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Anemia and anti-tuberculosis treatment outcome in persons with pulmonary tuberculosis: A multi-center prospective cohort study

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Ethics Statement

This study was conducted following the principles of the Declaration of Helsinki. Study participants enrolled into the Regional Prospective Observational Research in Tuberculosis (RePORT-Brazil) cohort [12]. The study was approved by the Institutional Review Boards at all enrollment sites (CAAE: 25102412.3.1001.5262) and at Vanderbilt University Medical Center. An written informed consent was obtained from all voluntary participants in RePORT-Brazil cohort.

CRediT authorship contribution statement

Conceptualization, M.A.P, T.R.S., M.C.F., M.C.S., V.C.R., and B.B.A.; Data curation, M.M.T., M.A-P., and B.B.A.; Investigation, M.A-P. M.C.F., A.L.K., V.C.R., T.R.S., M.C.S., and B.B.A.; Formal analysis, M.A-P., and B.B.A.; Funding acquisition, A.L.K., V.C.R., T.R.S., M.C.S., M.C.F., and B.B.A.; Methodology, M.A-P., and B.B.A.; Project administration, M.C.F., T.R.S., and B.B.A.; Resources, M.A-P., T.R.S., and B.B.A.; Software, M.A-P., M.C.F., and B.B.A.; Supervision, T.R.S., and B.B.A.; Writing—original draft, M.A-P., and B.B.A.; Writing—review and editing, all authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2023.04.009.

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Abstract

Background: Tuberculosis (TB) remains a major plague of humanity. People with TB (PWTB) are commonly anemic. Here, we assessed whether the severity of anemia in PWTB prior to anti-TB treatment (ATT) was a risk factor for an unfavorable outcome.

Methods: Patients ≥ 18 years old with culture-confirmed drug-susceptible pulmonary TB enrolled between 2015 and 2019 in a multi-center Brazilian cohort were followed for up to 24 months and classified according to anemia severity (mild, moderate, and severe), based on hemoglobin levels. A multinomial logistic regression model was employed to assess whether anemia was associated with unfavorable outcome (death, failure, loss to follow-up, regimen modification or relapse), compared to treatment success (cure or treatment completion).

Results: Among 786 participants who met inclusion criteria, 441 (56 %) were anemic at baseline. Patients with moderate/severe anemia were more HIV-seropositive, as well as more symptomatic and had higher frequencies of unfavorable outcomes compared to the other groups. Moderate/severe anemia (adjusted OR [aOR]: 7.80, 95 %CI:1.34–45.4, p = 0.022) was associated with death independent of sex, age, BMI, HIV and glycemic status.

Conclusion: Moderate/severe anemia prior to ATT was a significant risk factor for death. Such patients should be closely monitored given the high risk of unfavorable ATT outcomes.

Keywords

Tuberculosis; Tuberculosis treatment outcome; Anemia; Death; Hemoglobin

Background

Tuberculosis (TB) persists as a substantial global health challenge, with 1.6 million TB-associated deaths yearly, and 10.6 million cases worldwide in 2021 [1]. The management of persons with TB (PWTB) depends on understanding the risk factors associated with disease

progression and poor anti-TB treatment outcomes, such as HIV co-infection, consumption habits, diabetes mellitus (DM), and anemia [2–4].

Anemia is defined as a decrease in hemoglobin (Hb) values below well-established cut-offs (< 13 g/dL for men; and < 12 g/dL for women) and is commonly associated with inflammatory and/or infectious conditions [5]. This disorder is commonly identified in PWTB—noted in 61.5 % of TB cases in a recent meta-analysis—and is frequently described as a marker of greater disease severity and/or more advanced disease [6]. Anemia in PWTB is multifactorial and is often attributed to inflammation, malnutrition, chronic disease, and direct bone marrow suppression by TB infection [7]. Importantly, anemia is a major public health problem regardless of TB, and preferentially affects populations from low-middle income countries, demonstrating that such condition may be linked to a variety of multifactorial determinants, from nutritional deficiencies to co-infections [6].

