El impacto de la pandemia de COVID-19 en los nuevos casos de tuberculosis en pacientes hospitalizados

The Impact of COVID-19 Pandemic on New Active Tuberculosis in Hospitalized Patients

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ABSTRACT

Objectives: The COVID-19 pandemic has affected the global fight against Tuberculosis, although its impact is not fully known. We aimed to analyse the impact of the COVID-19 pandemic on the diagnosis and hospital care of tuberculosis patients.
Material and Method: We conducted a retrospective study in a Portuguese 804-bed hospital between March 2019 and March 2021. We compared the number of new diagnoses of active Tuberculosis in hospitalized patients in the 12-month period before (group A) and after (group B) the surge of COVID-19 in Portugal (March 2020), as well as patients' clinical characteristics.
Results: There were a total of 24.675 hospital admissions, of which 158 were due to new active tuberculosis. There were 60 new diagnoses of active tuberculosis in the first year of the COVID-19 pandemic (group B), compared to 98 in the previous year (group A) (0.5% vs. 0.8%, respectively, p=0.004). Gender distribution, age, symptoms at presentation and affected organs were similar in both groups. During the COVID-19 pandemic, there was a significant median 3-day delay in diagnosis after hospital admission (p=0.047) and a total of 18% of tuberculosis cases were co-infected with SARS-CoV-2 in the first month of antituberculosis therapy.
Conclusion: During the first year of the COVID-19 pandemic, hospitalised patients were 37% less likely to have a diagnosis of new active TB, compared to the previous year. Our study highlights the concern about underdiagnosis and diagnostic delay of active TB during the COVID-19 pandemic and the need for studies and policies addressing this matter.

Keywords: Tuberculosis, COVID-19, Pandemics, Health services management.

RESUMEN

Objetivos: Analizar el impacto de la pandemia de COVID-19 en el diagnóstico y la atención hospitalaria de los pacientes con tuberculosis.
Método: Estudio retrospectivo en un hospital portugués de 804 camas entre marzo de 2019 y marzo de 2021. Comparamos el número de nuevos diagnósticos de tuberculosis activa en pacientes hospitalizados en el período de 12 meses antes y después el repunte de la COVID-19 en Portugal (marzo 2020), así como las características clínicas de los pacientes.
Resultados: Se incluyeron 24.675 ingresos hospitalarios, de los cuales 158 fueron por tuberculosis activa nueva. Se observó 60 nuevos diagnósticos de tuberculosis activa en el primer año de la pandemia COVID-19 (grupo B), frente a los 98 del año anterior (grupo A) (p=0,004). La distribución por género, edad, presentación y órganos afectados fueron similares. Durante la pandemia de COVID-19, hubo una mediana de retraso significativo de 3 días en el diagnóstico después del ingreso hospitalario (p=0,047) y un total del 18 % de los casos de tuberculosis se infectaron con SARS-CoV-2 en el primer mes de terapia antituberculosa.
Conclusión: Durante el primer año de la pandemia COVID-19, los pacientes hospitalizados tuvieron 37% menos de probabilidad de tener un diagnóstico nuevo de TB. Nuestro estudio destaca la preocupación por el infradiagnóstico y el retraso en el diagnóstico de la TB activa durante la pandemia COVID-19 y la necesidad de estudios y políticas que aborden este tema.

Palabras clave: Tuberculosis, COVID-19, Pandemias, Gestión de servicios de salud.

INTRODUCTION

Tuberculosis (TB) is a global pandemic that has affected the world for thousands of years. TB is caused by a type of bacterium called *Mycobacterium tuberculosis* and it is a major infectious disease and one of the leading causes of death worldwide. Until the coronavirus disease 2019 (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent. Fortunately, TB incidence and mortality have been slowly declining over the years.[1]

In the World Health Organization (WHO) European Region and in the European Union/European Economic Area (EU/EEA) the average annual decline of the TB incidence rate was 5.1% between 2015 and 2019. In Portugal, which was one of the highest notification rates in the EU/EEA, the average annual decline was 5.0% (from 21.2 to 17.2/100.000).[2]

