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Incidence and predictors of mortality among persons with rifampicin-resistant tuberculosis and HIV in Mozambique

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Rifampicin-Resistant Tuberculosis (RRTB) is associated with a high risk of mortality during treatment. This study aims to describe the baseline characteristics associated with incidence of mortality in persons with rifampicin-resistant tuberculosis (P-RRTB) in a rural setting in Mozambique. We analyzed cohort data collected retrospectively from paper medical files and electronic medical records of P-RRTB who were routinely treated at Carmelo Hospital of Chokwe (Gaza province, Mozambique), from 1st January 2015 to 31st December 2020. Kaplan-Meier survival curves and adjusted Cox regression analyses were used to model the time to death and associated factors of mortality. Overall, 151 P-RRTB contributed to a total number of 1812 person-months (PM) of treatment follow-up. The overall mortality rate was 1.9 per 100 person-months (95% confidence interval [CI]: 1.3–2.1). Adjusted Cox regression predicted higher risk of mortality in those treated with injectable anti-RRTB second line drugs (SLD), (adjusted hazard ratio [aHR] 3.72, 95% CI 1.23–11.22, $p = 0.020$), had a parenchymal lesion with more than 50% fibrosis (aHR 3.06, 95% CI 1.38–6.79, $p = 0.006$), presented right ventricular dysfunction on the echocardiogram with venous assessment (aHR 3.18, 95% CI 1.15–8.83, $p = 0.026$), and manifested baseline hemoglobin (Hgb) = 8.0–9.9 g/dL (aHR 2.82, 95% CI 1.09–7.27, $p = 0.032$), as well Hgb < 7.9 g/dL (aHR 3.06, 95%CI 1.24–7 0.51, $p = 0.015$). However, lower risk of mortality was predicted in those who had an optimal immunovirological response to ART (aHR 0.18, 95% CI 0.04–0.93, $p = 0.040$). Kaplan-Meier analysis showed higher cumulative incidence of mortality after 3 months of follow-up, above 26% in those with immunovirological failure to ART therapy ($p = 0.006$), 45% with Hgb < 7.9 g/dL ($p < 0.001$), 23% in treated with injectables-based drugs ($p = 0.03$), 39% with parenchymal lesion > 50% fibrosis on the chest X-ray ($p < 0.001$), 56% with right ventricular dysfunction ($p = 0.003$). Mortality risk among P-RRTB was higher in those with anemia, injectable anti-RRTB medications, lung lesions > 50% fibrosis, and right ventricular dysfunction.

Abbreviations

aHR	Adjusted hazard ratios
ART	Antiretroviral therapy
BDQ	Bedaquiline
BPaLM	Bedaquiline (B), pretomanid (Pa), linezolid (L), and moxifloxacin (M)
BPaL	Bedaquiline (B), pretomanid (Pa), linezolid (L)
CI	Confidence intervals
CHC	Carmelo Hospital of Chókwè
CXR	Chest X-ray examination
DLM	Delamanid
RRTB	Rifampicin-resistant Tuberculosis
EPTB	Extrapulmonary tuberculosis
ESA	Eastern and Southern Africa

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FASH	Focused Assessment with Sonography for HIV/TB
IVF	Immunovirological failure to ART
IVC	Inferior vena cava
IVS	Immunovirological status
INR	Immunovirological Non-Responder to ART
IQR	Interquartile range
LAM	Mycobacterial lipoarabinomannane assay
LPA	Line Probe Assay
LZD	Linezolid
MDR	Multi Drug Resistant Tuberculosis
NTP	Mozambican National TB Program
OIVR	Optimal immunovirological response to ART
P-RRTB	Persons with rifampicin-resistant tuberculosis
PHC	Primary healthcare clinic
PLHIV	Persons living with HIV
POCUS	Point-of-care ultrasound
RRTB	Rifampicin-resistant tuberculosis
HF	Health facility
Hgb	Hemoglobin
SLD	Second line drugs
XDR-TB	Extensively drug resistant tuberculosis

Rifampicin-resistant tuberculosis (RRTB) is a disease caused by a strain of *Mycobacterium tuberculosis complex* (MTBC) that is resistant to at least rifampicin, with or without resistance to other medications typically used to treat the disease. The term "RRTB" will be used broadly to refer to all categories of drug-resistant tuberculosis, including rifampicin mono-resistant TB (RRTB), multidrug-resistant TB (MDR-TB), pre-extensively drug-resistant TB (pre-XDR-TB), and extensively drug-resistant TB (XDR-TB)[1].

The World Health Organization's (WHO) Global Tuberculosis Report 2023 indicates that RRTB represented approximately 1.26% of all reported tuberculosis cases in Mozambique during 2022[2]. Although this percentage falls below expectations, its relevance is underscored by the context of Sustainable Development Goal 3 (SDG 3), which aims to end the tuberculosis epidemic by 2030[2]. Concurrently, Mozambique's 2020 tuberculosis treatment success rate of 75%[2] continues to constrain the overall efficacy of the National Tuberculosis Program (NTP) and hampers implementation of the End TB Strategy. This strategy defines ambitious 2035 targets, notably a 95% reduction in tuberculosis incidence and tuberculosis mortality[3,4].

In 2022, Mozambique estimated approximately 4,300 cases of RRTB (2,400–6,200), according to WHO's 2023 TB report[2]. This figure represents a subset of the total 119,000 tuberculosis cases estimated, which falls within a range of 72,000 to 177,000 cases[2]. However, an estimated 2.9% of new TB cases and 14% of previously treated TB cases involved RRTB. Therefore, the treatment success rate for RRTB stands at 75% with approximately 176,000 persons undergoing treatment for this condition[2].

High mortality rates among persons with RRTB (P-RRTB) are often linked to multiple risk factors and underlying health conditions. A recent study carried out in Ethiopia, revealed that elevated mortality in this P-RRTB is attributed to comorbidities, including HIV/AIDS and malnutrition[5]. Furthermore, a systematic review and meta-analysis identified several predictors of mortality in P-RRTB, which encompass: demographic profile (sex and age), and clinical characteristics (undernutrition, HIV co-infection, co-morbidity, diabetes, clinical complications, TB history, prior second-line anti-TB treatment, smear-positive TB, and XDR-TB)[6].

It is crucial to identify prognostic factors for survival among patients coinfected with RRTB/HIV. According to previous studies carried out in adults, the main factors of risk of death include immunovirological failure, response to antiretroviral therapy (ART), baseline CD4 T-lymphocyte counts and male gender[7,8].

This study aims to describe the incidence and factors associated with mortality in patients with RRTB in a rural setting, in Mozambique. It is necessary because it addresses the high mortality rates associated with RRTB, particularly in resource-limited rural settings such as Mozambique. First, by describing the incidence and baseline characteristics associated with mortality, it can identify key risk factors, such as comorbidities and delays in diagnosis, enabling targeted interventions to improve patient outcomes. Additionally, the findings can guide resource allocation in rural areas, ensuring the efficient use of limited healthcare resources, such as optimizing treatment regimens and improve management of coexisting conditions like HIV. Then, insights from the study also contribute to strengthening rural health systems by informing the design of context-specific strategies, including healthcare worker training and improved drug accessibility. After, beyond its local impact, the study adds to the global body of knowledge on RRTB, particularly in underrepresented settings, and supports evidence-based policymaking aligned with the WHO End TB Strategy. Ultimately, it provides valuable data to help reduce the burden of RRTB both in Mozambique and in similar high-burden, resource-constrained regions worldwide.

