

Can Baseline Complete Blood Count Parameters Predict Incident Anaemia Among Patients with Rifampicin-Resistant Tuberculosis Receiving Linezolid-Based Regimens in Uganda? A Multicenter Retrospective Cohort Study

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Abstract

Background

Anaemia is a frequent complication of linezolid-based treatment for rifampicin-resistant tuberculosis (RR-TB). It remains uncertain whether routinely available baseline complete blood count (CBC) parameters can identify patients at greater risk of developing new anaemia during treatment. This study determined the incidence of anaemia and evaluated associations between baseline CBC parameters and incident anaemia.

Methods

We conducted a secondary analysis of a multicentre retrospective cohort of adults with microbiologically confirmed RR-TB treated with linezolid at four Ugandan hospitals from 2020 to 2024. Participants were eligible if they had normal baseline haemoglobin, a complete baseline CBC, and at least one follow-up haemoglobin measurement. Incident anaemia was defined using sex-specific haemoglobin thresholds. Cox proportional hazards regression was used to estimate adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs).

Results

Among 101 eligible participants, 47 (46.5%) developed incident anaemia during 499 person-months of observation, corresponding to an incidence rate of 9.42 per 100 person-months (95% CI 6.92–12.53). The median time to anaemia was 2 months (IQR 1–3), and 34 of 47 events (72.3%) occurred within the first three months. Severe anaemia (haemoglobin < 8.0 g/dL) occurred in seven participants (6.9%). Higher baseline haemoglobin was independently associated with a lower hazard of incident anaemia (aHR 0.63 per 1 g/dL increase, 95% CI 0.45–0.90; $p = 0.011$). Male sex was also associated with a lower hazard (aHR 0.38, 95% CI 0.19–0.75; $p = 0.006$). Baseline white blood cell count and platelet count were not independently associated with incident anaemia.

Conclusions

Incident anaemia was common among RR-TB patients who began linezolid treatment with normal haemoglobin. Lower baseline haemoglobin and female sex identified patients at greater risk, while most events occurred during the first three months. These findings support closer early haemoglobin monitoring among patients with lower baseline values.

Background

Linezolid is a key component of contemporary all-oral regimens for rifampicin-resistant tuberculosis (RR-TB) and has contributed to improved treatment options for patients with highly drug-resistant disease. (1–3). Important toxicities, including peripheral and optic neuropathy, lactic acidosis, and bone marrow suppression, nevertheless limit its prolonged use. Anaemia is clinically important because it may cause fatigue, impair functional status, necessitate transfusion, and lead to dose reduction, treatment interruption, or discontinuation.(4–6).

Previous studies have identified treatment duration, renal or hepatic dysfunction, and increased linezolid exposure as factors associated with haematological toxicity (4, 7–9). Furthermore, safety reviews and programmatic evaluations have underscored the need for careful monitoring and risk stratification when deploying linezolid in diverse clinical settings (10, 11). However, relatively few studies have examined whether baseline CBC parameters can identify RR-TB patients who begin treatment without anaemia but later develop it. This question is particularly relevant in resource-limited settings, where laboratory monitoring may be constrained and simple baseline markers could help prioritise patients for closer follow-up.

Our earlier Ugandan multicentre study described the prevalence and factors associated with haematological adverse events among RR-TB patients receiving linezolid-based regimens (12). That analysis described the overall burden of anaemia, leukopenia, and thrombocytopenia, including abnormalities present at baseline. The present secondary analysis restricted the cohort to participants with normal baseline haemoglobin and aimed to determine the incidence and timing of new anaemia and to evaluate whether baseline haemoglobin, white blood cell count, and platelet count were independently associated with incident anaemia.

Methods

Study design and setting

This was a secondary analysis of a multicentre retrospective cohort study conducted using medical records from January 2020 to December 2024 at four RR-TB treatment centres in Uganda: Mbale Regional Referral Hospital, Iganga General Hospital, Moroto Regional Referral Hospital, and St. Kizito Matany Hospital. These facilities provide diagnosis, treatment, and routine clinical and laboratory monitoring for patients with drug-resistant tuberculosis under the Uganda National Tuberculosis and Leprosy Programme.