Recently, the world has faced a new challenging pandemic, COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), that led to a global health crisis. In Portugal, the first case was reported on the 2nd of March 2020. Since its beginning, and until March 2021, nearly 12 months after the WHO declared COVID-19 a pandemic, a total of 820 thousand cases of COVID-19 were identified among the Portuguese population (approximately 7%), with a total of 16.800 deaths. Globally, the scenario was not better, with a total of 4.000.000 infections and 2.700.000 deaths reported worldwide.[3]

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TB and COVID-19 are both airborne, transmissible diseases that primarily affect the lungs with similar symptoms, such as cough, fever and shortness of breath[4]. However, COVID-19 brought about a behavioural change characterised by social distancing, respiratory etiquette and a global lockdown.

The impact of the COVID-19 pandemic on the diagnosis, care and mortality of TB is not yet fully known. Recent studies found that policies adopted worldwide in response to the COVID-19 pandemic, particularly lockdowns and reassignments of health personnel and equipment, have affected the performance of TB prevention and care programmes, with missed opportunities for diagnosis and treatment initiation, giving rise to a rapidly growing pool of undetected and unreported TB cases. Consequently, an increase in TB mortality, as well as a regression of at least 5-8 years in the fight against TB, is estimated, even though some studies suggest a positive effect of lockdowns, respiratory etiquette and social use of masks in breaking chains of TB transmission.[5-7]

On the other hand, other studies suggest an unfavourable association between these two pandemics, with co-infection worsening COVID-19 severity and favoring TB disease progression[8]. Similarly, the potential role of drugs prescribed to treat COVID-19 (corticosteroids), and their interaction with anti-TB drugs, may influence the interaction between both.[9]

We aimed to analyse the impact of the COVID-19 pandemic on the diagnosis and hospital care of tuberculosis patients.

MATERIALS AND METHODS

Study design, population and outcomes

We performed a retrospective, observational, single-centre study including patients aged 18 years or older, admitted to a Portuguese 804-bed hospital, with a new diagnosis of active TB, from the 14th of March 2019 to the 15th of March 2021. Patients with active TB were identified by searching the electronic medical database of the hospital for the study period and patients were excluded if the diagnosis was made in a previous admission or at another hospital.

Inclusion criteria:

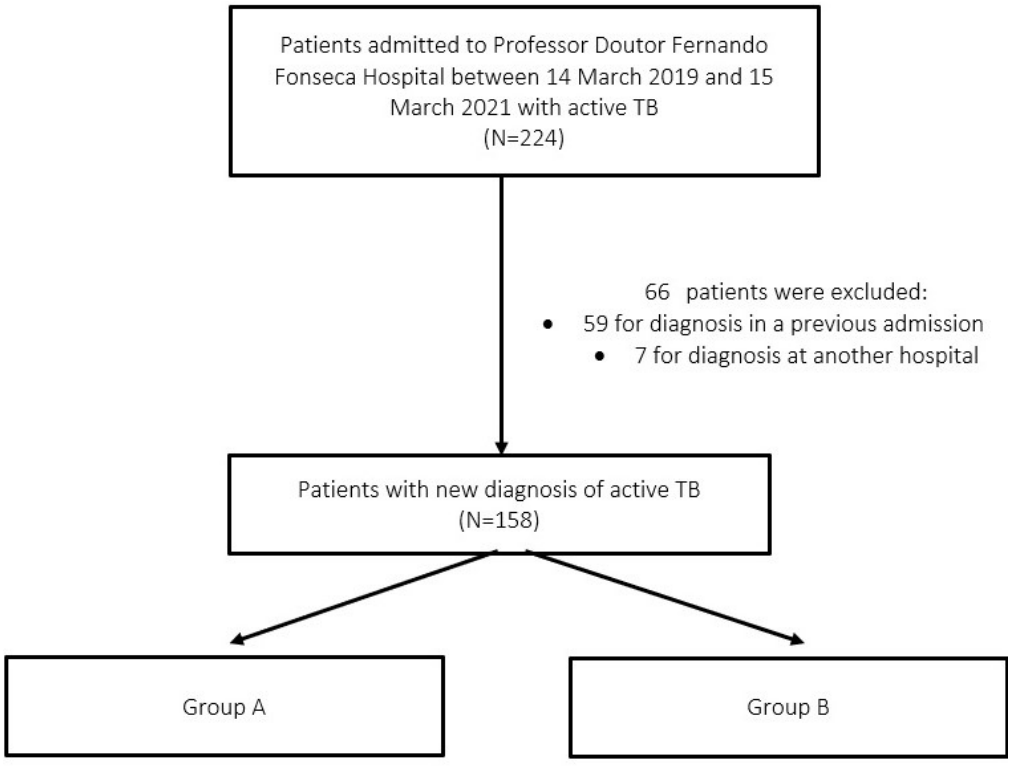
- Adults ≥18 years-old.
- Diagnosis of TB from the 14th of March 2019 to the 15th of March 2021 in the hospital where the study was carried out.

