH-FDC + Z was the only basic regimen used for new TB cases; in the period 2, they used exclusively the 4-FDC one.

The instruments to assess illicit drug consumption were already tested for validity and reliability in previous Brazilian studies [10]. The Cut down, Annoyed, Guilty, Eye-opener (CAGE) questionnaire was used to screen persons at high risk of alcoholism, considering two affirmative responses or more as a

high risk [11]. Tobacco addiction was considered to be the consumption of 10 or more cigarettes per day.

Data analysis

Descriptive epidemiology was done, and the chi-square test was used to compare characteristics of patients included and excluded who started TB treatment in both periods.

Survival analysis techniques were used to identify the variables associated with the time of occurrence of *LTFU* from TB treatment, especially the two treatment periods, which bring intrinsic each regime used. The magnitude of association was determined by the Hazard Ratio (HR).

Survival analysis considered *LTFU* and cure. The other outcomes, such as patients who failed or died during the study period were excluded from the analysis, because these explanatory variables could be associated with both *LTFU* and death or other negative outcomes. Thus, the use of the participation times of individuals censored with negative outcomes could bias resulting towards the null, as previously stated [12, 13].

The survival curves were estimated using the Kaplan-Meier method. Then, a comparison between the patients treated in the two treatment periods was done using the Log-rank statistical test. These survival curves were analyzed using the total of patients treated per period and stratifying them by treatment center.

Cox's proportional hazards model was used for univariate and multivariate analyses. All variables associated with the time of *LTFU* with a p-value ≤ 0.20 in the univariate analysis were included in the multiple regression model, performed hierarchically from the distal to the proximal level. The variables with significance $p \leq 0.05$ remained in the final model.

The assumption of proportional hazards for the final model was verified by graphic inspection and adjustment test by Schoenfeld residuals. This adjustment was considered adequate if $p > 0.05$.

Also, we compared by chi square whether each treatment period differed from the other with respect to the variables sex, skin color, age, education, dwelling type, institutionalization, place of residence, family income, alcoholism, illicit drugs, hospitalization during TB treatment and treatment center. Complementary, the variables considered different ($p \leq 0.05$) were added to the final multivariate model to assess whether even in an over-saturated model, adjusted for all possible confounding variables, the treatment period variable would still prevail as a significant predictor of *LTFU*, our main hypothesis tested in this study.

The IBM Statistical Package for the Social Sciences 21 software (IBM Corp., Armonk, NY, USA) was used for survival analysis and R 3.0.2 (R Foundation for Statistical Computing Platform, Vienna, Austria) for the evaluation of the goodness of fit of the multivariate model.

Results

Descriptive analyses

438 patients who started treatment for TB were interviewed, with 349 being classified as new cases. The treatment outcomes for new cases are described in figure 1.

Patients of potential interest (n = 349) were followed up during their TB treatment. From this group, 247 (70.8%) were successfully treated, 49 (14.0%) patients were *LTFU* and 53 (15.2%) had outcomes other than cure or *LTFU* and were not eligible for current analyses. This study therefore consisted of 296 patients (247 cures and 49 *LTFU*).

Most patients discontinued treatment after the intensive phase. There were 17 (34.7%) and 32 (65.3%) *LTFU* recorded from the beginning up to 90 days and after 90 days of treatment, respectively.

The characteristics of the patients were not significantly different ($p > 0.05$) between those included and not included in both study periods [14]. In the last period only sex ($p = 0.023$) was considered significantly different.

Kaplan-Meier Survival Curves

There was a significant difference ($p = 0.031$) in the comparison of survival function curves between patients treated in both periods. At the end of six months of treatment, the accumulated survival was approximately 82% for period 1 (RH-FDC+Z) and 90% for period 2 (4-FDC) (figure 2). Stratified by treatment center, the p-values were < 0.05 in both centers 1 and 3, and borderline ($p = 0.08$) in the center 2 (figure 3).

Cox's proportional hazards models

Table 1 and table 2 show the univariate analysis and the final multivariate model for LTFU from TB treatment, respectively. The variables treatment period, treatment center, alcoholism, excessive cigarette consumption, and use of illicit drugs were predictors of LTFU in the final model, which showed a good fit confirmed by the Schoenfeld's residuals analysis, reinforcing that this model met the assumption of proportional hazards.