Study population and eligibility

The source cohort comprised adults aged 18 years or older with microbiologically confirmed RR-TB who received a linezolid-containing regimen for at least one week. RR-TB was confirmed by Xpert MTB/RIF, line probe assay, or culture-based testing. For the present analysis, participants were eligible if they had a complete baseline CBC, normal baseline haemoglobin, and at least one haemoglobin measurement

after linezolid initiation. Normal baseline haemoglobin was defined as at least 13.0 g/dL in males and at least 12.0 g/dL in females (13). Participants were excluded if baseline haemoglobin was missing, anaemia was present at baseline, the baseline CBC was incomplete, or no follow-up haemoglobin measurement was recorded.

Data sources and variables

Data were abstracted from patient medical records and RR-TB treatment registers using a standardised electronic data collection form. Extracted information included age, sex, residence, HIV status, treatment site, baseline haemoglobin, baseline white blood cell count, baseline platelet count, serial haemoglobin measurements, and duration of observation. Data quality procedures included completeness checks, internal consistency checks, and verification against source records.

The primary outcome was incident anaemia, defined as the first follow-up haemoglobin value below 13.0 g/dL in males or below 12.0 g/dL in females. Time to event was measured in months from linezolid initiation to the first documented anaemia episode. Participants who did not develop anaemia were censored at their final recorded month of observation. Severe anaemia was defined as haemoglobin below 8.0 g/dL (13). The primary predictors were baseline haemoglobin (g/dL), white blood cell count ($\times 10^9/L$), and platelet count ($\times 10^9/L$). Age and sex were included as potential confounders.

Statistical analysis

Data were analysed using Stata version 18.0 (StataCorp LLC, College Station, Texas, USA). Continuous variables were summarised using medians and interquartile ranges (IQRs), and categorical variables were summarised using frequencies and percentages. Baseline characteristics were presented according to incident anaemia status. Because the primary inferential analysis was time-to-event modelling, Table 1 was treated as descriptive and no separate hypothesis-test p-values were reported.

The cumulative proportion of participants who developed anaemia was calculated as the number of incident events divided by the number of eligible participants. The incidence rate was calculated as the number of incident events divided by total person-time at risk and expressed per 100 person-months; its 95% CI was calculated using an exact Poisson method. Cox proportional hazards regression was used to estimate hazard ratios and 95% CIs. The multivariable model included baseline haemoglobin, baseline white blood cell count, baseline platelet count, age, and sex. The CBC parameters were included as the primary variables of interest, while age and sex were included a priori based on clinical relevance. Statistical significance was defined as a two-sided p value below 0.05.

Ethical considerations

The Mbale Regional Referral Hospital Research and Ethics Committee approved the parent study (reference MRRH-2024-497) and granted a waiver of individual informed consent for use of routinely

collected data. The study was conducted in accordance with the ethical standards of the institutional research committee and the 2013 revision of the Declaration of Helsinki. Data used for this analysis were de-identified and accessed only by authorised study personnel.

Results

Participant selection and baseline characteristics

Of the 412 patients in the parent cohort, 243 had a documented baseline haemoglobin measurement and were assessed for eligibility. Patients were subsequently excluded because of baseline anaemia (n = 92), incomplete baseline complete blood count results (n = 19), or the absence of at least one follow-up haemoglobin measurement (n = 31), leaving 101 participants for the incident anaemia analysis (Fig. 1).

The median age of the 101 participants was 42 years (IQR 29–54), 61 (60.4%) were male, 80 (79.2%) lived in rural areas, and 17 (16.8%) were living with HIV. The median baseline haemoglobin concentration was 13.7 g/dL (IQR 12.9–14.5). Baseline characteristics according to incident anaemia status are shown in Table 1. Smoking and alcohol use were omitted because 37 participants had missing information for these variables.