The risk of developing active TB among anemic patients is described to be 3.6 times greater than in non-anemic patients; such risk appears to increase as the severity of anemia increases [8]. Anemia is associated with severe clinical forms of TB, such as meningeal and disseminated TB [9]. Understanding the association between anemia and outcomes of anti-TB therapy (ATT) can provide insight for more focused and optimized, clinical management to improve outcomes.

In previous studies, we demonstrated that persons affected by TB-HIV co-infection exhibited an increased dysregulation of immune activation [10,11]. Furthermore, TB-HIV individuals who persist with low levels of Hb during the course of ATT have an augmented risk of unfavorable outcomes, such as treatment failure and death [3]. Whether the severity of anemia prior to ATT is differentially associated with treatment outcome regardless of HIV co-infection is not fully understood. The present study aimed to answer this question in a multi-center prospective cohort that has been shown to be representative of PWTB reported to the Brazilian National Tuberculosis Program registry [12]. The findings provide the basis to support implementation of decision-making strategies to systematically screen for anemia in all newly-diagnosed TB cases and to closely monitor those with severe anemia to minimize the risk of unfavorable ATT outcomes.

Methods

Study design

The Regional Prospective Observational Research for Tuberculosis (RePORT)-Brazil is a network of researchers with the aim of studying active and latent TB in the Brazilian population (www.reportbrazil. org). It is composed of five sites (3 in Rio de Janeiro, 1 in Amazonas, and 1 in Bahia) that followed the same inclusion and exclusion criteria, with patients being enrolled between June 2015 and June 2019, and with follow-up through June 2021 in all sites. This resulted in a cohort of 1187 cases of active TB and 2700 close contacts of these patients.

All participants in the RePORT-Brazil cohort were at least 18 years old, with new or recurrent pulmonary TB, and had culture-positive sputum. For this study, only confirmed

drug-susceptible patients were included. Epidemiological information was collected using standardized clinical research forms during study visits at baseline, during and at the end of treatment, and up to 24 months after enrollment. The collected variables included sex, age, self-reported race, weight, height, education level, use of alcohol, illicit drugs or tobacco, presence of co-morbidities, and HIV status. Additionally, Hb values, radiographic evaluation of chest X-ray, drug susceptibility testing for anti-TB drugs, and CD4 counts (if HIV positive) were performed. In RePORT-Brazil, the treatment outcome was recorded at the last study visit (24 months after the initiation of treatment). Outcome definitions are described below.

Dysglycemia was defined according to HbA1c measure prior to ATT initiation, following American Diabetes Association (ADA) guidelines [13]. Participants were classified as having DM (HbA1c ≥ 6.5 %), pre-diabetes (HbA1c=5.7–6.4 %) or normoglycemia (HbA1c < 5.7 %). In this study, participants with HbA1c ≥ 5.7 % were classified as having dysglycemia.

Anemia definition

To define anemia, we used the WHO guideline criteria [5]. Anemia was defined as levels of Hb below 13 g/dL for men or < 12 g/dL for women. Mild anemia was defined as Hb value > 10 g/dL and < 13 g/dL for men; and > 10 and < 12 g/dL for women, whereas moderate anemia was defined as Hb > 8 g/dL and ≤ 10 g/dL for both sexes. Severe anemia was defined as Hb < 8 g/dL for both sexes [5].

Outcome definition

A favorable treatment outcome was defined as cure or completed treatment. An unfavorable outcome was defined as treatment failure, lost to follow-up, recurrence, or death during treatment. The definitions for clinical and bacteriological cure, failure, lost to follow-up, recurrence, and death corresponded with the recently updated WHO guidelines [14]. The definitions in details of treatment outcomes for RePORT-Brazil cohort were previously described by our group [15] and reported in Supplementary Table 1.

Statistical analysis

In this study, we used as measures of central tendency and dispersion the median and interquartile range (IQR), respectively. The Mann-Whitney U (between two groups) or Kruskal Wallis (> two groups) test were used to compare continuous variables based on TB and anemia grade. Categorical variables were reported as absolute values or relative frequencies (%), and they were compared using the Fisher’s exact test (between two groups) or the Pearson’s chi-square test (between more than two groups).