The variables sex, dwelling type, institutionalized, hospitalization during TB treatment, and those variables that were already in the final model, were significantly ($p < 0.05$) associated with the two treatment periods. Then, in an over-saturated model with all these variables, the treatment period variable remained as a predictor for *LTFU* from TB treatment ($p = 0.05$), and as expected, all other variables lost their significance.

Table 1

Univariate Cox regression analysis of selected variables associated with LTFU from tuberculosis treatment

Table 2

Multivariate Cox regression model for LTFU from tuberculosis treatment

*CAGE: Cut down, Annoyed by criticism, Guilty, and Eye-opener.

Summary of multivariate model: Rsquare = 0.312 (max possible= 0.796); Likelihood ratio test = 83.31 on 7 df, p=2.887e-15; Wald test = 61.13 on 7 df, p=8.967e-11; Score (logrank) test = 95.36 on 7 df, p=0; Schoenfeld residuals = 11.387, p = 0.123

Discussion

This study showed that the variable *treatment period* (corresponding to the two different treatment regimens) was an independent predictor of *LTFU* from TB treatment. *LTFU* for new TB cases in this study was 14% when considering all outcomes, almost three times the 5% limit recommended by WHO. The study population represent those seen in the municipality.

The Kaplan-Meier curves, as well as the Cox regression analysis, demonstrated a reduction in LTFU rates in the most recent treatment period, in which patients exclusively experienced the 4-FDC regimen.

We consider this change for the 4-FDC regimen the main reason for this reduction. Although the two groups were followed at different times, the treatment centers were the same and the epidemiological TB situation in the study municipality remained similar for many aspects, such as the high centralization of treatments in secondary and tertiary care centers, as well as low adherence to strategies such as search for respiratory symptomatic patients and DOTS [9].

Most of the previous studies that compared TB treatment outcomes of FDC versus separate antituberculosis formulation (rifampicin, isoniazid, pyrazinamide, and ethambutol) were RCTs and found no protective effects on cure, relapse, adherence, or smear conversion rates [15–17]. However, one meta-analysis showed that 4-FDC therapy provides greater patient comfort and reduced the incidence of gastrointestinal adverse effects, in addition to simplifying pharmaceutical management at all levels [17].

Observational studies, on the other hand, have explored other outcomes, such as *LTFU* from TB treatment. A broad matched cohort showed an incidental finding of reducing deaths among 4-FDC compared to the RHZE group, however the rates of noncompliance, failure, and success had no

Variable	Total (N = 296)	LTFU (%)	Univariate Analysis	
			HR (CI 95%)	p-value
Group 1 (distal)				
Skin color				0.172
White	92	9 (9.8)	1.0	
Black or brown	149	25 (16.8)	1.70 (0.79 – 3.65)	
Education				0.012
Incomplete high school to complete postgraduate	105	8 (7.6)	1.0	
None to complete elementary school	174	34 (19.5)	2.69 (1.24 – 5.80)	
Dwelling type				0.068
Own, rented or assigned	238	34 (14.3)	1.0	
Homeless or institutionalized	43	11 (25.6)	1.89 (0.95 – 3.72)	
Family income				NS*
Greater than 2 minimum wages	107	13 (12.1)	1.0	
Less than or equal to 2 minimum wages	136	21 (15.4)	1.24 (0.62 – 2.48)	
Group 2 (intermediate)				
Treatment period				0.035
2 (2018-2019)	107	12 (11.2)	1.0	
1 (2007-2010)	189	37 (19.6)	2.07 (1.05 – 4.07)	
Hospitalization at some stage of treatment				<0.001
No	138	6 (4.3)	1.0	
Yes	158	43 (27.2)	6.95 (2.95 – 16.34)	
Treatment center				
Center 1	158	7 (4.4)	1.0	<0.001
Center 2	26	6 (23.1)	5.62 (1.89 – 16.77)	
Center 3	112	36 (32.1)	8.38 (3.72 – 18.85)	

