ORIGINAL ARTICLE

Effect of age, gender, and linezolid use on MDR-TB Patient survival rate with short-course treatment in Central Java, Indonesia: survival analysis and cox regression

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ABSTRACT

Treatment regimens for MDR-TB lasting 9 to 12 months offer effective therapy with a reduced duration. However, data from Central Java, Indonesia, indicate that 9.22% of patients undergoing short-term MDR-TB treatment between 2021 and 2023 died during the course of treatment. This study seeks to examine the survival probability and identify risk factors associated with mortality among patients receiving short-term treatment for MDR-TB. A retrospective cohort design was employed, including 236 MDR-TB patients treated with a short-term regimen (STR) between 2022 and 2023, whose outcomes were either cure or death. STR is a 9-month all-oral short regimen consisting of: 6 *Bedaquiline (Bdq)* with 4-6 *Levofloxacin (Lfx)/Moxifloxacin (Mfx)-Clofazimin (Cfz)-Pyrazinamide (Z)-Etambutol (E)-Isoniazid (H) high dose-Etionamide (Eto)*/5 *Levofloxacin/Moxifloxacin-Clofazimin-Pyrazinamide-Etambutol.* The Kaplan-Meier method was applied to estimate incidence rates and median survival time until death. To identify predictors including age group, gender, employment status, treatment history, diabetes status, HIV infection, use of Linezolid, and timing of treatment initiation, the Cox Proportional Hazards model was employed. All statistical analyses were conducted using RStudio, with a significance threshold set at $p < 0.005$. The Kaplan-Meier analysis revealed a significant difference in survival probabilities among the three age groups. Patients aged 19 to 35 years demonstrated a higher likelihood of survival compared to those in the middle-aged group (36-55 years) and the older group ($\geq$56 years) (Chi-Square = 17, $p < 0.001$). Additionally, Cox regression analysis indicated that individuals aged 56 and above faced a 3.7-fold increased risk of death compared to younger patients (95% CI: 1.49–3.65; HR = 3.705, $p = 0.001$). This study emphasizes the importance of implementing age-specific interventions for MDR-TB patients aged 56 and older, with particular attention to managing comorbidities such as diabetes and HIV. The results underscore the necessity of tailoring treatment protocols for older adults in clinical settings to enhance survival outcomes, given their increased vulnerability linked to immunosenescence and the burden of multiple health conditions.

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INTRODUCTION

The MDR/RR-TB Tracking Report 2024 generated by WHO states that by the year 2023, there have been approximately 400,000 new cases of MDR/RR-TB worldwide. These cases constitute 3.2 percent of all new TB diagnoses and 16 percent of previously treated TB cases with approximately 150,000 deaths associated to the disease. Indonesia contributes to approximately 7.4 percent of the global burden of MDR/RR-TB cases.[1,2] Even after adopting treatment methods such as short-term regimens (STRs), the number of patients receiving drug-resistant TB (TBRO) treatment remained at 58% as of March 2025. That figure is far below the WHO benchmark of 90%.[3] Furthermore, an analysis of 3,100 TBRO patients demonstrated a declining trend in the success rates of short-term treatment, which fell from 53.28% in 2017 to 47.85% in 2018, and then dropped further to 36.98% in 2019. Central Java Province holds the second highest position in Indonesia for reported TB cases, with 985 individuals diagnosed with and actively undergoing treatment for MDR-TB.[4,5]