Methods

Study setting or area

Carmelo Hospital of Chokwe (CHC) acts as the referral center for 26 primary healthcare clinics (PHC) in the predominantly rural Chókwè District, southern Gaza province[6]. The district covers an area of approximately 1864 km^2 and is home to around 186,597 Changana-speaking residents. The hospital has a total capacity of 150 beds, allocated among general medical patients, adults and pediatrics, with a separate ward dedicated to TB and DR-TB cases. Every year, the CHC handles approximately 10,000 outpatient visits including follow-

ups for chronic conditions, and 1600 admissions. The CHC specializes in TB/HIV care and has been managed by Catholic missionaries (the Daughters of Charity, Saint Vincent de Paul) since 1993. It is responsible for TB (including RRTB) screening and treatment, HIV care and treatment, and management of inpatient and outpatient care. Available diagnostics tools include chest X-ray (CXR), point-of-care ultrasound (POCUS), standard hematology and biochemistry laboratory tests, parasitology, TB culture, Xpert MTB/RIF assay, urine Determine Tuberculosis Lipoarabinomannan Antigen test (Determine TB-LAM Ag), CD4 counts, and RNA HIV viral load[7–10].

Study design and population

This retrospective cohort study was carried out at a single healthcare facility from January 1, 2015, to December 31, 2020. The study's target population comprised individuals of all ages who were documented as P-RRTB. The data collection instrument was meticulously developed through document analysis, leveraging both existing paper medical files and electronic records of P-RRTB routinely managed at CHC (Fig. 1).

Inclusion and exclusion criteria

Eligibility criteria included all P-RRTB confirmed by either phenotypic (culture, drug susceptibility testing/antibiogram) or genotypic (GeneXpert MTB/RIF, Line Probe Assay [LPA-1,2]) tests for of MTBC. Patients with isoniazid monoresistance (rifampicin-susceptible) or missing information on the treatment outcome, were excluded from the study (Fig. 2).

Study sample size

The sample consisted of all eligible patients registered as having RRTB on admission to the CHC; therefore, no sampling calculation criteria were applied (Fig. 1).

Study variables

The primary outcome was mortality during RRTB treatment follow-up. This outcome was categorized as either death or censored observation (encompassing treatment completion/cure, loss to follow-up, and treatment failure)[11]. Independent variables were categorized into five fields. First, the length of RRTB treatment follow-up (starting and ending date). Second, demographic profile: biological sex (female and male), age band (< 25 years old, 25–44 years old, and > 45 years old). Third, clinical features: basal hemoglobin (Hgb > 10.0, 8.0-9.9 and < 7.9 g/dL); immunovirological status (IVS) to ART (HIV negative, optimal immunovirological response [OIVR], immunological non-responders [INR], immunovirological failure [IVF]); TB drug exposure (naïve, 1st line drug exposure, 2nd line drugs exposure), RRTB regime (injectable second-line drugs [SLD], non-injectable SLD). Fourth, chest X-ray (CXR): (A) lung parenchyma (normal parenchyma or with < 50% fibrosis, > 50% parenchymal fibrosis), and (B) lung cavitation (normal, cavitation). Fifth, ultrasound profile: (A) abdominal ultrasound (normal, ascites); and (B) standard transthoracic echocardiogram with central venous system assessment (normal, right ventricular dysfunction [suprahepatic vein > 3.0 cm, inferior vena cava (IVC) > 3.0 cm].

Adoptions of study-specific subvariables

For a better understanding, we adopted the categories of some independent variables, such as basal hemoglobin, standard transthoracic echocardiography with central venous system assessment, and age band as study-specific subvariables.

Standard transthoracic echocardiography with central venous system assessment An echocardiogram with central venous system assessment serves as a valuable diagnostic tool for identifying *COR PULMONALE*, a condition characterized by right ventricular (RV) enlargement and failure resulting from pulmonary hypertension, frequently due to chronic lung disease[12]. This comprehensive diagnostic procedure integrates two evaluations: a standard transthoracic echocardiogram and an assessment of the central venous system. A key indicator of cor pulmonale is the presence of a dilated Inferior Vena Cava (IVC) measuring greater than 2.1 cm, with less than 50% collapse during inspiration, which suggests elevated right atrial pressure[13] (Supplementary Table 1).

Hemoglobin (Hgb) concentration The classification of hemoglobin (Hgb) levels is derived from prior studies conducted in Mozambique[14] and is aligned with WHO clinical management algorithm for anemia[15] that has been tailored to the specific context of Mozambique. This classification is based on clinical significance and is utilized to evaluate the severity of anemia and other conditions associated with Hgb concentration (Supplementary Table 2).

Age band Age bands are widely utilized in demographic analysis, marketing, and research to segment populations by life stages, behaviors, and needs. Although broad, these categories are essential for understanding and addressing the unique requirements and behaviors of different life stages[16–18] (Supplementary Table 3).

Data collection protocol

Personnel, Sources, and security framework

Hospital clinical staff systematically digitized all paper-based medical records prior to study initiation. The research team—trained in Good Research Practices (GCP)[19,20]—subsequently extracted patient data from both digitized archives and existing electronic health records. To ensure confidentiality, all directly identifiable information (names, birthdates, addresses) was excluded from the research dataset during initial coding. Each patient record was assigned a unique alphanumeric identifier to anonymize data while preserving traceability.