HIV testing				0.001
Negative	204	23 (11.3)	1.0	
Positive	27	6 (22.2)	1.97 (0.8 – 4.86)	
Unrealized	65	20 (30.8)	3.12 (1.71 – 5.7)	
Group 3 (proximal)				
Sex				0.005
Female	85	5 (5.9)	1.0	
Male	211	44 (20.8)	3.74 (1.48 – 9.43)	
Alcoholism				<0.001
No (CAGE 0-1) *	140	7 (8.1)	1.0	
Yes (CAGE 2-4)	129	32 (32.9)	5.34 (2.36-12.1)	
Excessive cigarette consumption (10 or more cigarettes per day)				<0.001
No	145	11 (7.6)	1.0	
Yes	88	27 (30.7)	5.04 (2.49 – 10.21)	
Use of illicit drugs				<0.001
Never used or never used in the last year	171	9 (5.3)	1.0	
Former user	57	8 (14)	2.69 (1.03 – 6.98)	
Current user of cocaine or crack as hardest drug	41	21 (51.2)	12.64 (5.77 – 27.71)	

*LTFU: Loss to follow up; CAGE: Cut down, Annoyed by criticism, Guilty, and Eye-opener; NS: Not significant.

significant difference in both groups [18].

Among Brazilian research, a retrospective study, using secondary data, showed that the 4-FDC had a protective effect against *LTFU* compared to RH-FDC + Z, reducing it by 14% [19]. Accordingly, the present study showed a reduction in the accumulated incidence of *LTFU* in the second treatment period (4-FDC) of around 40%. Conversely, two Brazilian studies from secondary data did not find significant differences in the rates of recurrence, cure, and *LTFU* between the RH-FDC + Z and RHZE-FDC groups [20, 21].

Unlike the previously reported studies, Brazilian studies used two different regimens, and not only the formulation are compared. Thus, as previously stated [19] we cannot conclude that the benefits of the 4-FDC regimen were due exclusively to its fixed-dose presentation, since doses were different and an additional drug, ethambutol, was included [19].

Variable	Multivariate Analysis	
	HR (95% CI)	p-value
Group 2 (intermediate)		
Treatment period		0.042
2 (2018-2019)	1.0	
1 (2007-2010)	2.25 (1.03 – 4.94)	
Treatment center		<0.001
Center 1	1.0	
Center 2	3.92 (0.69 – 22.10)	
Center 3	9.43 (3.52 – 25.27)	
Group 3 (proximal)		
Alcoholism		0.044
No (CAGE 0-1) *	1,0	
Yes (CAGE 2-4)	2.42 (1.02 – 5.71)	
Excessive cigarette consumption (10 or more cigarettes per day)		0.002
No	1.0	
Yes	3.50 (1.59 – 7.69)	
Use of illicit drugs		<0.001
Never used or never used in the last year	1.0	
Former user	2.73 (0.92 – 8.11)	
Current user of cocaine or crack as hardest drug	8.84 (3.73 – 20.96)	

The discrepant results between Brazilian epidemiological studies may be due to differences in design, the data origin, as well as the type of data analysis. In a previous study of our team, some quality problems were evidenced with secondary TB data from this municipality of study [14]. Therefore, we chose to follow the TB treatment outcomes directly in the first and in the second treatment periods, using the same outcome classification criteria.

Because randomization is not possible in cohort studies, we adjusted for potential confounding variables at the individual and additional levels. It was confirmed that patients with RH-FDC + Z regimen had a higher risk for *LTFU* from TB treatment. Additionally, patients treated by hospital and those with

substance abuse were likely to *LTFU*. There is extensive evidence reinforcing that substance abuse can compromise adherence to drug treatment for TB and cause *LTFU* [1, 13, 22, 23].

The high percentage of patients assisted by the hospital (37.8%) in this study suggests that it exceeds the cases for which the tertiary care level is recommended and underestimates the importance of primary health care in TB control [5]. This concentration at secondary and tertiary care levels has hampered the effective implementation of DOTS in this priority place. Thus, it was not possible to analyze the effect of the DOTS strategy on *LTFU*, because the use of this strategy was incipient in both treatment periods.

This is the first Brazilian prospective cohort study that highlights that the change for the 4-FDC regimen had a protective effect against *LTFU* compared to RH-FDC + Z among new TB cases in Brazil. To further strengthen this result found, a model over-saturated was tested in this study, by inclusion of several additional confounding variables to those already present in the final multivariate model. The last treatment period (4-FDC regimen) remained significantly associated to lower risk of *LTFU*, which reinforced the evidence we advocated.