We utilized logistic regression (as an explanatory model) to ascertain whether anemia is associated with the treatment outcomes independent of other factors. The odds ratio (OR) and 95 % confidence intervals (Cis) of the associations with clinical and epidemiological characteristics and unfavorable outcomes were estimated using a multinomial logistic regression model (stepwise method) including all available variables described in Table 1. After the logistic regression model adjustment, the results on anemia severity were reported.

A statistically significant p-value cut-off point < 0.05 was used. A conceptual model towards identifying the risk factors of unfavorable outcomes is detailed in Supplementary Figure 2. Statistical analyses were performed using R language (version 4.5.1), with the following packages: compareGroups, nnet, stepAIC and ggplot2.

Results

Characteristics of the study participants

A total of 1187 PWTB were enrolled in the RePORT-Brazil cohort. For this study, 401 individuals were removed from the analyses due to first line drug resistance, lack of Hb levels or ATT outcome information, resulting in 786 TB cases for this study (details depicted in Supplementary Figure 1 and Supplementary Table 2). Of those, 441 (56 %) had anemia. Anemic patients were more frequently of non-white race (anemic: 83 %; non-anemic: 71.3 %, $p < 0.001$) and had higher frequency of HIV infection (anemic: 23 %; non-anemic: 7.2 %, $p = 0.003$) and of dysglycemia (anemic: 65.2 %; non-anemic: 54.7 %, $p = 0.03$). Anemia was also associated with an increased proportion of tobacco use (anemic: 49.7 %; non-anemic: 42.3 %, $p = 0.048$) compared to non-anemic patients (Supplementary Table 3).

Following stratification of the study participants according to anemia severity, we observed that 333 (42 %) individuals had mild, 80 (10 %) had moderate, and 28 (4 %) had severe anemia (Fig. 1a). Anemia severity was not significantly associated with consumption habits (Fig. 1b). In contrast, increased anemia severity was associated with a lower body mass index (BMI) ($p < 0.001$) (Fig. 1c) and a higher frequency of HIV infection ($p < 0.001$) (Fig. 1d). Furthermore, such subgroups of anemic patients also more regularly presented with TB-related symptoms, such as fever ($p < 0.001$), weight loss ($p = 0.003$) and fatigue ($p = 0.002$). In addition, the frequency of cough decreased according to anemia severity ($p = 0.015$) (Fig. 1e, Table 1).

Determinants of TB treatment outcomes

During the follow-up period, 592 (75.3 %) patients had a favorable outcome (Cure: 360; Treatment completed: 232) whereas 194 (24.7 %) experienced an unfavorable outcome (Death: 41; Failure:27; Loss to follow-up (LTFU): 117; Recurrence: 9). The frequency of unfavorable outcomes increased with severity of anemia ($p < 0.001$) (Fig. 2a). Such trend was apparently driven by death, which substantially increased according to the severity of anemia ($p < 0.001$) (Fig. 2b).

Patients with unfavorable outcomes were more frequently anemic (favorable: 51.9 %; unfavorable: 69.1 %, $p < 0.001$), reported tobacco consumption (favorable: 44.3 %; unfavorable: 53.1 %, $p = 0.040$), alcohol use (favorable: 79.1 %; unfavorable: 89.2 %, $p = 0.002$), and illicit drug use (favorable: 23.5 %; unfavorable: 35.2 %, $p = 0.006$) (Table 2). Patients who developed unfavorable outcomes also had higher frequency of HIV infection (favorable:12.9 %; unfavorable: 27.1 %, $p < 0.001$) (Table 2).

Next, we performed analyses to assess the association between occurrence of anemia (or its different severity levels) and each type of unfavorable outcome individually (treatment failure, death, LTFU and recurrence), using cure/complete treatment as the reference

outcome. Due to the low number of participants in the severe anemia group, moderate and severe anemia cases were combined in a single category. We also combined treatment failure and recurrence in a single category. The multinomial logistic regression analysis demonstrated that moderate/severe anemia (adjusted OR [aOR]: 6.88, 95 %CI:1.184–40.1, p = 0.032) was independently associated with death after controlling for other confounding factors used in the final adjusted model, which included sex, age, BMI, HIV status and glycemic levels (Fig. 3). Of note, among the patients who died, only 5 (12.2 %) were non-anemic, and the overall median time to death was 104 days (IQR:38.0–360). In addition, no associations between anemia and other types of unfavorable outcomes were observed, arguing that the impact of anemia severity was more specifically focused on mortality. Relevant details of the model including odds ratios for the confounding variables are described in Supplementary Table 4.