Patients with multidrug-resistant TB (MDR-TB) poses immense concern for global TB control due to isoniazid and rifampicin, the primary drugs used in treatment, not being effective. The mortality rate in MDR-TB patients is alarmingly high within the small population that is diagnosed and treated. The risk of dying and of spreading the disease to the community increases greatly due to lack of treatment in these patients, which creates a public health nightmare for controlling TB.[6–8]
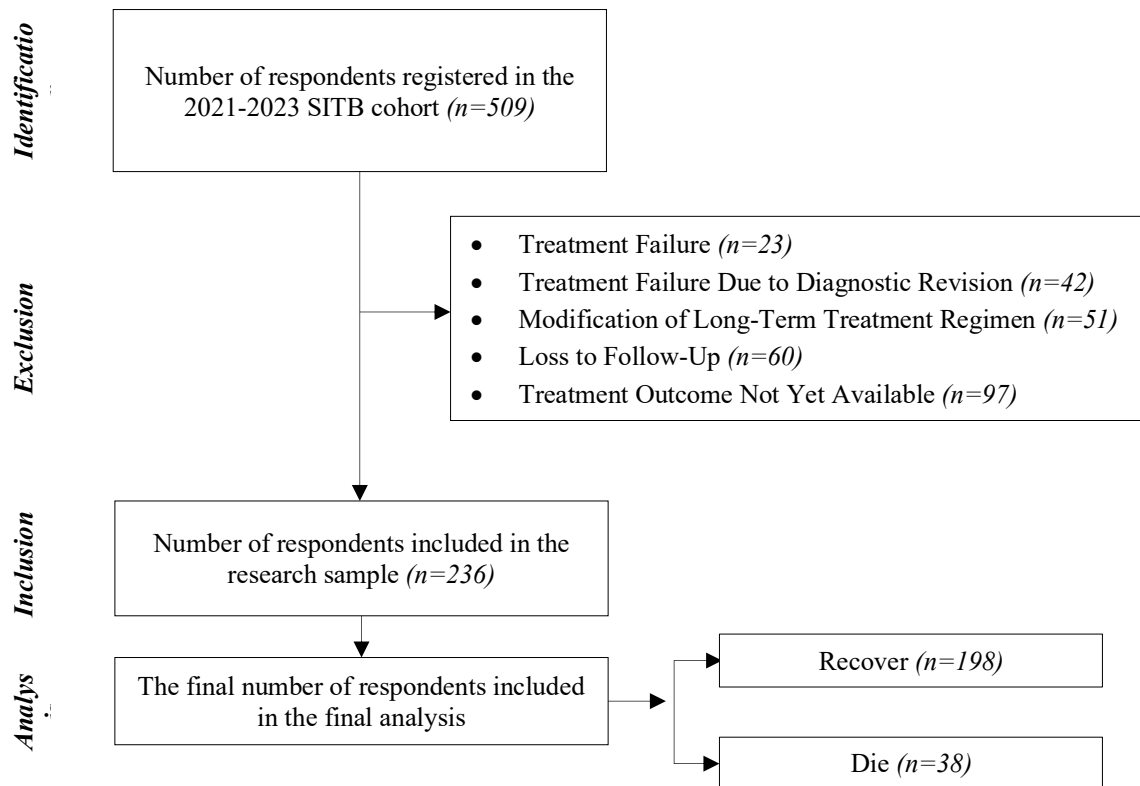
Research in Cambodia shows that pulmonary TB morbidity has a significant impact on household production and economy, various efforts are made to reduce TB morbidity,[9] in Indonesia there is a study related to clinical flow which states that there is no significant difference in length of stay, mortality, or cost efficiency before and after the implementation of clinical flow,[10] Age is a challenge in treating TB. A study conducted in Myanmar identified that being 35 years or older and having limited knowledge were key factors contributing to delays in treatment. Additionally, lower medical and transportation expenses, along with the absence of symptoms, were associated with increased delays, which may result in worsened patient conditions and higher mortality.[11]

The short-term regimen (STR) is a nine-month oral treatment that has demonstrated effectiveness in multiple international studies, with the advantage of causing fewer side effects. Research from various countries has reported treatment success rates with STR ranging from 44.3% to 83.7%, which are generally higher compared to those observed with longer-term treatments.[5,12] Recent research has indicated that older age, low educational attainment, and the presence of diabetes are significant factors contributing to lower treatment success and higher mortality rates among MDR-TB cases.[13]

A retrospective study was conducted to evaluate data of multidrug-resistant tuberculosis (MDR-TB) patients under the age of 40 in Central Java Province, covering the period from 2021 to 2023. The study took place during 2021 through a series of meetings, with a primary focus on post-treatment care for MDR-TB patients. The research, titled "Risk Factors and Treatment Outcomes in MDR-TB Patients in Central Java", aimed to identify key determinants influencing treatment outcomes. Interestingly, several risk factors associated with poor survival among patients undergoing short-course MDR-TB treatment appeared to be paradoxical. The ultimate goal of the study was to contribute to a better understanding of these factors and to provide evidence to support improvements in the currently limited care pathways available for MDR-TB patients in the Central Java region.