Regarding the time of occurrence, most patients were considered *LTFU* after the intensive phase, as evidenced in other studies [2, 24]. The prolonged treatment time is a factor that hampers adherence, being essential the establishment of effective schemes in lower times.

Conclusions

In summary, this study highlights that the 4-FDC regimen significantly reduced the *LTFU* from TB treatment in Brazil. In particular, this research strengthens the premise that presentation in 4-FDC facilitates adherence to TB treatment.

Additionally, in priority countries and regions for TB prevention and care, such as this study county, aspects such as substance abuse should be investigated more carefully in the anamnesis of each patient and systematically recorded as risk markers of treatment default, to contribute to better outcomes.

The primary health care capacitation to diagnose TB cases and manage its treatment properly, especially expanding the coverage of the DOTS strategy according to WHO recommendations, is a fundamental strategy to further reduce the high *LTFU* rates seen in this study.

Finally, although the TB treatment 4-FDC regimen analyzed is already in use, these new regimens should be implemented with simultaneous pharmacovigilance studies and pragmatic cohort or trial designs to simulate real-world clinical practice [18, 19, 25], as done by this study. Accordingly, the results of the present study were communicated to health managers as a knowledge translation process.

Abbreviations

CAGE: Cut down, Annoyed by criticism, Guilty, and Eye-opener

DOTS: Directly Observed Treatment Short-course

FDC: Fixed-dose combination

LTFU: Loss to follow up

RCT: Randomized controlled clinical trials

RH-FDC + Z: regimen with rifampicin and isoniazid in fixed-dose combination, plus pyrazinamide

RHZE: regimen with rifampicin, isoniazid, pyrazinamide, and ethambutol in separate formulation

RHZE-FDC: regimen with rifampicin, isoniazid, pyrazinamide, and ethambutol in fixed-dose combination

TB: Tuberculosis

4-FDC: regimen with rifampicin, isoniazid, pyrazinamide, and ethambutol in fixed-dose combination

Declarations

Ethics approval and consent to participate

The two follow-up studies were approved by the Research Ethics Committee of the Federal University of Juiz de Fora (UFJF), opinion number 166/2006 and number 2 939 612 / CAAE 94862618500005147; and the Hospital Foundation of the State of Minas Gerais, opinion number 52/08 and number 3 007 560 / CAAE 94862618530015119. The procedures used in this study adhere to the tenets of the 1964 Declaration of Helsinki.

All individual participants were included in the study by signing the Free and Informed Consent Form. A printed copy was given to each participant, and another signed copy was filed by the responsible researcher.

Consent for publication

All participants signed an informed consent on the use of data collected for research purposes.

Availability of data and material

The data underlying the main analysis of this article is available in supplementary data (see Additional file 1). Data relating to additional analyzes will be shared upon reasonable request to the corresponding author.

Competing interests

The authors declare that they have no conflict of interest and no competing interests.

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Author’s contributions

All authors contributed to the design of the research project. MAO and JLB performed the data collection and organization. MAO and MRS performed the statistical analysis of the data. MAO drafted the manuscript. MRS, ICGL, and RRC made critical revisions of the manuscript. All authors read and approved the final manuscript.