Discussion

Our study of persons with pulmonary TB from a Brazilian multi-center prospective cohort revealed a high prevalence of anemia. Indeed, this condition is frequently diagnosed in PWTB, with reported frequencies between 32 % and 86 % [6]. In our study, 56 % of patients were anemic and 14 % had moderate or severe anemia. Importantly, most of the participants with moderate/severe anemia were living with HIV. Previous studies have reported diminished Hb values in persons with TB-HIV co-infection compared to persons living with HIV without TB [10] or to PWTB who were not HIV infected [11,16]. Of note, the high frequency of people living with HIV among individuals with moderate/severe anemia may also explain the negative association between the severity of anemia and cough, a classic symptom of TB, given that an atypical clinical presentation of TB has already been described in TB-HIV co-infected patients [17–19]. Therefore, the results of this study confirm these prior findings.

Nevertheless, the findings described here, in a cohort which is representative of the Brazilian population of TB patients [12], add to the body of evidence that moderate to severe anemia is a robust risk factor for death in PWTB undergoing ATT. Noteworthy, this was independent of the effect of other important and well-known risk factors for death such as BMI [20], HIV infection [21,22] and pre-DM or DM [4]. These observations concur with a recent report from South India demonstrating that severe anemia prior to ATT commencement was associated with increased risk of death during the course of treatment [23]. In this South Indian study, only 0.4 % (n = 5) of the study population were living with HIV. In addition, a prospective case-control study which enrolled pulmonary TB patients admitted to the emergency department of a referral TB hospital also found that severe anemia composed a prediction score to infer early mortality, which was defined as death within one week of hospital admission [24]. In a previous study of our group, we demonstrated that increased neutrophil count prior to ATT initiation was associated with unfavorable treatment outcomes [25]. Herein, neutrophil count and Hb levels had a negative correlation. Altogether, the results strongly advocate that Hb values could be used as a predictor of mortality. Identification of anemic TB patients prior to ATT and the consequent estimation of prognosis may lead to optimized clinical management in an attempt to improve treatment outcomes.

In PWTB with moderate and severe anemia, we found an increased frequency of disseminated TB and DM compared to those without anemia. The relationship between anemia and severe clinical forms of TB has been described by Kerkhoff et al. [26]. The authors demonstrated that the combination of anemia, low hepcidin levels and disseminated TB disease led to poor prognosis in TB-HIV patients. Yet, such relationships in the absence of HIV infection were not explored. In persons with DM and without TB, the frequency of anemia was of 30 % in a distinct study [27]. In that scenario, anemia was shown to be an independent indicator of increased risk for DM-related macrovascular and microvascular complications. Even though both HIV co-infection and DM comorbidity have already been described to influence the occurrence and severity of anemia in persons with TB, our results argue that anemia directly links to increased mortality independent of these conditions.

The present study had some limitations. In this prospective cohort, measurements of Hb were performed only at baseline, precluding an exploration of whether transient vs. persistent anemia over the course of ATT could impact outcomes. The study design also limited the ability to decipher whether anemia itself caused the poor prognosis, or whether it was a hallmark of disease progression or an underlying process such as an inflammatory disturbance. Moreover, it was not possible to determine whether anemia was caused by nutritional factors, or medications that may have affected erythrocyte lifespan.