Table 1
Baseline characteristics according to incident anaemia status (n = 101)

Characteristic	No incident anaemia (n = 54)	Incident anaemia (n = 47)
Age, median (IQR), years	44 (31–54)	46 (28–55)
Male sex, n (%)	43 (79.6)	18 (38.3)
Rural residence, n (%)	43 (79.6)	37 (78.7)
HIV positive, n (%)	8 (14.8)	9 (19.1)
Baseline haemoglobin, median (IQR), g/dL	14.3 (13.1–14.8)	13.1 (12.9–14.0)
Baseline white blood cell count, median (IQR), x 10 ⁹ /L	5.1 (4.1–6.4)	4.9 (4.0–6.2)
Baseline platelet count, median (IQR), x 10 ⁹ /L	203 (153–258)	237 (158–333)
<i>Note. Values are median (IQR) or n (%). Percentages are calculated within outcome groups. Smoking and alcohol use were omitted because 37 participants had missing data.</i>		

Occurrence and timing of incident anaemia

During 499 person-months of observation, 47 participants developed incident anaemia. This corresponded to a cumulative incidence of 46.5% and an incidence rate of 9.42 per 100 person-months

(95% CI 6.92–12.53). The median time to the first anaemia episode was 2 months (IQR 1–3). Thirty-four of the 47 events (72.3%) occurred within the first three months: 19 in month 1, six in month 2, and nine in month 3. The remaining events occurred in month 4 (n = 2), month 5 (n = 2), month 6 (n = 5), month 7 (n = 1), month 8 (n = 1), and month 9 (n = 2) (Fig. 2). Severe anaemia occurred in seven participants, representing 6.9% of the cohort and 14.9% of incident events.

Thirty-four events (72.3%) were first documented during months 1–3.

Baseline CBC parameters and incident anaemia

Participants who developed incident anaemia had a lower median baseline haemoglobin than those who remained free of anaemia (13.1 versus 14.3 g/dL). Among participants who developed anaemia, 18 of 47 (38.3%) were male, compared with 43 of 54 (79.6%) among those who did not develop anaemia. Baseline white blood cell counts were similar between the two groups, while the median platelet count was higher among participants who developed anaemia (Table 1).

In the multivariable Cox model, each 1 g/dL increase in baseline haemoglobin was associated with a 37% lower hazard of incident anaemia (aHR 0.63, 95% CI 0.45–0.90; p = 0.011). Male sex was also independently associated with a lower hazard of anaemia (aHR 0.38, 95% CI 0.19–0.75; p = 0.006). Baseline white blood cell count (aHR 0.88, 95% CI 0.76–1.03; p = 0.103), platelet count (aHR 1.003 per 1 x 10⁹/L, 95% CI 0.9996–1.006; p = 0.092), and age (aHR 1.00, 95% CI 0.99–1.02; p = 0.687) were not independently associated with incident anaemia. The overall model was statistically significant (likelihood-ratio chi-square = 34.62; p < 0.001) (Table 2).

Table 2
Multivariable Cox regression model for incident anaemia (n = 101; 47 events)

Predictor	Adjusted HR	95% CI	p value
Baseline haemoglobin (per 1 g/dL increase)	0.63	0.45–0.90	0.011
Baseline white blood cell count (per 1 x 10 ⁹ /L)	0.88	0.76–1.03	0.103
Baseline platelet count (per 1 x 10 ⁹ /L)	1.003	0.9996–1.006	0.092
Age (per year)	1.00	0.99–1.02	0.687
Male sex (vs female)	0.38	0.19–0.75	0.006
<i>Note. Likelihood-ratio chi-square (5) = 34.62, p < 0.001. HR = hazard ratio; CI = confidence interval.</i>			

Discussion

In this multicentre cohort of RR-TB patients who started linezolid treatment with normal haemoglobin, almost one-half developed incident anaemia. Higher baseline haemoglobin was independently associated with a lower hazard of anaemia, and male sex was also associated with a lower hazard.

Baseline white blood cell and platelet counts were not independently associated with the outcome. Importantly, nearly three-quarters of anaemia events were first documented within the initial three months of observation.