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Figures

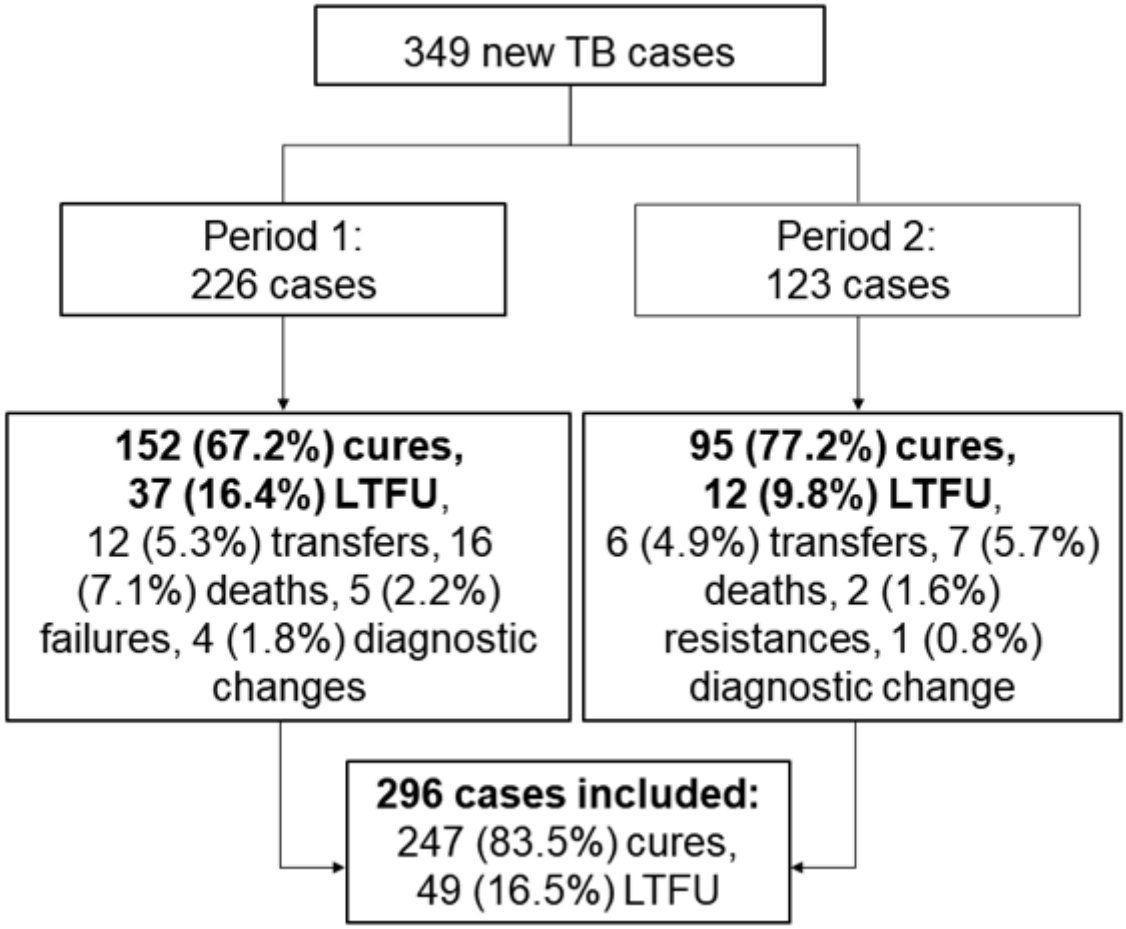

Figure 1

Flowchart showing tuberculosis treatment outcomes from periods 1 and 2

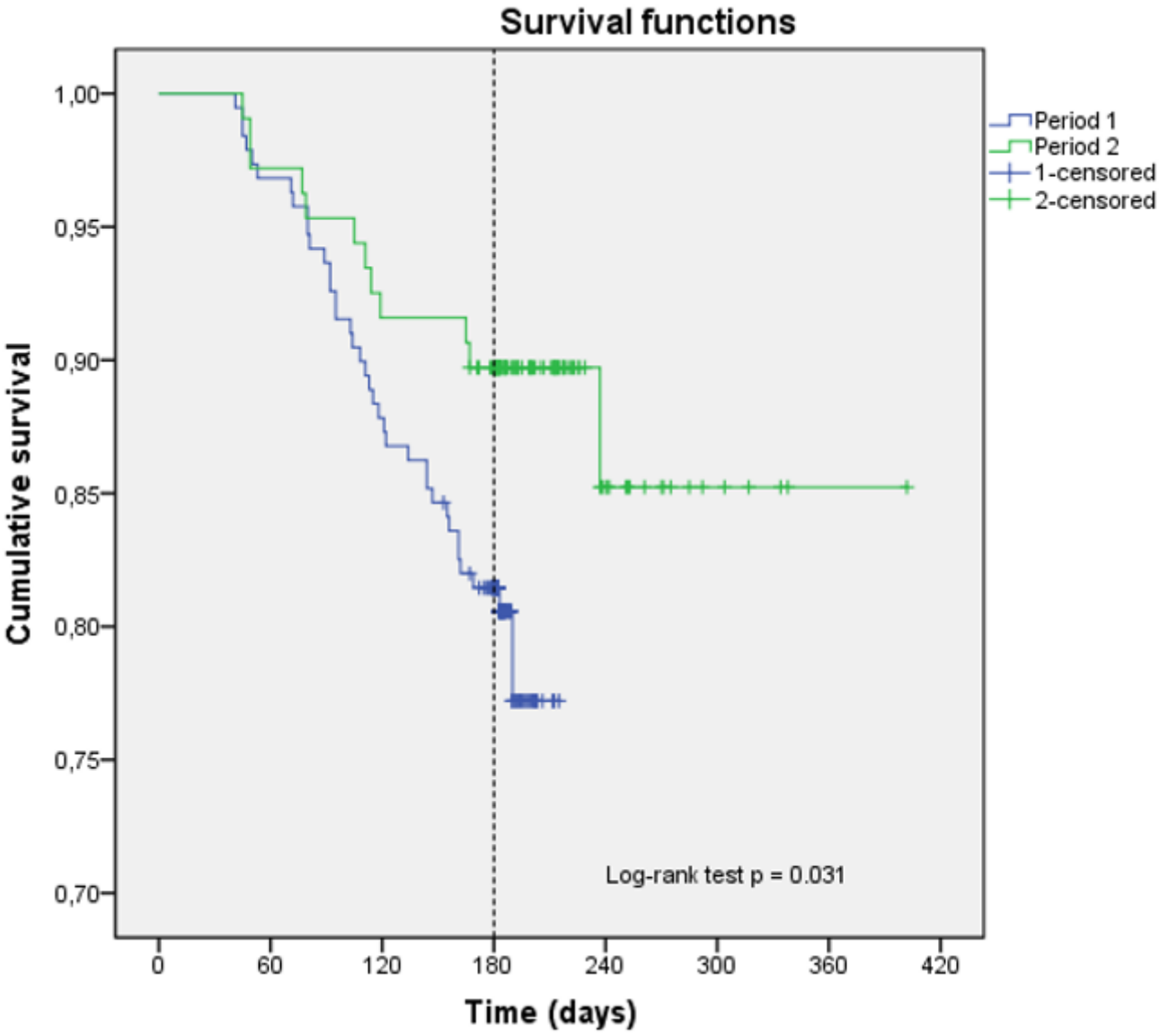

Figure 2