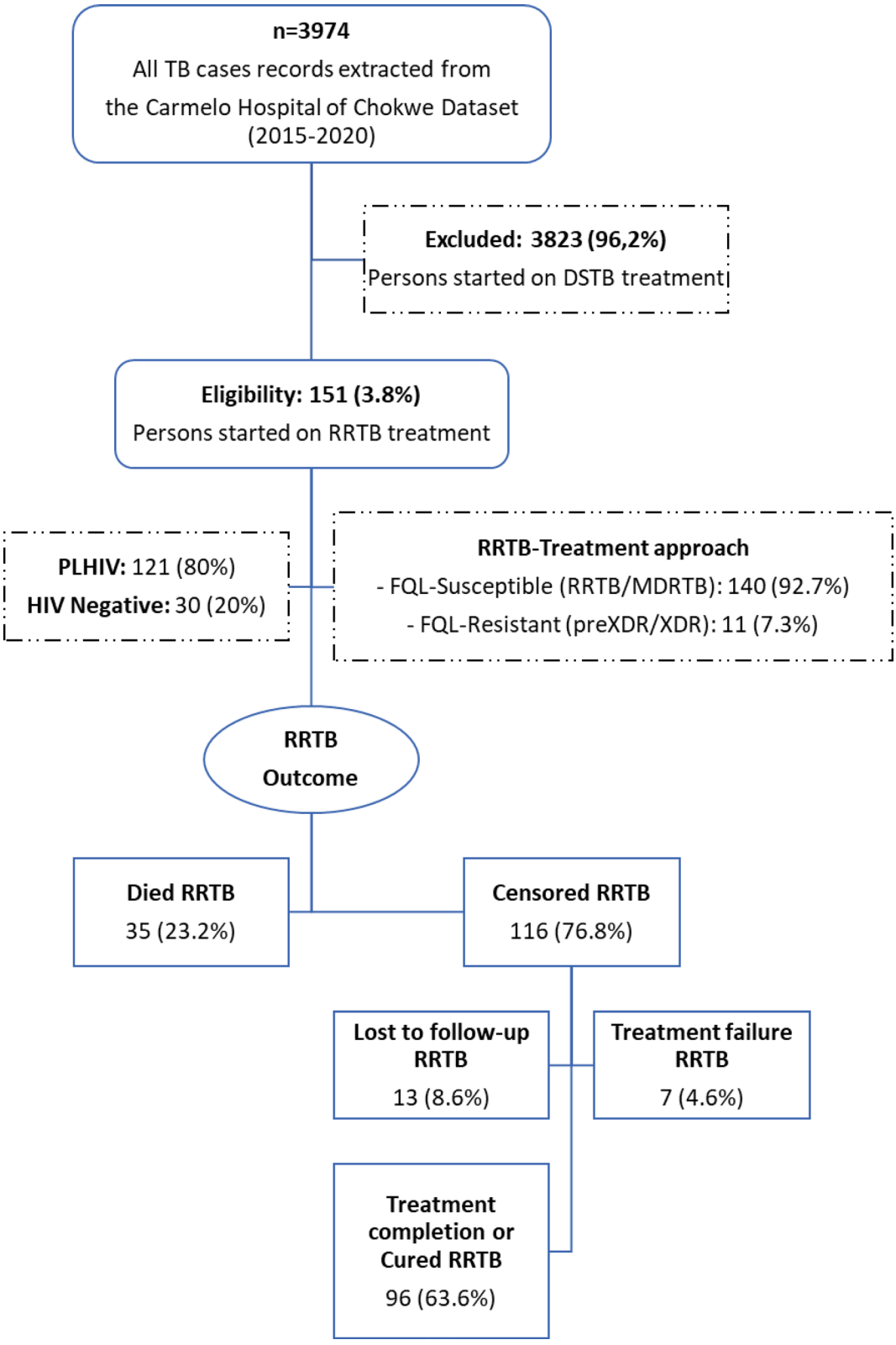

Fig. 1. Flowchart of study population.

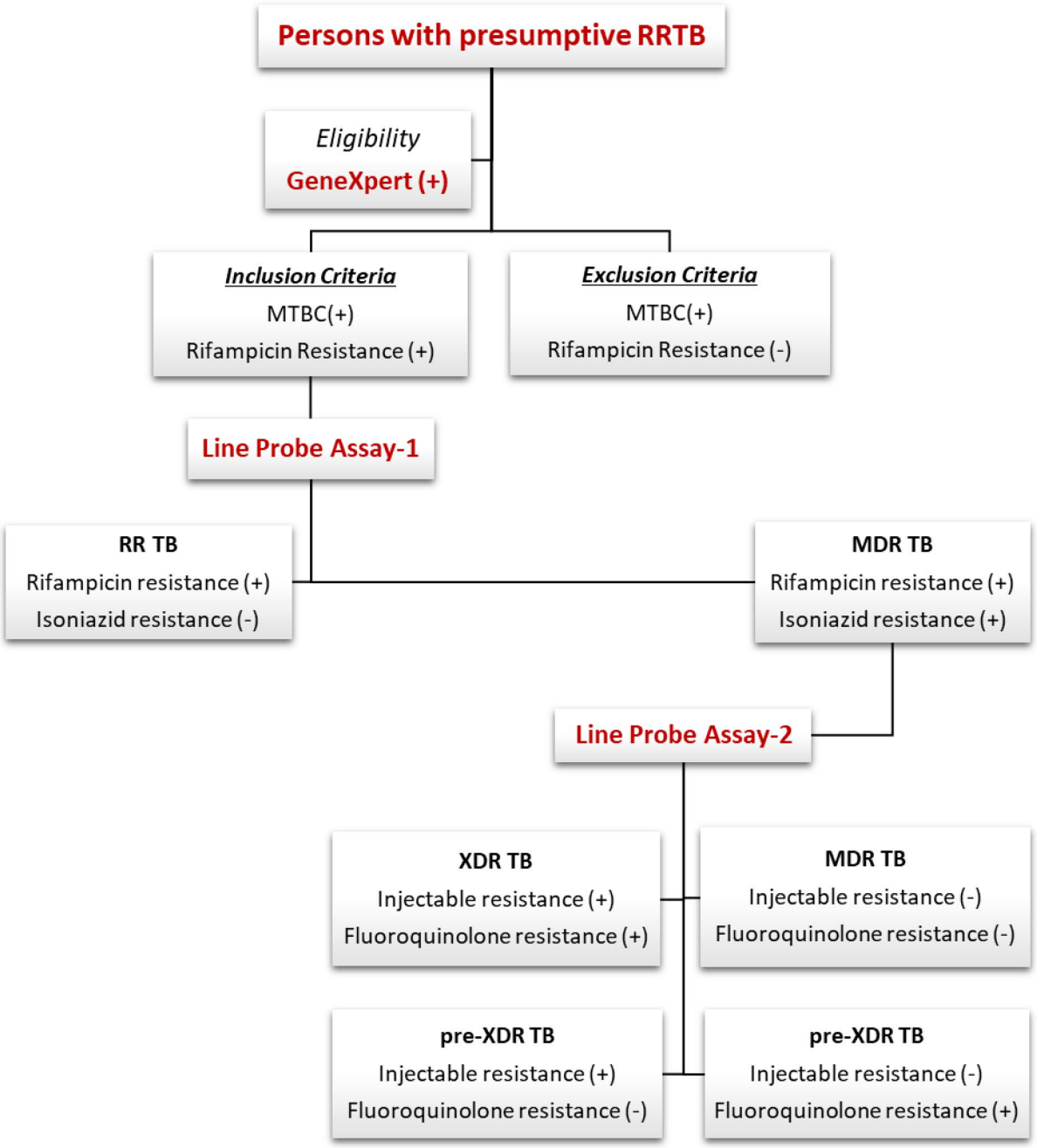

Fig. 2. Rifampicin-resistant Tuberculosis diagnosis algorithm.

Physical data management
Primary collection forms were securely stored in locked cabinets within access-controlled rooms at the health facility, adhering to national data security standards mandated by the Ministry of Health. The study team conducted daily audits of source documents to verify completeness and consistency before transcribing validated records into the assessment dataset.

Digital workflow
Following anonymization and coding, data were structured using standardized Excel® templates. These datasets were subsequently transferred to a cloud-based SQL server, employing synchronization protocols for secure storage. The final evaluation dataset—containing exclusively de-identified records—was safeguarded via password-encrypted authentication, with access restricted to authorized research personnel. Data were ultimately exported to SPSS for statistical analysis.