Conclusion

With the above limitations noted, our study established that moderate to severe anemia pre-ATT directly predicted the risk of death in PWTB, independent of HIV status. Consequently, new policy may be needed to implement a systematic assessment of Hb values in all pulmonary TB patients prior to ATT initiation to estimate mortality risk. This simple test could lead to early interventions that might decrease the risk of poor treatment outcomes, including in limited-resource settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations:

ATT	Anti-tuberculosis therapy
BMI	Body mass index
CI	Confidence intervals
DM	Diabetes mellitus
IQR	Interquartile range
Hb	Hemoglobin
HbA1c	Glycated hemoglobin
LTFU	Loss to follow-up
OR	Odds ratio
PWTB	Persons with tuberculosis
TB	Tuberculosis

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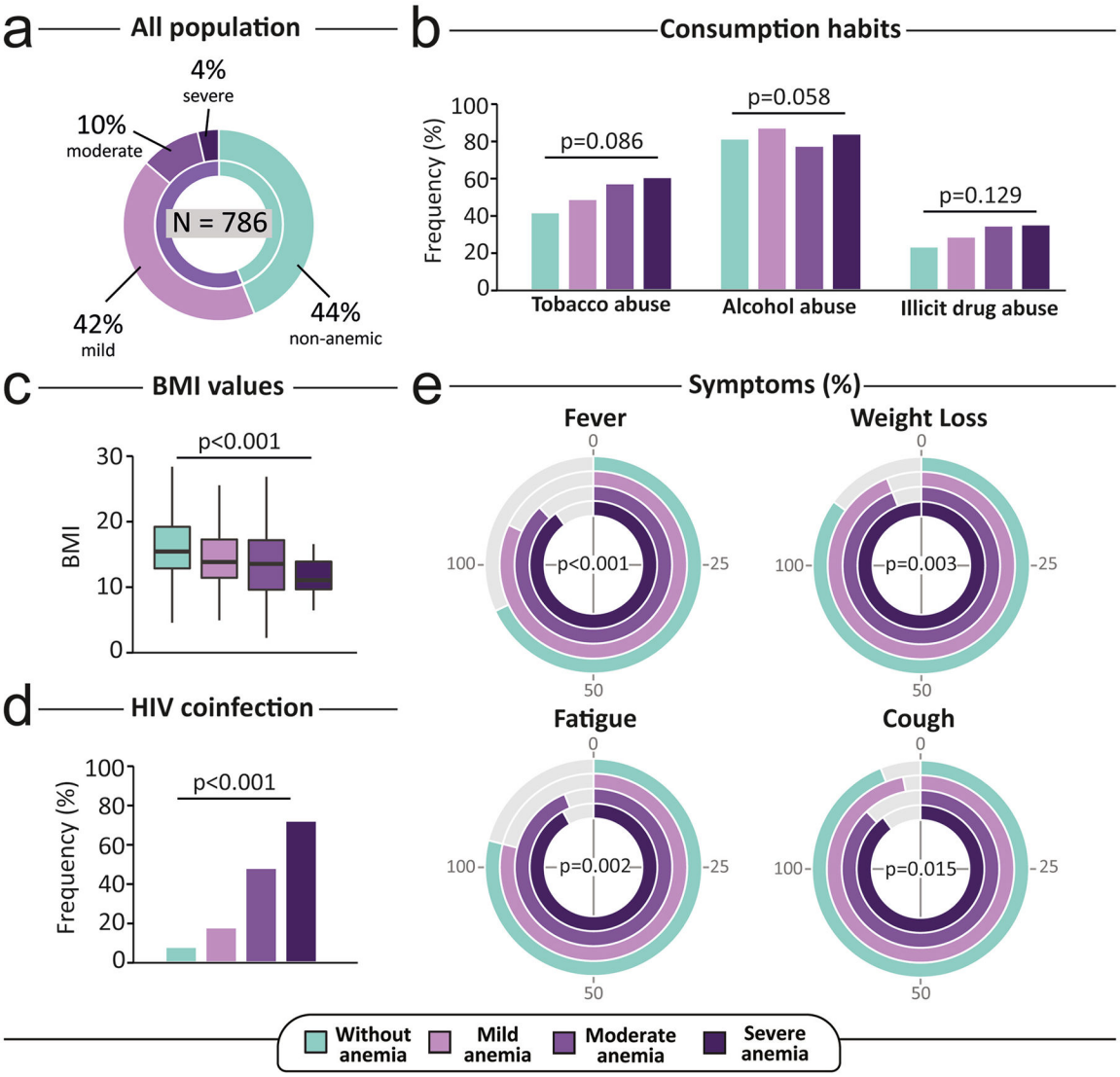

Fig. 1.