Exclusion criteria:

- Diagnosis of TB made in other hospital or health service.
- Diagnosis of TB made in a previous admission.

The included patients were divided into two groups, according to the hospital admission date, whether it was in the 12-month period before or after the surge of COVID-19 in Portugal: group A (A) from the 14th of March 2019 to the 14th of March 2020, and group B (B) from the 15th of March 2020 to the 15th of March 2021. The primary outcome was the proportion and the absolute number of new active TB

Figure 1. Flow-chart of patient selection.



Group A: patients admitted from 14 March 2019 to 14 March 2020;
Group B: patients admitted from 15 March 2020 to 15 March 2021.

cases diagnosed in the two groups. The secondary outcomes were to (1) describe and compare the characteristics of TB in the two groups, (2) as well as to determine the presence of co-infection with TB and COVID-19, and (3) the timing of its occurrence.

This study was approved by the Ethics Committee of HFF (Comissão de Ética para a Saúde do Hospital Prof. Dr. Fernando Fonseca, EPE) with the approval number 092/2021 and the requirement for written informed consent was waived.

Data Collection and definitions

The following data were extracted from the clinical electronic records: symptoms (nature and duration at hospital admission), chest radiograph presentation, risk factors for TB, date of laboratory confirmation of TB diagnosis and organs affected by *Mycobacterium tuberculosis*. Active TB was considered when there was laboratory confirmation of TB.

For patients in group B, all positive results in the reverse-transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2 available either on the hospital medical database or on the Trace COVID-19 database of the Portuguese Ministry of Health were registered as well as the date of the test. Patients with active TB and a positive PCR test for the SARS-CoV-2 test were considered co-infected with TB and COVID-19.

Statistical Analysis

For statistical analysis, we used the Statistical Package for the Social Sciences (SPSS®) software (26.0 version), and the significance level was defined at 0.05. The 95% Confidence Intervals were calculated using the Wald modified approximation. The categorical variables were presented as absolute and relative frequency, in percentage (%). The continuous variables were presented as median with interquartile range (IQR). For comparative analysis, the Mann-Whitney U test and Chi-square or Fisher's exact tests were applied on continuous and categorical variables, respectively, when appropriate.

RESULTS

There were 224 patients admitted with active TB during the study period (shown in Fig. 1). Of these, 158 were included in the analysis. Patients' characteristics are described in Table 1.

There were 60 new diagnoses of active TB among 12.202 hospital admissions in the year after the surge of COVID-19 (Group B), compared with 98 new cases in 12.473 hospital admissions in the previous year (Group A) [0.5% in B vs 0.8% in A, p=0.004; absolute risk difference: -0.29% (95% Confidence Interval (CI): -0.49, -0.09); relative risk: 0.63 (95% CI: 0.45, 0.86)].

Both groups had a comparable gender (60% male, p=0.72) and age distribution, with a median age of 41 years (28-55; p=0.19). Regarding risk factors considered for TB, the most frequent were recent travel or being born in high prevalence areas of TB (43%), previous TB infection (15%), human immunodeficiency virus (HIV) infection (13%) and close contact with TB infected people (13%), with statistically non-significant differences between groups. Though less frequent, other risk factors for TB, such as active tobacco smoking and poor living conditions were significantly more prevalent in A (p=0.018 and p=0.009, respectively).