Conceptual definition of drug-resistant tuberculosis categories

According to the WHO Guidelines on drug-resistant tuberculosis[21] approaches implemented in Mozambique[11], the adopted conceptual definition of drug-resistant tuberculosis was categorized as follows (Figs. 2 and 3):

Rifampicin-resistant TB (RRTB)
As clearly outlined in the introduction[1].

Multidrug-resistant TB (MDR-TB)
TB disease caused by a strain of MTBC that is resistant to isoniazid and rifampicin with or without resistance to other anti-TB drugs[11,21].

Pre-extensively drug-resistant TB (pre XDR-TB)
TB disease caused by a strain of MTBC that is resistant to rifampicin (and potentially isoniazid) as well as fluoroquinolones[11,21].

Extensively drug-resistant TB (XDR-TB)
TB disease caused by a strain of MTBC resistant to rifampicin (and possibly isoniazid), as well as at least one fluoroquinolone (FQ; levofloxacin or moxifloxacin) and at least one additional Group A drug, either bedaquiline (BDQ) or linezolid (LZD)[11,21].

Mono-resistant TB
TB disease caused by a strain of MTBC that is resistant to only one anti-TB drug, without resistance to other drugs, (e.g., "rifampicin mono-resistant [RRTB]"; "isoniazid mono-resistant TB")[11,21], .

Poly-drug resistant TB
TB disease caused by a strain of MTBC that is resistant to multiple anti-TB drugs, excluding both isoniazid and rifampicin[11,21].

Extensive (or advanced) pulmonary TB disease
Presence of bilateral cavitary disease or extensive parenchymal damage on CXR. In children aged below 15 years, severe disease is defined by the presence of cavities, parenchymal involvement of more or equal to one full lobe, miliary pattern, or mediastinal lymphadenopathy with airway compression on CXR[11,21].

Fibrothorax TB: lung lesion with more than 50% parenchymal fibrosis The term "fibrothorax TB" refers to the radiographic appearance of severe lung lesions with more than 50% of the parenchymal fibrosis affecting both the visceral and the parietal pleura, fusing the lung to the chest wall[22]. The main radiographic features of tuberculous fibrothorax include adhesions in the interlobar fissures, pleural thickening, cavitary consolidations, and fibrocaseating lesions, often accompanied by atelectasis or sublobar bronchiectasis. Other typical signs are upward displacement of the pulmonary hilum, mediastinal shift toward the affected side, and a narrow intercostal space[23].

Conceptual definition of drug-resistant tuberculosis categories

	Major categories	Non Injectables Regime Era (Since 2019)						Injectables Regime Era (Before 2019)				
		1st Line		2nd Lines				1st Line		2nd Lines		
		R	H	FQs	BDQ	LZD	Z/E/Et/Pto/ or Eto	R	H	FQs	Km/Am/Cm	Z/E/Et/Pto/ or Eto
RRTB	RRTB	R	S	S	S	S	R or S	R	S	S	S	R or S
	MDR-TB	R	R	S	S	S	R or S	R	R	S	S	R or S
	pre XDR-TB	R	S	R	S	S	R or S	R	S	R	S	R or S
	pre XDR-TB	R	R	R	S	S	R or S	R	R	S	R	R or S
	XDR-TB	R	S	R	R	S	R or S	R	S	R	R	R or S
	XDR-TB	R	R	R	S	R	R or S	R	R	R	R	R or S
	XDR-TB	R	R	R	R	R	R or S					
Non-RRTB	Poly-drug Resistant	S	S	S	S	S	R	S	S	S	S	R

R= Rifampicin, H= Isoniazid, FQs= Fluoroquinolonas (Lfx= Lexofloxacin, Mfx= Moxifloxacin), BDQ= Bedaquiline, LZD= Linezolid, Z= pyrazinamide, E= ethambutol, Eto= Ethionamide; Pto= Prothionamide, Injectable (Km= kanamycin, Am= Amykacin, Cm= Capreomycin), Colours (Red cell= Resistance, Green cell= Sensitive, Yellow cell= either resistance or sensitive)

Adaptation based WHO Guidelines on drug resistance tuberculosis

Courtesy of Edy Nacarapa, ORCID ID: 0000-0002-0617-9609

Fig. 3. Conceptual definition of drug-resistant tuberculosis categories.

Severe extrapulmonary TB (EPTB)
This includes meningitis, pericarditis, osteoarticular, abdominal, or disseminated/miliary disease. In children aged below 15 years, severe EPTB is any extrapulmonary form of disease other than lymphadenopathy (peripheral nodes) or simple pleural effusion[11,21].

Second-line injectable anti-TB drugs on MDR/XDR TB treatment
Aminoglycosides (kanamycin, amikacin, and capreomycin) are the main injectable second-line antituberculosis drugs (SLD) used in the treatment of drug-resistant tuberculosis[21,24].

Non-injectable SLD regime era in the treatment of MDR/XDR TB
Since 2019, the WHO issued new guidelines to treat patients with RRTB which consist of replacing injectable SLD with oral drugs (BDQ and/or delamanid [DLM][21]. These were adopted in Mozambique at 4th quarter of 2019.

Treatment of persons with RRTB
All P-RRTB were treated according to the Mozambican national RRTB guidelines[21]. (Fig. 2) If patients were persons living with HIV (PLHIV), they were offered ART according to Mozambican national ART guidelines. The first-line ART regimen includes tenofovir, lamivudine, and either efavirenz or dolutegravir[25].

Conceptual definition of Immunovirological status (IVS) to ART
According to several literature review[26–28] and in alignment with the WHO Guidelines on ART therapy[29] as well as approaches implemented in Mozambique[25,30,31] the adopted conceptual definition of IVS is as follows:

Optimal Immunovirological response (OIVR) to ART
PLHIV on ART at least ≥ 3 months with suppressed HIV viremia and acceptable immune reconstitution CD4 + cell count > 350 cells/mm3. Viral suppression is defined as achieving an HIV viral load (VL) level less than 200 copies per milliliter of blood (VL < 200cop/mL)[32–34].

Immunological non-responders (INR) to ART
PLHIV on ART for at least ≥ 2 years who are unable to normalize their CD4 + T cell count to > 500 cells/μL count even with persistent virological suppression[35], generally defined as having a CD4 + cell count < 350 cells/μL despite suppressed HIV-1 RNA[27].

Immunovirological failure (IVF) to ART
PLHIV on ART at least ≥ 3 months with unsuppressed HIV viremia, regardless of CD4 count cell[25,29].

Outcome data and statistical analysis of data
The primary outcome was the incidence of mortality over the person-time accrued from the date of starting (study enrollment) to the date of ending. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25.

First, to describe participants' baseline characteristics, we calculated frequencies and proportions for categorical data and median and interquartile range (IQR) for normally distributed data. Then, we calculated mortality rate using the number of patients who experienced death during study follow-up divided by the person-time (months) at risk throughout the observation period, prior to the outcome of the respective cohort. Next, we conducted a Kaplan-Meier analysis to assess the period during RRTB treatment until time of death. Subsequently, we compared the proportion of patients who died according to exposure variables using crude and adjusted Cox regression modeling, reporting adjusted hazard ratios (aHR) with corresponding 95% confidence interval (CIs). Variables with p-value less than 0.5 in univariate analyzes were entered into the multivariable model.