Increased in anemia severity is associated with poor consumption habits, higher frequency of comorbidities, and of TB-related symptoms. (a) Among all the study participants (n = 786), 56 % had anemia: 42 % mild, 10 % moderate, and 4 % severe. (b) Frequency of consumption habits in patients stratified according to anemia severity. (c) BMI according to anemia severity. (d) Frequency of HIV according to anemia severity. (e) Frequency of TB clinical symptoms following the anemia severity. Groups were compared using the Pearson's chi-square test or the Kruskall-Wallis test.

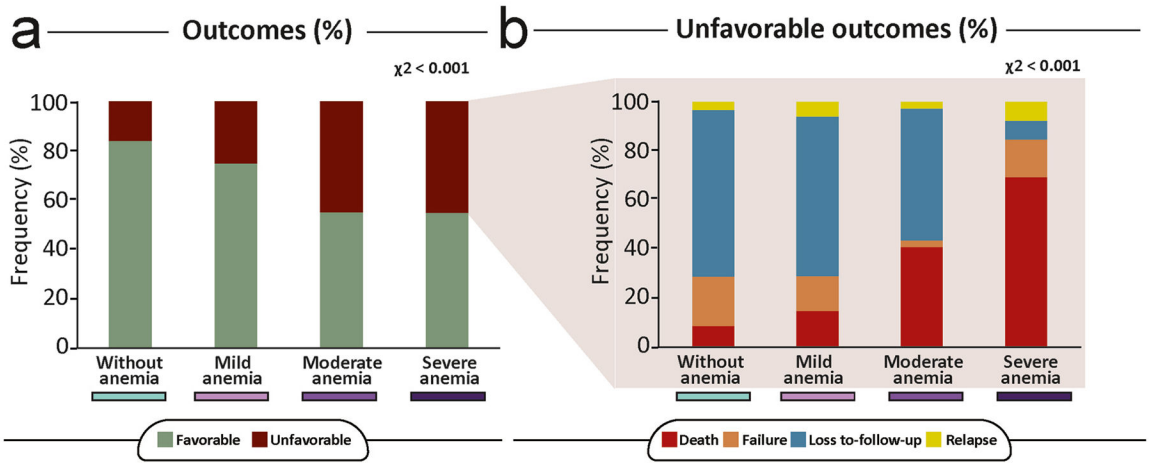

Fig. 2.

Anemia severity was associated with increased occurrence of unfavorable outcomes. (a) Frequency of unfavorable TB treatment outcomes according to anemia severity. (b) Frequency of each type of TB unfavorable outcome according to anemia severity. Groups were compared using the Pearson's chi-square test.

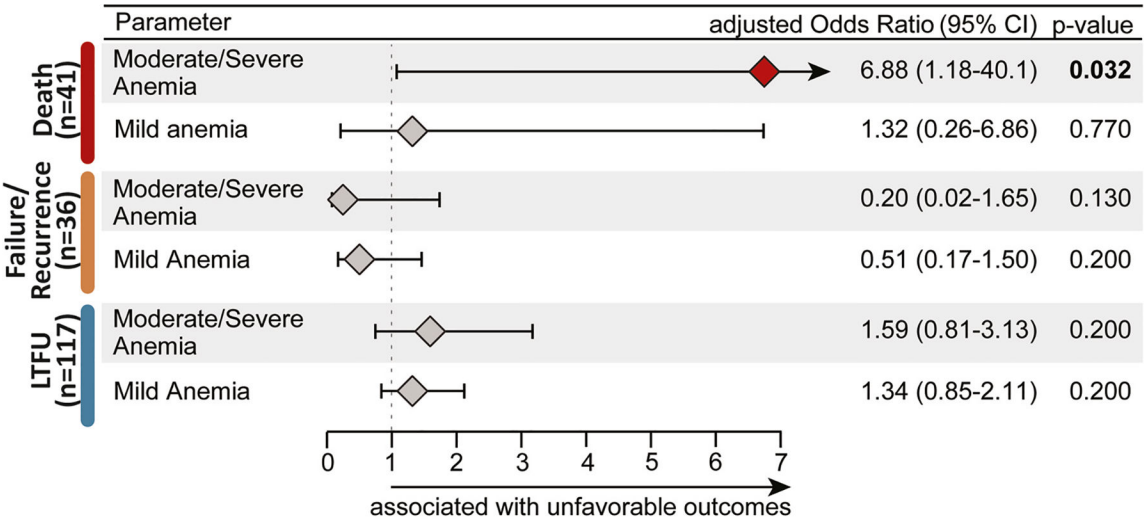

Fig. 3.