The 46.5% cumulative incidence observed in this study confirms that a normal haemoglobin value at treatment initiation does not eliminate the risk of subsequent anaemia. In the Nix-TB trial, anaemia was reported in 37% of participants receiving a bedaquiline-pretomanid-linezolid regimen, including some episodes with haemoglobin below 8.0 g/dL ((1, 3). Direct comparison is limited by differences in patient populations, linezolid dose, outcome definitions, and follow-up. A prospective South African cohort similarly found that linezolid toxicity was common in programmatic RR-TB care and demonstrated an exposure-toxicity relationship (14, 15). Broad clinical reviews and safety evaluations have further emphasized that linezolid tolerability requires vigilant oversight in routine clinical practice ((9, 15). Together, these studies indicate that clinically important haematological adverse events remain a major challenge even as linezolid-containing regimens improve treatment options for drug-resistant TB.

The present analysis complements our earlier Ugandan multicentre study, which described the overall prevalence and determinants of haematological adverse events in the full source cohort ((12). By excluding participants with anaemia at baseline and focusing on time to first new anaemia episode, this analysis addresses a different clinical question: whether information available before treatment can identify patients who remain vulnerable despite initially normal haemoglobin.

Baseline haemoglobin was the CBC parameter most clearly associated with incident anaemia. Each 1 g/dL increase was associated with a 37% reduction in hazard. Patients whose haemoglobin is nearer the lower limit of the normal range have less reserve before crossing the diagnostic threshold for anaemia and may also be more vulnerable to treatment-related suppression of erythropoiesis. Linezolid can impair mammalian mitochondrial protein synthesis, reduce mitochondrial respiratory-chain activity, and damage mitochondrial ultrastructure, thereby suppressing rapidly dividing haematopoietic precursors (16, 17). These mechanisms provide biological support for progressive haemoglobin decline during prolonged exposure.

Recent studies have emphasised prolonged treatment, renal or hepatic dysfunction, and elevated linezolid exposure as determinants of haematological adverse events (4, 7, 18). Specifically, Zhang and colleagues identified cumulative duration and impaired clearance pathways as significant risk factors for linezolid-induced myelosuppression. Dai and colleagues reported associations between anaemia and renal or hepatic dysfunction. They identified high trough concentrations as a marker of toxicity, while Wasserman and colleagues demonstrated an exposure-toxicity relationship in patients treated for drug-resistant tuberculosis. Our findings add that, among RR-TB patients with initially normal haemoglobin, the baseline haemoglobin value itself carries useful prognostic information.

Male sex was independently associated with a lower hazard of incident anaemia. Men usually have higher physiological haemoglobin concentrations than women, and this difference may provide greater reserve during treatment. However, sex may also represent unmeasured differences in iron stores,

nutritional status, body size, menstruation, pregnancy history, or other biological and social factors. The association should therefore be interpreted as a risk marker rather than evidence of a direct protective mechanism. In addition, the sex association should be interpreted cautiously because incident anaemia was defined using sex-specific haemoglobin thresholds, and baseline haemoglobin distributions also differ by sex; these features may contribute to the observed association.

Baseline white blood cell count and platelet count were not independently associated with incident anaemia. Although linezolid can suppress multiple cell lines, the absence of significant associations suggests that these baseline measurements may not identify patients who will later develop isolated anaemia. The platelet estimate was close to the conventional significance threshold, but the effect per unit was small and the confidence interval included the null. This finding should not be interpreted as evidence that higher platelet counts cause anaemia; it may reflect chance, residual confounding, or limited precision.

The concentration of events in the first three months has practical implications. Patients with lower baseline haemoglobin values may benefit from closer haemoglobin monitoring during this early period, when a substantial proportion of events emerged. The results do not establish a new treatment threshold or monitoring schedule, and they should not be used to withhold linezolid. Rather, baseline haemoglobin can be incorporated into clinical judgement alongside symptoms, serial CBC results, renal and hepatic function, nutritional assessment, and the overall benefit-risk balance of the RR-TB regimen.

This study has several strengths. It used data from four treatment centres, restricted the analysis to participants without baseline anaemia, and applied time-to-event methods that accounted for differing observation times. It also evaluated inexpensive and routinely available CBC parameters that could be applied in resource-limited settings. Limitations include the retrospective design, modest sample size, and missing information on smoking and alcohol use. Only 101 of the 412 participants in the source cohort met the eligibility criteria for this analysis, which may introduce selection bias and limit generalisability if included participants differed systematically from those excluded. Nutritional status, iron indices, vitamin B12 and folate levels, inflammatory markers, menstrual and pregnancy-related factors, and linezolid plasma concentrations were unavailable. The analysis also did not quantify cumulative linezolid exposure or time-varying dose modifications. Residual confounding and outcome misclassification due to irregular laboratory monitoring are therefore possible. Finally, the findings were derived from specialised Ugandan RR-TB centres and require validation in other populations.