Results
Baseline clinical and demographic characteristics of patients with RRTB
Between 2015 and 2020, 3974 individuals were diagnosed with TB at CHC. Of these, 151 (3.8%) had RRTB and met the eligibility criteria (Fig. 1). Significantly, 121 (80%) of the RRTB patients were PLHIV. Most RRTB cases (140, 92.7%) were susceptible to fluoroquinolones (FQL) [RRTB/MDRTB], while 11 (7.3%) were FQL-resistant [preXDR, XDR] (Fig. 1). Mortality occurred in 35 (23.2%) RRTB patients. Demographically, 55.6% (84) were men and 64.9% (98) were aged 25–44 years, including 37.1% (57) in the 35–44 year standard reporting group. Median RRTB treatment follow-up was 12 months (IQR 11; 18) (Table 1).

Among 121 PLHIV, the median CD4 cell count was 228 cells/μL (IQR 82; 433), and more than a third ($n = 55$; 36.4%) of new enrollees had a CD4 count < 200 cells/μL, of whom median CD4 count was 76 (IQR 28; 123).

Nearly three-quarters of the patients ($n = 109$, 72.2%) were treated with RRTB injectable-based drugs, and over a third ($n = 52$, 35.1%) had hemoglobin levels between 8.0 and 9.9 g/dL. Additionally, more than half ($n = 89$, 58.9%) were on ART more than 3 months prior to TB diagnosis and treatment initiation, and almost half ($n = 66$, 43.7%) exhibited immunovirological non-response (INR) to ART. (Table 1)

Approximately two-thirds ($n = 95$, 62.9%) of enrollees were naïve TB. Moreover, on the CXR examination showed that, more than a quarter ($n = 40$, 26.5%) of enrollees had a large lesion with over than 50% parenchymal fibrosis; and nearly a third ($n = 45$, 29.8%) exhibited cavitations (Table 1).

	Total *P*-RRTB	Deaths	Person-months	Incidence per 100 PM
	n (%)	*n* (%)	(PM)	(95% CI)
Total	**151**	**35 (23.2)**	**1812**	1.9 (1.3–2.1)
Biological sex				
Female	67 (44.4)	14 (40.0)	1206	1.2 (1.0–1.4)
Male	84 (55.6)	21 (60.0)	840	2.5 (1.9–2.8)
Standard Age Group for TB Reporting [[years]				
≤ 14	5 (3.3)	0 (0.0)	100	0.0 (0.0–0.0)
[15–24]	18 (11.9)	3 (8.6)	333	0.9 (0.8–1.4)
[25–34]	41 (27.2)	11 (31.4)	451	2.4 (1.5–3.0)
[35–44]	57 (37.7)	13 (37.1)	627	2.1 (1.2–2.3)
[45–54]	17 (11.3)	4 (11.4)	289	1.4 (1.1–2.6)
[55–64]	10 (6.6)	3 (8.6)	85	3.5 (2.7–6.0)
≥ 65	3 (2.0)	1 (2.9)	27	3.7 (3.0–6.7)
Hemoglobin (g/dL)				
Hgb ≥ 10.0	62 (41.9)	8 (22.9)	868	0.9 (0.6–1.2)
Hgb [8.0-9.9]	52 (35.1)	12 (34.3)	624	1.9 (1.1–2.3)
Hgb ≤ 7.9	34 (23.0)	15 (42.9)	289	5.2 (3.7–44.1)
On ART prior TB treatment initiation				
HIV Negative	30 (19.9)	7 (20.0)	525	1.3 (1.1–2.6)
On ART ≥ 90 days prior to TB treatment	89 (58.9)	22 (62.9)	979	2.2 (1.4–2.5)
On ART < 90 days prior to TB treatment	10 (6.6)	1 (2.9)	200	0.5 (0.4–0.8)
ART started after TB treatment	22 (14.6)	5 (14.3)	231	2.2 (1.2–3.2)
CD4 Cell count [Cell/µL]				
(Median, [IQR]), N = 121				
CD4 Cell count	228 [82; 433]	159 [56; 397]		
CD4 ≥ 200	411 [276; 568]	495 [267; 896]		
CD4 < 200	76 [28; 123]	76 [21; 106]		
CD4 Cell Range [Cell/µL]				
HIV Negative	30 (19.9)	7 (20.0)	525	1.3 (1.1–2.6)
CD4 ≥ 200	66 (43.7)	11 (31.4)	759	1.4 (0.9–1.9)
CD4 < 200	55 (36.4)	17 (48.6)	605	2.8 (1.9–3.1)
CD4 < 200 Subgroup [Cell/µL]				
• CD4: [101–199]	21 (13.9)	6 (17.1)	315	1.9 (1.2–2.9)
• CD4: [51–100]	16 (10.6)	5 (14.3)	184	2.7 (1.6–7.8)
• CD4 ≤ 50	18 (11.9)	6 (17.1)	189	3.2 (2.6–33.3)
Immunovirological status				
HIV Negative	30 (19.9)	7 (20.0)	525	1.3 (1.1–2.6)
Optimal immunovilogical response	42 (27.8)	2 (5.7)	462	0.4 (0.2–0.5)
INR - Immunological non-responders	13 (8.6)	5 (14.3)	117	4.3 (2.0–38.5)
Immunovirological failure	66 (43.7)	21 (60.0)	858	2.4 (1.7–2.9)
TB Drugs Exposure				
Naïve	95 (62.9)	20 (57.1)	1235	1.6 (1.1–1.9)
1st Line drugs	42 (27.8)	10 (28.6)	441	2.3 (2.0–2.6)
2nd Line drugs	14 (9.3)	5 (14.3)	266	1.9 (1.5–11.9)
RRTB Regime				
Non-Injectables SLD	42 (27.8)	4 (11.4)	483	0.8 (0.7–1.1)
Injectables SLD	109 (72.2)	31 (88.6)	1417	2.2 (1.5–2.6)
Chest X-ray: parenchymal fibrosis				
Normal + ≤ 50% Fibrosis	111 (73.5)	17 (48.6)	1443	1.2 (0.8–1.3)
> 50% Fibrosis	40 (26.5)	18 (51.4)	360	5.0 (3.5–6.4)
Chest X-ray: cavitation				
Normal	106 (70.2)	20 (57.1)	1325	1.5 (1.0–1.7)
Cavitation	45 (29.8)	15 (42.9)	405	3.7 (1.9–4.2)
Abdominal ultrasound: ascites				
Normal	146 (97.3)	32 (91.4)	1752	1.8 (1.2–2.0)
Ascites	4 (2.7)	3 (8.6)	38	7.9 (4.2–75.0)

Continued

	Total *P*-RRTB	Deaths	Person-months	Incidence per 100 PM
	n (%)	*n* (%)	(PM)	(95% CI)
Transthoracic echocardiogram with central venous system assessment				
Normal	137 (90.7)	28 (80.0)	1781	1.6 (1.1–1.7)
Right Ventricular dysfunction; Suprahepatic Vein > 3.0 cm, IVC > 3.0 cm	14 (9.3)	7 (20.0)	112	6.3 (5.0–50.0)
SLD: Second Line Drugs IVC: Inferior vein cava				

Table 1. Demographic and clinical characteristics of 151 persons with rifampicin-resistant tuberculosis at Carmelo hospital of Chokwe, in Mozambique 2015–2020, by mortality outcome.