Among all patients, pulmonary TB was the most frequent (95%), followed by ganglionic (14%), pleural (10%), and disseminated (9.6%) without statistical difference between groups. A comparable distribution of symptoms at admission was found in both groups, with fever being the most prevalent one (55%), followed by fatigue (50%), productive cough (45%), pleuritic chest pain (45%), weight loss (43%) and loss of appetite (34%). Similarly, at presentation, the thorax radiologic findings revealed mainly cavitation (32%), and an opacity of the upper lobe (25%) and lower lobe (12%). Bilateral infiltrates were found mostly in B (p=0.002) and bilateral opacity of the hemithorax was found only in group A (p=0.001).

Regarding hospital care, there was a significant median 3-day delay in diagnosis after hospital admission (2 [1-10] days in A vs. 5 [2-13] days in B, p=0.047). Moreover, patients in B presented to the hospital, in median, 6 days later than those in A, though there was no statistically significant difference (p=0.589).

During the first 12 months of the COVID-19 pandemic, we found that 18% of the admitted patients with active TB were co-infected by SARS-CoV-2 in the first month of tuberculostatic therapy.

DISCUSSION

During the first year of the COVID-19 pandemic, there were 29 less diagnoses of new active TB per 10.000 hospitalized patients and a significant delay in diagnosis after hospital admission, compared to the previous year.

COVID-19 triggered a lockdown in many countries, namely Portugal, to control the exponential spread of the SARS-CoV-2 virus[10]. With this measure, a change in TB transmission was expected: an increase in the transmission in home clusters and a decrease in transmission in social circumstances[7]. Respiratory etiquette and social use of face masks also contributed to breaking the chains of transmission of both diseases[11]. We found that hospitalized patients were 37% less likely to have a new diagnosis of active TB during the first year of the COVID-19 pandemic, which was superior to the WHO expectations that predicted a global reduction of 25% in detected TB cases[4].This reduction can have two interpretations: it was either a real reduction in the number of new infections, as a result of the social behavioural change and the disseminated use of face masks[11,12]; or it was a reduction in the number of notifications/diagnoses caused by the focus of health care systems on the diagnosis, treatment and stoppage of the spread of SARS-CoV-2, therefore missing TB diagnosis.[13]

In the Portuguese Health System, TB is considered a priority given its high prevalence, thus clinical activities related to TB were not particularly compromised. However, a disruption in the access to diagnostic centres may have resulted in a diagnosis delay, which means an increased risk for TB outbreaks.[7]

Our study did not find any clinical or radiographic differences in TB presentation before and during the COVID-19 pandemic. Pulmonary involvement was the most frequent presentation, followed by gangli-

Table 1. Demographic and clinical characteristics of inpatients with active tuberculosis in the year before and after the surge of COVID-19 pandemic.