METHOD

Identificatio

Number of respondents registered in the
2021-2023 SITB cohort *(n=509)*

Exclusion

- Treatment Failure *(n=23)*
- Treatment Failure Due to Diagnostic Revision *(n=42)*
- Modification of Long-Term Treatment Regimen *(n=51)*
- Loss to Follow-Up *(n=60)*
- Treatment Outcome Not Yet Available *(n=97)*

Inclusion

Number of respondents included in the
research sample *(n=236)*

Analys

The final number of respondents included
in the final analysis

Recover *(n=198)*

Die *(n=38)*

Figure 1. Sample Selection Chart

This study used data integrated into the Tuberculosis Information System (SITB-*Sistem Informasi Tuberkulosis*) through the TB-03 form at the provincial level of Central Java. The data were sourced from 42 Health Care Facilities participating in the Integrated Management of Drug-Resistant TB (MTPTRO-*Manajemen Terpadu Pengendalian TB Resistan Obat*), consisting of 3 primary health centers (*Puskesmas*) and 39 hospitals. Based on ownership, these facilities include: 6 operated by the Ministry of Health, 4 by non-profit organizations, 27 by district/municipal governments, 2 by the provincial government, 1 by a private company, and 2 by the military (TNI-*Tentara Nasional Indonesia*). The SITB system collects data on TB patients and tracks their treatment progress as reported by DR-TB officers at each health facility. For this study, data were extracted from TB patient registers covering the years 2021 to 2023. Among 509 MDR-TB patients registered in the SITB cohort during this period, only 236 had definitive treatment outcomes classified as either recovery (cured or treatment completed) or death. Patients who experienced treatment failure, were re-diagnosed and switched to a long-term regimen, or who were lost to follow-up were excluded from the analysis. [14,15] This research represents a secondary analysis of data collected from the same group of respondents in a prior study.[16]

This study utilizes a dataset containing a range of demographic and medical variables to examine survival time and event outcomes. The primary outcome measured is death status, classified as either recovered or deceased. Key independent variables include age group (young: 19–35 years, middle-aged: 36–55 years, and elderly: 56 years and above), gender (male

and female), and the use of linezolid (yes or no). Variables including employment status (employed or unemployed), treatment history (new case or resumed treatment after interruption), diabetes status (diabetic or non-diabetic), HIV status (positive, negative, or unknown), and timing of treatment initiation (within 10 days or after 10 days of diagnosis) were considered potential confounders. To account for their possible impact on the outcomes, these variables were included simultaneously in a multivariate analysis.

The data were analyzed using R Studio, with survival analysis conducted to determine the median time to treatment outcomes (cure and death). Kaplan-Meier analysis was employed to illustrate survival over time by month. To assess the impact of independent variables on treatment outcomes, the Cox proportional hazards model was applied. The stepwise Cox regression model was developed based on bivariate analysis, selecting variables with a p-value less than 0.10. While the conventional threshold for including variables in multivariate analysis is $p < 0.25$ (source), this study used a stricter cutoff to reduce bias and minimize the risk of overfitting. All data utilized had been previously collected, securely anonymized, and stored following institutional data protection guidelines to maintain patient confidentiality and ensure the integrity of the research.