Additionally, over a fifth ($n = 4$, 2.7%) of enrollees showed ascites on abdominal ultrasound, while close to a tenth ($n = 14$, 9.3%) presented with right ventricular dysfunction, indicated by suprahepatic vein dilation (> 3.0 cm) and IVC dilation (> 3.0 cm). (Table 1)

Risk factors associated with mortality in the follow-up of RRTB treatment

In this study, the 151 P-RRTB contributed a cumulative total of 1812 person-months (PM) of follow-up data. The overall mortality rate was 1.9 per 100 PM (95% CI 1.3–2.1).

Multivariable Cox regression analysis revealed that patients with an optimal immunovirological response (OIVR) to antiretroviral therapy (ART) experienced an 82% reduction in mortality risk compared to those who were HIV-negative (aHR 0.18, 95% CI 0.04–0.93; $p = 0.040$) (Table 2). The association between Hemoglobin (Hgb) levels and mortality was significant. Compared to patients with Hgb levels ≥ 10.0 g/dL, those with Hgb levels between 8.0 and 9.9 g/dL, as well as those with Hgb < 7.9 g/dL, had nearly three times higher risk of mortality (aHR 2.82, 95% CI 1.09–7.27, $p = 0.032$), while those with Hgb levels < 7.9 g/dL had three times the risk (aHR 3.06, 95% CI 1.24–7.51, $p = 0.015$).Patients treated with RRTB injectable SLD had nearly four times the risk of mortality compared to those treated with non-injectable RRTB drugs (aHR 3.72, 95% CI 1.23–11.22, $p = 0.020$).

Parenchymal lesions with more than 50% fibrosis on chest X-ray (CXR) were associated with a risk of mortality that was about three times higher compared to those with normal parenchyma or lesions with less than 50% fibrosis (aHR 3.06, 95% CI 1.38–6.79, $p = 0.006$).

Right ventricular dysfunction, as observed on standard transthoracic echocardiogram with central venous system assessment, was linked to a mortality risk that was approximately three times higher compared to patients with normal findings (aHR 3.18, 95% CI 1.15–8.83, $p = 0.026$).

No significant associations were found between RRTB mortality and baseline characteristics such as biological sex, age group, TB drug exposure, or cavitation on chest X-ray. (Table 2).

Cumulative mortality rate

Figure 4 presents the Kaplan-Meier cumulative probability of mortality among P-RRTB at CHC according to baseline characteristics including: Hgb, IVS to ART, drug resistant TB regime, CXR, and echocardiogram with central venous system assessment. P-RRTB with Hgb below 7.9 g/dL had higher cumulative incidence of death above 45% after 3 months of follow-up (log Rank test, p = < 0.001; Fig. 4A). Having IVF to ART therapy had higher cumulative incidence of death above 26% after 3 months of follow-up (log Rank test, $p = 0.006$; Fig. 4B). Taking injectables SLD had higher cumulative incidence of death above 23% after 3 months of follow-up (log Rank, $p = 0.03$; Fig. 4C). Patients with parenchymal lesions involving more than 50% fibrosis on chest X-ray had a cumulative mortality rate exceeding 39% after 3 months (log-rank test $p < 0.001$; Fig. 4D). Moreover, individuals presenting with the right ventricular dysfunction showed a cumulative mortality rate of 56% after 3 months (log-rank test $p = 0.003$; Fig. 4E).

Discussion

In this study we evaluated the overall mortality and baseline characteristics associated with mortality among persons with rifampicin-resistance tuberculosis undergoing anti-RRTB treatment at a rural district TB clinic in Mozambique. Our retrospective cohort study enrolled 151 P-RRTB, of whom 80.1% were PLHIV; during the follow-up period of anti-RRTB treatment, 23.2% of participants died, resulting in an overall mortality rate of 1.9 per 100 person-months. These findings were consistent with other two following studies: a bicentric retrospective cohort study conducted in eSwatini, which recruited 174 P-RRTB from 2011 to 2013, where 89.7% were PLHIV, and reported a mortality rate of 21.3%[36]; a secondary analysis of the SAPiT trial in Durban, South Africa (2008–2012), involving 23 P-RRTB, all PLHIV, reported a mortality incidence rate of 2.26 per 100 person-months (conversion from 27.1 per 100 person-years[37]. The studies from Durban and eSwatini have identified key predictors of unfavourable outcomes in the anti-RRTB treatment, including low body mass index (BMI), low CD4 T-Cell count, prolonged laboratory delays in diagnosis at the initiation of anti-RRTB treatment. These findings provide crucial evidence for healthcare providers and policymakers, highlighting the importance of implementing integrated care approaches[36,37]. Such approaches should focus on nutritional support, prompt and accurate diagnosis, and coordinated management of HIV and TB co-infections to enhance treatment outcomes for P-RRTB.

	Crude cHR (95% CI)	*p*-value	Adjusted aHR (95% CI)	*p*-value
Biological sex				
Female	Reference			
Male	1.39 (0.70–2.74)	0.343		
Age band [years]				
< 25	Reference			
[25–44]	2.16 (0.65–7.19)	0.209		
≥ 45	2.53 (0.67–9.55)	0.171		
Hemoglobin (g/dL)				
Hgb ≥ 10.0	Reference		Reference	
Hgb [8.0-9.9]	1.89 (0.77–4.63)	0.163	2.82 (1.09–7.27)	0.032
Hgb ≤ 7.9	4.58 (1.93–10.87)	0.001	3.06 (1.24–7.51)	0.015
Immunovirological status				
HIV Negative	Reference		Reference	
Optimal immunovirological response	0.20 (0.04–0.95)	0.043	0.18 (0.04–0.93)	0.040
Immunological non-responders	1.87 (0.59–5.90)	0.285	2.20 (0.66–7.35)	0.201
Immunovirological failure	1.55 (0.66–3.65)	0.317	1.30 (0.53–3.19)	0.571
TB Drugs Exposure				
Naïve	Reference			
1st Line drugs	1.27 (0.59–2.72)	0.540		
2nd Line drugs	1.64 (0.61–4.37)	0.325		
RRTB Regime				
Non Injectables Drugs	Reference		Reference	
Injectables Drugs	2.95 (1.04–8.35)	0.042	3.72 (1.23–11.22)	0.020
Chest X-ray: parenchymal fibrosis				
Normal + ≤ 50% Fibrosis	Reference		Reference	
> 50% Fibrosis	3.58 (1.84–6.96)	< 0.001	3.06 (1.38–6.79)	0.006
Chest X-ray: cavitation				
Normal	Reference			
Cavitation	1.93 (0.99–3.77)	0.055		
Abdominal ultrasound: ascites				
Normal	Reference		Reference	
Ascites	3.84 (1.17–12.59)	0.026	1.39 (0.37–5.24)	0.625
Transthoracic echocardiogram with central venous system assessment				
Normal	Reference		Reference	
Right Ventricular dysfunction. Suprahepatic Vein > 3.0 cm, IVC > 3.0 cm	3.27 (1.41–7.58)	0.006	3.18 (1.15–8.83)	0.026
SLD: Second Line Drugs IVC: Inferior vein cava				

Table 2. Cox proportional hazards model for mortality in 151 persons with rifampicin-resistant tuberculosis at Carmelo hospital of Chokwe, in Mozambique 2015–2020.