Moderate and severe anemia are associated with increased mortality in patients with TB undergoing treatment. A multinomial logistic regression model (backward stepwise regression) was designed to test independent associations between clinical characteristics and the indicated TB treatment outcomes. Cure or treatment completed was considered as reference outcome. The variables included in the adjusted model were anemia severity, sex, age, BMI, HIV status and dysglycemia status.

Table 1

Characteristics of the study participants at baseline according anemia severity.

		Without anemia (n = 345)	Mild anemia (n = 333)	Moderate anemia (n = 80)	Severe anemia (n = 28)	P value	P trend
Baseline characteristics and consumption habits	**Hemoglobin (g/dL), median (IQR)**	13.6 (13.0–14.4)	11.4 (10.8–12.0)	9.25 (8.79–9.70)	7.58 (7.30–7.73)	**NA**	**NA**
	Sex (male), n (%)	212 (61.4)	224 (67.3)	43 (53.8)	16 (57.1)	0.098	0.954
	Age, median (IQR)	37.0 (27.0–49.0)	36.0 (25.0–49.0)	37.5 (25.8–49.0)	39.0 (30.5–48.5)	0.640	0.732
	BMI, median (IQR)	21.0 (19.3–23.4)	19.9 (18.4–22.2)	19.7 (17.2–22.1)	18.1 (17.2–20.0)	**< 0.001**	**< 0.001**
	Race (non-white), n (%)	246 (71.3)	271 (81.4)	71 (88.8)	25 (89.3)	**< 0.001**	
	Tobacco use, n (%)	146 (42.2)	159 (47.7)	43 (53.8)	17 (60.7)	0.086	**0.010**
	Alcohol use, n (%)	271 (78.6)	282 (84.7)	62 (77.5)	37 (92.5)	0.058	0.114
	Illicit drug use, n (%)	78 (23.2)	80 (26.0)	24 (25.8)	6 (35.3)	0.129	**0.032**
TB Data and comorbidity	**Prior TB, n (%)**	49 (14.2)	48 (14.4)	14 (17.5)	1 (3.57)	0.411	0.819
	HIV, n (%)	24 (7.19)	50 (15.0)	29 (36.2)	11 (39.3)	**< 0.001**	**0.001**
	Abnormal X-ray, n (%)	337 (98.3)	317 (96.9)	74 (92.5)	26 (96.3)	0.052	0.921
	Dysglycemia, n (%)					**< 0.001**	0.650
	Diabetes	82 (23.8)	65 (19.6)	20 (25.0)	11 (39.3)		
	Prediabetes	116 (33.6)	164 (49.4)	20 (25.0)	7 (25.0)		
	Normoglicemia	147 (42.6)	103 (31.0)	40 (50.0)	10 (35.7)		
TB Symptoms at baseline	**Fever, n (%)**	238 (69.0)	276 (82.9)	71 (88.8)	25 (89.3)	**< 0.001**	**< 0.001**
	Weight loss, n(%)	295 (86.0)	311 (93.4)	74 (92.5)	28 (100)	**0.003**	**0.001**
	Fatigue, n (%)	270 (78.3)	258 (77.5)	75 (93.8)	26 (92.9)	**0.002**	**0.006**
	Night sweat, n (%)	230 (66.7)	242 (72.9)	51 (63.7)	21 (75.0)	0.193	0.439
	Chest pain, n (%)	232 (67.2)	205 (61.7)	49 (61.3)	20 (71.4)	0.363	0.431
	Cough, n (%)	320 (95.2)	298 (96.8)	59 (88.1)	15 (88.2)	**0.015**	0.077