	Group A (n=98)	Group B (n=60)	Total (n=158)	p-value
Demographic data				
Age, in years, median (IQR)	43(28,55)	40(28, 54)	41(28,55)	0.19
Male sex, n (%)	63 (64)	32 (53)	95 (60)	0.72
Organ distribution of TB				
Pulmonary, n (%)	64 (65%)	31 (52%)	95 (60%)	0.89
Pleural, n (%)	11 (11%)	6 (10%)	17 (10%)	0.967
Ganglionic, n (%)	14 (14%)	8 (13%)	22 (14%)	0.867
Disseminated, n (%)	7 (7%)	9 (15%)	16 (9.6%)	0.252
Peritoneal, n (%)	2 (2%)	0	2 (1.2%)	0.526
Bone, n (%)	0	3 (5%)	3 (2%)	0.154
Genitourinary, n (%)	0	1 (2%)	1 (0.6%)	1
The central nervous system, n (%)	0	2 (2%)	2 (1.2%)	0.526
Symptoms at admission				
Fever, n (%)	52 (53%)	35 (58%)	87 (55%)	0.51
Productive cough, n (%)	49 (50%)	22(37%	71 (45%)	0.778
Dry cough, n (%)	40 (67%)	12 (34%)	52 (33%)	0.11
Night sweats, n (%)	30 (31%)	19 (32%)	49 (31%)	0.79
Loss of appetite, n (%)	27(36%)	27 (45%)	54 (34%)	0.339
Fatigue, n (%)	44 (45%)	35 (58%)	79 (50%)	0.101
Dyspnoea, n (%)	29 (30%)	24 (40%)	53 (34%)	0.179
Weight loss, n (%)	39 (40%)	29 (48%)	68 (43%)	0.293
Pleuritic chest pain, n (%)	39 (40%)	32 (53%)	71 (45%)	0.097
Diarrhoea, n (%)	12 (12%)	12 (20%)	24 (15%)	0.187
Adenopathy, n (%)	11 (11%)	13 (22%)	24 (15%)	0.076
Haemoptysis, n (%)	8 (8%)	2 (3%)	10 (6%)	0.322
Headache, n (%)	16 (16%)	5 (8%)	21 (13%)	0.151
Nausea/vomit, n (%)	5 (5%)	6 (10%)	11 (6%)	0.24
Confusion, n (%)	6 (6%)	7 (12%)	13 (8%)	0.226
Odynophagia,	5 (1%)	6 (10%)	11 (6%)	0.24
Myalgia, n (%)	2 (2%)	4 (7%)	6 (4%)	0.202
Back pain, n (%)	2 (2%)	2 (3%)	4 (3%)	0.635
Delay in diagnosis (in days)				
Delay in diagnosis after hospital admission, median (IQR)	2 (1,10)	5(2, 13)	3(1-11)	0.047
Days of symptoms at admission, median (IQR)	40(27, 115)	46(22-90)	45 (25-92)	0.589
Chest radiographic findings				
Bilateral infiltrate, n (%)	8 (8%)	16 (27%)	24 (15%)	0.002
Unilateral opacity of the hemithorax, n (%)	7 (7%)	8 (13%)	15 (9%)	0.198
Bilateral opacity of the hemithorax, n (%)	7 (7%)	0	7 (4%)	0.001
Opacity of the upper lobe, n (%)	24 (25%)	9 (15%)	33 (21%)	0.192
Opacity of the lower lobe, n (%)	12 (12%)	10 (17%)	22 (14%)	0.451
Cavitation, n (%)	32 (32%)	19 (32%)	51 (32%)	0.85

Table 1 (cont.). Demographic and clinical characteristics of inpatients with active tuberculosis in the year before and after the surge of COVID-19 pandemic.

Risk factors for TB				
HIV infection, n (%)	13 (13%)	8 (13%)	21 (13%)	0.99
HBV infection, n (%)	2 (2%)	3 (5%)	5 (4%)	0.369
HCV infection, n (%)	6 (6%)	4 (7%)	10 (6%)	1
Immunosuppressive drugs, n (%)	2 (2%)	4 (7%)	6 (4%)	0.369
Active cancer, n (%)	1 (1%)	4 (7%)	5 (3%)	0.069
Diabetes, n (%)	5 (5%)	1 (2%)	6 (4%)	0.409
Previous TB infection, n (%)	16 (16%)	7 (11%)	23 (15%)	0.42
Close contact with TB infection, n (%)	11 (11%)	9 (15%)	20 (13%)	0.49
Recent travel/being born in a high prevalence area of TB, n (%)	45 (46%)	21 (35%)	36 (43%)	0.177
Prisoner, n (%)	0	1 (2%)	1 (0.6%)	0.380
Poor living environment, n (%)	22 (22%)	4 (7%)	26 (16%)	0.009
Alcohol abuse, n (%)	20 (20%)	10 (17%)	30 (19%)	0.561
Active tobacco smoking, n (%)	27 (28%)	7 (12%)	34 (22%)	0.018
Active cannabis smoking, n (%)	3 (3%)	2 (3%)	5 (3%)	0.369
Cocaine use, n (%)	2 (2%)	2 (3%)	4 (3%)	0.635
IV drug use, n (%)	3 (3%)	2 (3%)	5 (3%)	0.369

Group A: patients admitted from 14 March 2019 to 14 March 2020; Group B: patients admitted from 15 March 2020 to 15 March 2021.
HIV - human immunodeficiency virus; HBV - hepatitis B virus; HCV - hepatitis C virus; IV - intravenous; TB - Tuberculosis.