RESULT
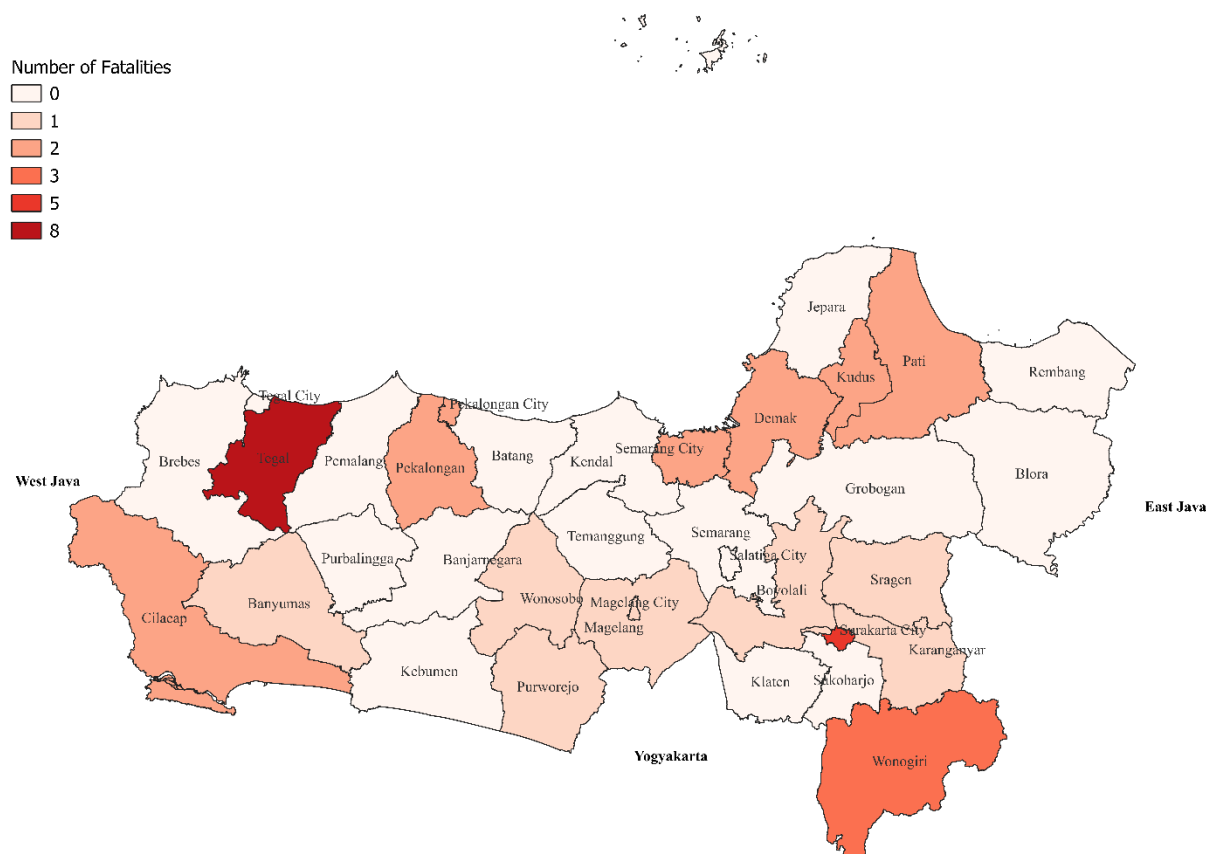
Figure 2. Distribution of MDR-TB Short Regimen Fatalities by District/City in Central Java

There were 52 cases of MDR TB deaths on short-term treatment in Central Java. The highest number of cases occurred in Tegal District (8 cases), followed by Wonogiri (5 cases). In Central Java Province, the success rate for treating Drug-

Resistant TB patients using the Short-Term Regimen was 48.96%, with 192 patients recovering (46.60%) and 6 patients completing treatment (1.46%). This success rate is slightly higher than that reported in a study from India, which found a 48% success rate. On the other hand, 51.94% of patients experienced unsuccessful outcomes. Among these, 26 patients (12.15%) experienced treatment failure, 91 patients (42.52%) had a change in diagnosis, 38 patients (17.76%) died, and 150 patients (27.57%) were lost to follow-up.[17]

Table 1. Characteristics of Study Respondents (n: 1893)