We also found in our evaluation those who had an optimal immunovirological response to ART had an 82% lower risk of mortality (aHR 0.18, 95% CI 0.04–0.93; $p = 0.040$) compared those who were HIV-negative. Our findings were consistent with other published reports, a published literature review found that PLHIV with RRTB have a lower mortality when taking ART optimally[26]. Following this line of reasoning, it is important to highlight that an OIVR to ART (CD4 cell count > 200 cells/μL, undetectable viral load[26], at the time of diagnosis of RRTB, is a protective marker against the risk of death. It reduces the chances of occurrence of advanced HIV disease (clinical events related to AIDS: extrapulmonary manifestation of TB [including central nervous system], *Pneumocystis jirovecii*, cryptococcal meningitis, *Toxoplasma gondii*, JC virus)[38]. In response to these facts, The International Union Against Tuberculosis and Lung Disease Disease[39] and Mozambican national MDR-TB management guidelines promote an integrated, multidisciplinary approach. Essential elements include RRTB-specific treatment (anti-TB medication, intolerance management, patient monitoring), ART provision, and psychosocial support addressing adherence and mental health[11,40].

Our analysis reported a three-fold higher hazard of death among patients with Hgb (8.0-9.9) g/dL as well as Hgb < 7.9 g/d, (aHR 2.82 and 3.06,) respectively. Our findings are similar to the results of an Ethiopian institutional-based retrospective cohort study ($n = 498$) of P-RRTB between 2010 and 2017, indicating a

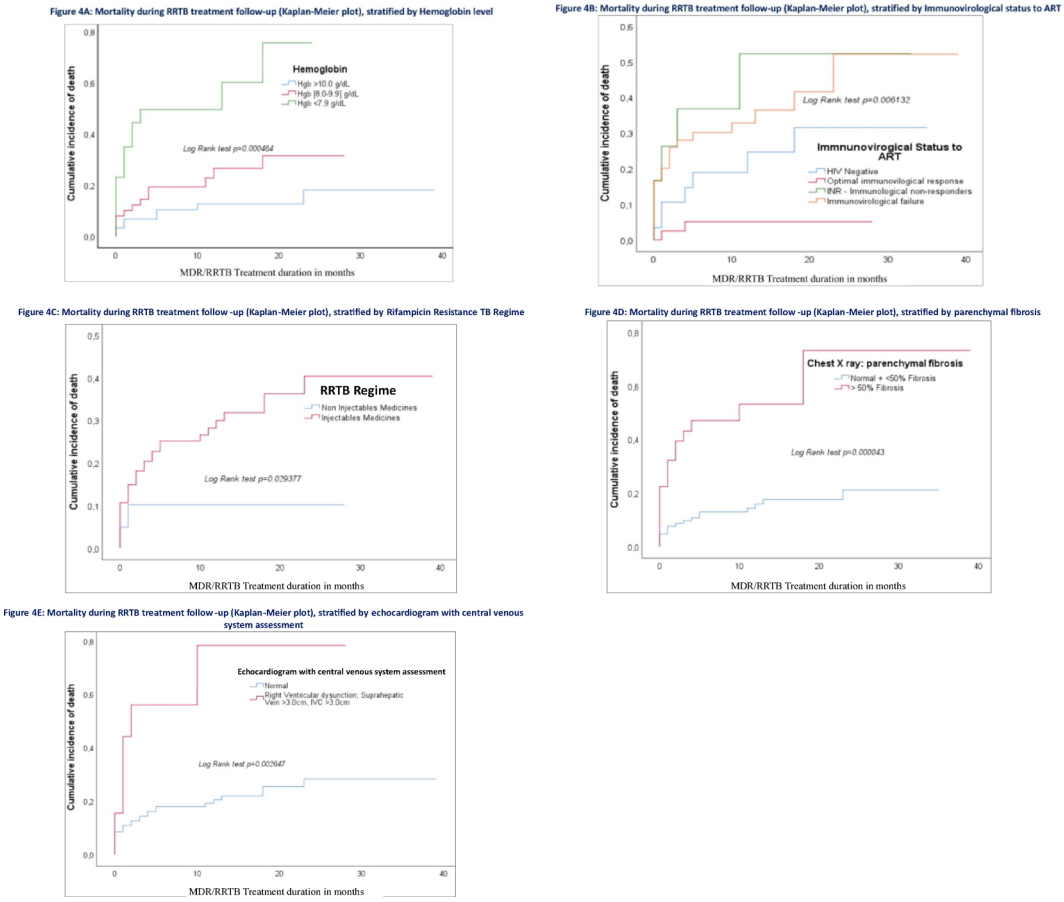

Fig. 4. Kaplan-Meier plot for 151 persons with rifampicin-resistant tuberculosis at TB Clinic, in Mozambique 2015–2020 by: (**A**) Hemoglobin, (**B**) immunovirological status to ART, (**C**) rifampicin- resistance TB regime, (**D**) Chest X-ray immunovirological response, and (**E**) echocardiogram with venous assessment findings. (**A**) Persons with RR-TB (P-RRTB) having Hemoglobin below 7.9 g/dL had higher cumulative incidence of death above 45% after 3 months of follow-up (log Rank test p=0.000464). (**B**) Presenting immunovirological failure to ART therapy had higher cumulative incidence of death above 26% after 3 months of follow-up (log Rank test p=0.006132). (**C**) Taking injectables-based medicines had higher cumulative incidence of death above 23% after 3 months of follow-up (log Rank p=0.029377). (**D**) Presenting a parenchymal fibrosis more than 50% on the chest X ray had higher cumulative incidence of death 39% after 3 months of follow-up (log Rank p=0.000043). (**E**) Presenting right ventricular dysfunction had higher cumulative incidence of death 56% after 3 months of follow-up (log Rank p=0.002647).

higher risk of mortality among those presenting anemia (aHR 3.04)[41]. Therefore, we may consider a plausible hypothesis that anemia serves as an early biomarker of advanced TB disease that develops prior to onset of clinical manifestation[42]. Pathophysiologically, anemia is the result of Hgb sequestration by a chronic infectious inflammatory process[41,43].