Conclusion

Incident anaemia was common among RR-TB patients receiving linezolid despite normal haemoglobin at baseline. Higher baseline haemoglobin and male sex were associated with lower hazards of anaemia, whereas baseline white blood cell and platelet counts were not independently associated. The early concentration of events supports careful haemoglobin monitoring during the first three months, particularly among patients whose baseline values are closer to the lower limit of normal.

Declarations

Ethics approval and consent to participate

The Mbale Regional Referral Hospital Research and Ethics Committee approved the parent study (MRRH-2024-497) and granted a waiver of individual informed consent for use of routinely collected data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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No funding was received for this study.

Author Contribution

EA: Conceptualisation, Methodology, Data Curation, Formal Analysis, Writing Original Draft Preparation, and Project Administration. JBB and RK: Writing – Review & Editing, Validation, Supervision, contributed to the design and ensured adherence to the research protocols during implementation. EK contributed to the conceptualization of the study and data collection

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Data Availability

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

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Figures

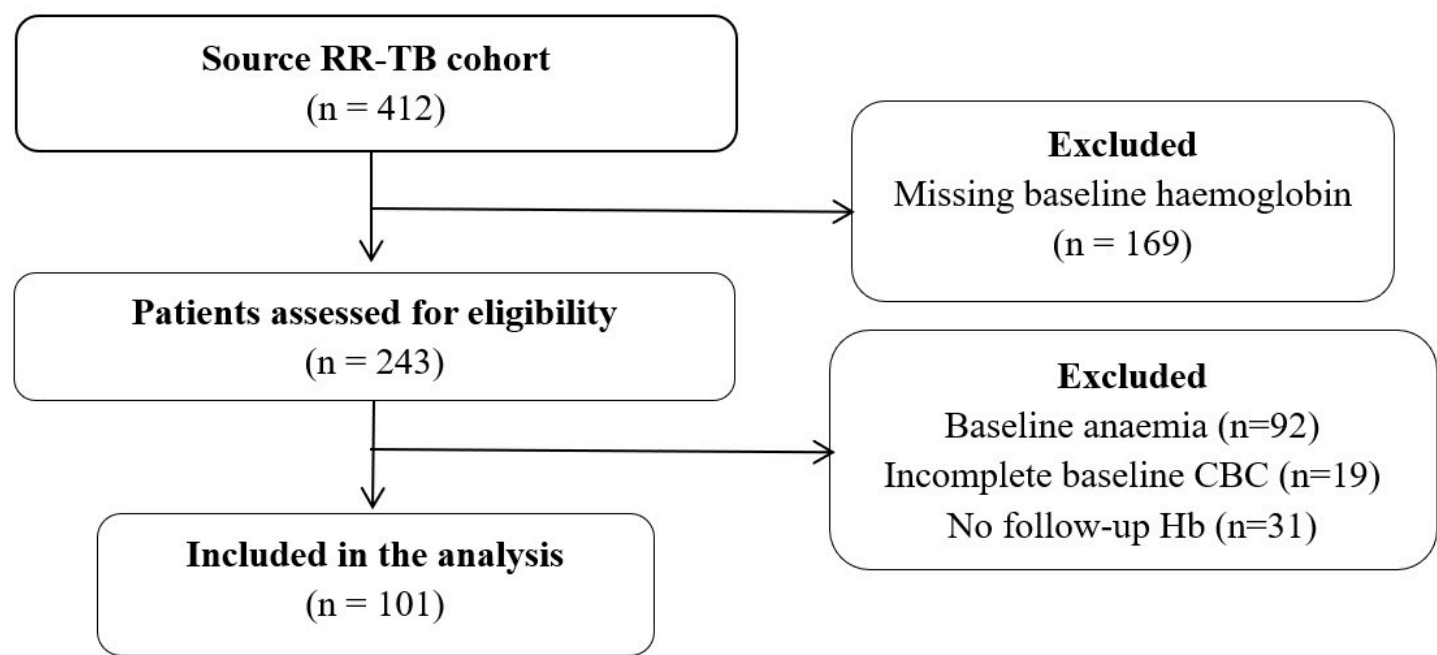


Figure 1

Participant flow diagram

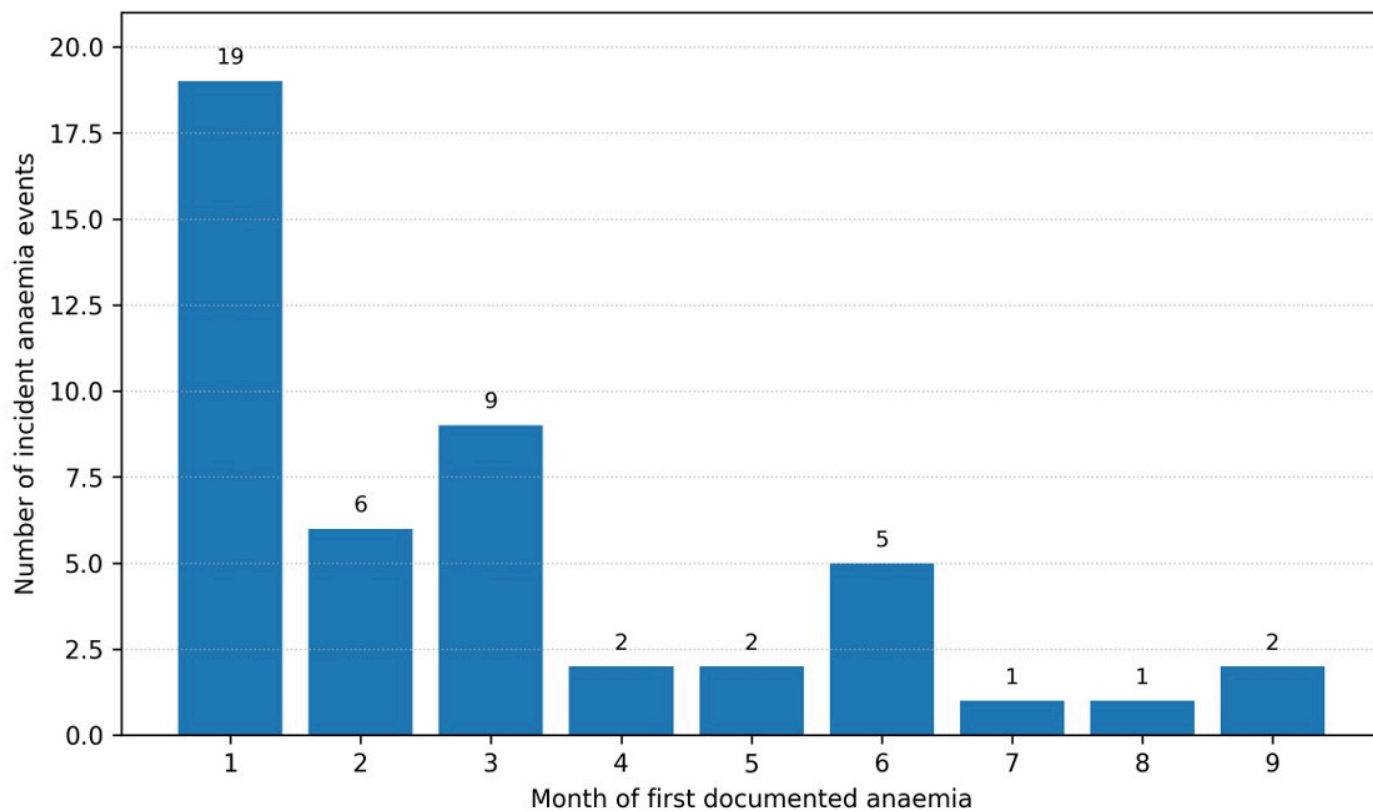


Figure 2

Monthly distribution of incident anaemia events (n = 47)