Kaplan-Meier survival curves for tuberculosis patients attended at Juiz de Fora by periods 1 and 2

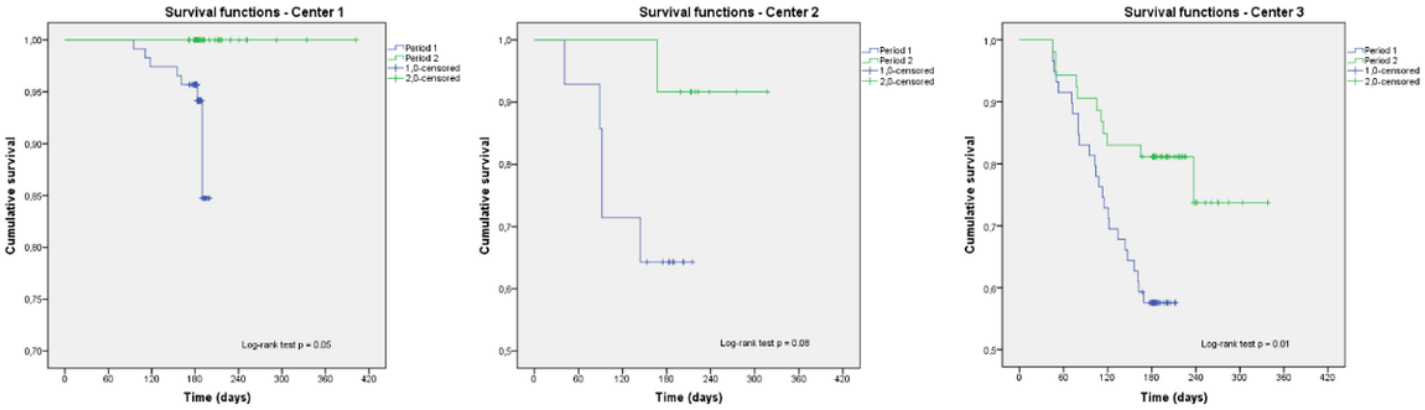

Figure 3

Kaplan-Meier survival curves for tuberculosis patients attended at Juiz de Fora by periods 1 and 2 at centers 1, 2, and 3