onic and pleural, which goes in line with what has been described in the literature[14]. Thorax radiographic findings were globally similar in both groups, with a higher prevalence of cavitation and opacity of the upper lobe patterns, also in agreement with the literature[15,16]. The bilateral infiltrate pattern was more commonly described during the COVID-19 pandemic, but since it is also associated with SARS-CoV-2 pneumonia[17,18], pressure to diagnose COVID-19 may have led to an increase in bilateral infiltrate pattern search and its description in the clinical records. Also, a statistically significant reduction in poor living conditions as a risk factor (from 22% to 7%) could have been associated with an effort to reduce homelessness by increasing the number of shelters, to limit the SARS-CoV-2 spread.[19]

The significant three-day delay in TB diagnosis since hospital admission during the COVID-19 pandemic may be justified by the imperious need to first exclude SARS-CoV-2 infection, when a patient was admitted with respiratory symptoms, with a differential diagnosis being left for a second observation. The fact that hospitals were faced with unprecedented pressure, with healthcare systems being stretched beyond their capacity, may have also contributed to this delay. Furthermore, the delay in TB diagnosis led to the postponement of anti-TB treatment initiation and, thus, an increased risk of poorer outcomes for both patients and the community[20], and further studies should evaluate these consequences.

There was also an increase in the number of days from the onset of symptoms until hospital admission during the COVID-19 pandemic, although not statistically significant. This could be explained by the avoidance of medical care services due to fear of nosocomial SARS-CoV-2 infection[6,21]. Furthermore, government advertisements promoting the "stay-at-home" order, and worldwide media encouraging home isolation if only mild symptoms were present, in order to reduce the risk of catching or spreading COVID-19, may have also contributed to this delay and the reduction of TB diagnosis.

Many hypotheses have been published about the relationship between COVID-19 and TB.[7-8,22,23]

In the study population, only 15% had a previous history of TB and there were no reports of TB following a SARS-CoV-2 infection, therefore it could not be established whether corticosteroid use in SARS-CoV-2 represents a risk factor for TB reactivation. However, TB and SARS-CoV-2 co-infection was reported in 18% during the first month of tuberculostatic therapy, bringing into question whether the immunosuppressed state associated with TB could have led to SARS-CoV-2 infection. Another hypothesis could be that the co-infection took place in the emergency room, since all patients presenting with dyspnoea, fever, myalgia, and cough (symptoms of both diseases) were placed together in respiratory dedicated rooms until a negative COVID-19 test result. This may have facilitated the SARS-CoV-2 spread inside the hospital, creating a bias in the analysed data. Further studies will be needed to understand better the interplay between these two diseases.

To the best of our knowledge, this is the first Portuguese study with demographic, clinical and radiographic findings of active TB during the first 12 months of the COVID-19 pandemic. However, it is an observational and retrospective analysis of a single centre (TB diagnosis made only in inpatients) which limits the generalisation of conclusions and the establishment of causality. The results found are also

limited for any extrapolation as they cover a single hospital/community. Nonetheless the study results are aligned with other international studies and should be a red flag for healthcare authorities as they can represent a higher risk for poor outcomes in TB patients, as well as an imminent rise in TB deaths.

CONCLUSION

Since the beginning of COVID-19, not only did we report a higher-than-expected decrease in new diagnoses of TB but also a delay in this diagnosis in the hospital setting. This was probably due to the strain on the Public Health Care System caused by COVID-19 since all efforts were focused on stopping the pandemic, introducing social behavioural changes, the use of face masks and the avoidance of medical care services. Our study highlights the concern about underdiagnosis and diagnostic delay of active TB during the COVID-19 pandemic and the need for studies and policies addressing this public health matter.

Despite the high pressure of COVID-19, TB is still one of the most common causes of infectious disease-related deaths worldwide and we must keep it in mind as a differential diagnosis of COVID-19. Further studies will be needed to clarify whether there is a causal association between TB and COVID-19 and which risk factors contribute to co-infection.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of HFF (Comissão de Ética para a Saúde do Hospital Prof. Dr. Fernando Fonseca, EPE) with the approval number 092/2021 and the requirement for written informed consent was waived.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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Authors are to provide non-specific funding information.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from Catarina Negrão.

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