note: Continuous variables are displayed as median and interquartile ranges (IQR) whereas categorical variables are shown as absolute number and frequency (%). Data were compared between the clinical groups using the Kruskal-Wallis (continuous) or the Pearson's chi square (categorical) tests. Mild anemia was defined as Hb value > 10 g/dL and < 13 g/dL for men; and > 10 and < 12 g/dL for women, whereas moderate anemia was defined as Hb > 8 g/dL and < =10 g/dL for both sexes. Severe anemia was defined as Hb < 8 g/dL for both sexes. *Definition of alcohol use:* Past or current any consumption of alcohol. *Definition of tobacco use*: Past or current smoking of tobacco. *Definition of illicit drug use:* Past or current illicit drug use (marijuana, cocaine, heroin or crack). *Definition of non-white:* The following self-reported races: Asian, Black, Pardo and Indigenous. *Definition of type of TB*: Clinical form of TB regarding the disease's location. *Definition of prior-TB:* Previous TB history. **Abbreviations**: TB: tuberculosis, PTB: Pulmonary Tuberculosis, EPTB: Extrapulmonary Tuberculosis, HIV: Human Immunodeficiency Virus, DM: Diabetes Mellitus.

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Table 2

Characteristics of the study participants at baseline according outcome category.

		Favorable (n = 592)	Unfavorable (n = 194)	P value
Anemia severity	**Anemia severity, n (%):**			**< 0.001**
	Non-anemic	285 (48.1)	60 (30.9)	
	Mild	249 (42.1)	84 (43.3)	
	Moderate	43 (7.26)	37 (19.1)	
	Severe	15 (2.53)	13 (6.70)	
Baseline characteristics and consumption habits	**Hemoglobin (g/dL), median (IQR):**	12.3 (11.3–13.5)	11.2 (9.9–12.9)	**< 0.001**
	Sex (male), n (%):	365 (61.7)	130 (67.0)	0.210
	Age, median (IQR):	37.0 (26.0–49.0)	37.0 (26.0–51.0)	0.693
	BMI, median (IQR):	20.6 (18.5–22.9)	20.3 (18.4–22.3)	0.245
	Race (non-white), n(%):	456 (77.0)	157 (81.3)	0.246
	Tobacco use, n (%):	262 (44.3)	103 (53.1)	**0.040**
	Alcohol use, n (%):	468 (79.1)	173 (89.2)	**0.002**
	Illicit drug use, n (%):	137 (23.5)	51 (35.2)	**0.006**
TB presentation and comorbidities	**Prior TB, n (%):**	93 (15.7)	19 (9.79)	0.095
	HIV, n (%):	75 (12.9)	39 (27.1)	**< 0.001**
	Abnormal X-ray, n (%):	572 (97.3)	182 (96.3)	0.665
	Dysglycemia,n(%):			0.279
	Normoglicemia	231 (39.1)	69 (35.6)	
	Prediabetes	234 (39.6)	73 (37.6)	
	Diabetes	126 (21.3)	52 (26.8)	
TB symptoms at baseline	**Fever, n (%):**	453 (76.5)	157 (80.9)	0.238
	Weight loss, n(%):	531 (89.8)	177 (91.7)	0.536
	Fatigue, n (%):	457 (77.2)	172 (88.7)	**0.001**
	Night sweat, n(%):	420 (71.1)	124 (63.9)	0.075
	Chest pain, n (%):	390 (66.0)	116 (59.8)	0.139
	Cough, n (%):	561 (96.2)	131 (90.3)	**0.007**

note: Continuous variables are displayed as median and interquartile ranges (IQR) whereas categorical variables are shown as absolute number and frequency (%). Data were compared between the clinical groups using the Kruskal-Wallis (continuous) or the Pearson's chi square (categorical) tests. Mild anemia was defined as Hb value > 10 g/dL and < 13 g/dL for men; and > 10 and < 12 g/dL for women, whereas moderate anemia was defined as Hb > 8 g/dL and < =10 g/dL for both sexes. Severe anemia was defined as Hb < 8 g/dL for both sexes. *Definition of alcohol use:* Past or current

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