One of the key strengths of our study was the ability to examine the relationship between mortality rates and RRTB therapy history. We found that nearly three-quarters of P-RRTB were treated with injectable SLD had an almost quadrupled risk of death (aHR 3.72). Our findings are in line with the results of other studies, for example: a systematic scoping review revealed that injectable SLD therapy for P-RRTB (aminoglycoside-based RRTB regimen [kanamycin]) was less effective than non-injectable SLD (BDQ-based RRTB regimen); nevertheless, compared with BDQ, injectables SLD were associated with poorer treatment outcomes (death and default) and greater severity of adverse effects (nephro-ototoxicity) in the P-RRTB follow-up[44]. This is why, as of mid-2019, the NTP recommended replacing injectables SLD (kanamycin) with non-injectables SLD (bedaquiline)[11]. Given that, since 2021, a multicenter implementation study entitled "Shorter TB treatment regimen – SHOORT initiative" was piloted[45]. Supported by Ministry of Health (MOH) of 13 countries and WHO, this initiative investigated a shorter, 6-month regimen for rifampicin-resistant TB (RRTB) that incorporated non-injectables, bedaquiline (BDQ)[45,46]. Its recommendations centered on deploying 6-month all-oral regimens (BPaLM/BPaL [bedaquiline (B), pretomanid (Pa), linezolid (L), and moxifloxacin (M)]) to align with global goals of simplifying care and accelerate TB elimination[45].

An additional strength of our study was to observe the relationship between the mortality rate and the magnitude of the pulmonary parenchymal lesion on the CXR. We observed a three-fold higher hazard of

death among patients with parenchymal lesion > 50% fibrosis (aHR 3.06). In this reasoning, we should consider the hypothesis that patients with RRTB who present with fibrotic lesions involving more than 50% of lung parenchyma are likely to have a history of exposure to multiple TB therapies, delayed recovery, and/or Rifampicin resistance[23]. Therefore, it is essential to consider the association of multiple factors that significantly contribute to the increased risk of death, including extrapulmonary manifestation[9], opportunistic infections (aspergillomas[47], or advanced HIV disease[26], or mechanical complications (abnormal spirometry[48], and cardiovascular complications such as (cor pulmonale[49]. Thus, pulmonary fibrosis with 50% of the parenchymal lesion at baseline is a biomarker of the presence of an enormous burden of morbidity, which requires a medical approach not focused solely on the specific treatment of RRTB, but a parallel multifaceted approach targeting multiple other factors, such as ART therapy for those co-infected with HIV[8], pulmonary physiotherapy[48], treatment of aspergillomas[47], and surgery if necessary[23].

Lastly, we analyzed the association between mortality rate and compliance of large veins on ultrasound. We verified a three-fold higher hazard of death among patients with right ventricular dysfunction (aHR 3.18). These findings are novel, revealing associations between mortality and right ventricular dysfunction in P-RRTB. However, there is limited evidence on this variable. Interestingly, a systematic review and meta-analysis highlights the significant burden of pulmonary hypertension: 15.3% in a pooled cohort of 2,577 individuals with active TB and 48.1% in a pooled cohort of 1,069 individuals with post-TB 21[49]. In our pathophysiological understanding we consider the following hypothesis that right ventricular dysfunction in this study population is a direct consequence of pulmonary vascular resistance caused by the magnitude of pulmonary parenchymal fibrosis[50]. A less compliant dysfunctional right ventricle can compromise the electrical conduction system of the sinoatrial nodes and atrioventricular nodes, leading in turn to primary and secondary ventricular arrhythmias[51]. Furthermore, the mechanical consequences of a dysfunctional right ventricle are the following: a combination of systemic venous congestion, portocaval venous hypertension and low systemic output, which in turn triggers a systemic inflammatory reaction that affects several organ systems, including the kidney (salt and water balance), liver (cardiac cirrhosis), brain (decreased cognitive function) and skeletal muscle (volitional muscular atrophy)[50]. Ultimately, end organ damage increases the risk of death.

The strength of our updated cohort research lies in its ability to demonstrate overall mortality, and the baseline characteristics associated with mortality among individuals with RRTB at a rural district TB clinic in Mozambique. But some limitations should also be acknowledged: first, it was a retrospective cohort analysis, so data were limited to recorded variables; second, over the period under review, RRTB guidelines have changed from injectable-based towards non-injectables regimes and anti-RRTB regimens have also become better; third, adherence characteristic during RRTB follow-up was not analyzed; fourth, Side-effects to RRTB during the follow-up period was not analyzed; fifth, due to the higher proportion above 92.7% of P-RRTB treated as susceptible to FQL (RRTB/MDR) compared to resistant to FQL (preXDR/XDR), the risk of death associated with this characteristic was not estimated; sixth, the CHC is a referral district hospital for TB/HIV, receiving critically ill patients with very advanced disease, which may explain the high mortality rate in this health facility; seventh, and last, this analysis may have limited generalizability because the recruited participants were individuals enrolled in one health facility in Mozambique which poses a challenge to generalizability. Thus, our results do not reflect the results of RRTB mortality across the country, considering the resource limitations in the public sector, death estimates across the national health service may be higher.

Conclusion

This study highlights a high mortality rate among P-RRTB at a rural Mozambique clinic, with increased risks associated with anemia, injectable RRTB treatments, extensive lung fibrosis, and right ventricular dysfunction. To improve patient outcomes, it is crucial to strengthen and streamline training for healthcare workers on updated RRTB management guidelines and early detection strategies. Additionally, optimizing treatment by focusing on more effective and less toxic regimens, including non-injectable SLD, is essential. A comprehensive approach that addresses comorbidities such as anemia and chronic lung diseases, along with integrating multidisciplinary care, is necessary to manage the complexity of P-RRTB cases and reduce mortality.

To minimize the risk of death, it must be ensured that all P-RRTB patients are assessed for impaired lung function, and interventions designed to improve it, assess baseline hemoglobin, report adverse events, and make the appropriate correction, manage complications.

Data availability

The datasets analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Author contributions

E.N. contributed to the study design, data acquisition, study implementation, data analysis and its interpretation, with a major contribution to writing the first draft, reviewing, and editing. He read and approved final version. B.J equally contributed on study design, data acquisition, data analysis and its interpretation, writing review and editing, and approved the final version. I.M. and D.O. equally contributed on data analysis and its interpretation, writing, reviewing, editing, and approved the final version. J.M.R.R. contributed on study design, data analysis and its interpretation, writing, reviewing, editing, and approved the final version.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval and consent to participate

Ethical clearance was obtained from the Institutional Bioethics Committee for Health of Gaza *(IRB0002657 – Comité Institucional de Bioética para a Saúde de Gaza*, *19/CIBS-Gaza/2021* and permission to perform the study was also obtained from the Gaza Health Directorate *(Direcção Provincial de Saúde de Gaza*, *DPS-Gaza/30-04-2019)*. This study received a Research Determination from the University Miguel Hernandez de Elche-Spain under the authorization code COIR *(Solicitud Código de Investigación Responsable [COIR]: ADH. SPU.JMRR.EEA.23)*. The need for written informed consent to participate in the study and for its publication was explicitly waived by IRB0002657 (*Comité Institucional de Bioética para a Saúde de Gaza*, *19/CIBS-Gaza/2021)*. All information obtained during the study was kept confidential. Analysis was performed on de-identified aggregated data. Furthermore, this study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

We performed analysis on routine administrative data; consent for publication is not applicable.

Additional information

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