Characteristic	Status			
	Recover		Die	
	n	%	n	%
Age Category				
Young Age (19-35 years)	97	92.4	8	7.6
Middle Age (36-55 years)	73	83.0	15	17.0
Old Age (56 years and above)	28	65.1	15	34.9
Gender				
Man	102	79.7	26	20.3
Woman	96	88.9	12	11.1
Employment Status				
Work	73	84.9	13	15.1
Not Working	125	83.3	25	16.7
Treatment History				
Treated after discontinuation of treatment	90	83.3	18	16.7
New	108	84.4	20	15.6
Diabetes Status				
DM	27	81.8	6	18.2
No DM	171	84.2	32	15.8
HIV Status				
Positive	3	75.0	1	25.0
Negative	135	87.1	20	12.9
Unknown	60	77.9	17	22.1
Linezolid **(Lzd) Usage**				
Using *Linezolid* (Lzd)	179	84.8	32	15.2
Not using *Linezolid* (Lzd)	19	76.0	6	24.0
Traeatment Initiation				
> 10 days	139	85.3	24	14.7
≤ 10 days	59	80.8	14	19.2

source: author, 2024

Table 1 outlines the characteristics of the respondents and the status of patients with Multi-Drug Resistant (MDR) Tuberculosis undergoing short-term treatment across various factors. The highest cure rate was observed among younger patients aged 19 to 35 years (92.4%), whereas the oldest group (56 years

and above) experienced the highest mortality rate (34.9%). Females demonstrated a higher cure rate (88.9%) compared to males (79.7%). Cure rates were similar between working and non-working patients. Patients treated with Linezolid showed a higher mortality rate (24.0%) than those who did not receive the drug (15.2%). Additionally, patients who began treatment after a delay of more than 10 days had a higher cure rate (85.3%) compared to those who initiated treatment within 10 days (80.8%).

Table 2. Analisis Kaplan-Meier

Variable	Chi-Square	df	Sig.
Age Category	17	2	0.000
Gender	3.6	1	0.059
Linezolid Usage	1.5	1	0.220

source: author, 2024

Table 2 presents the results of the Kaplan-Meier analysis for age category, gender, and linezolid use. For the age category variable, the Log-Rank test yielded a Chi-square value of 17 with 2 degrees of freedom and a p-value below 0.001, demonstrating a significant difference in survival among the different age groups receiving short-term MDR-TB treatment. In contrast, neither gender nor linezolid use demonstrated a significant difference in survival among patients undergoing short-term MDR-TB treatment. The Chi-square values were 3.6 and 1.5, with corresponding p-values of 0.059 and 0.220, respectively. Therefore, based on the Kaplan-Meier analysis, only the age category exhibited a significant difference in survival outcomes.

Table 3. Analisis Cox Proportional Hazards Model

| term	estimate	std.error	statistic	p.value	conf.low	conf.high
Age Category	0.8461	0.2283	3.705	0.000211	1.4896	3.646
Gender	-0.5414	0.3809	-1.421	0.155181	0.2759	1.228
Employment Status	0.1654	0.3685	0.449	0.653592	0.5730	2.429
Treatment History	0.198	0.3435	0.576	0.564300	0.6218	2.39
Diabetes	0.3714	0.4737	0.784	0.433000	0.5729	3.669
HIV Status	0.7143	0.3352	2.131	0.033060	1.0591	3.94
Linezolid Usage	0.8481	0.466	1.82	0.068786	0.9368	5.822
Treatment Initiation	0.4497	0.3487	1.29	0.197199	0.7915	3.106

source: author, 2024

Table 3 presents the findings from the Cox Proportional Hazards Model analyzing factors influencing the risk of events (death or recovery). The age category variable showed a positive coefficient of 0.8461 with a p-value below 0.001, indicating that older age groups faced a significantly higher risk of death compared to younger groups. In contrast, gender, employment status, medication history, and diabetes did not reach statistical significance, each having p-values greater than 0.05, suggesting these factors did not have a meaningful impact on the risk of events. HIV status demonstrated a significant association with mortality, evidenced by a p-value below 0.005, indicating that patients who were HIV-

positive faced a higher risk of death. The use of linezolid had a positive coefficient of 0.8481 and a p-value of 0.068, approaching but not reaching statistical significance, suggesting a potential link between linezolid use and increased mortality risk. In contrast, the timing of treatment initiation showed no significant effect on survival, with a p-value of 0.197.
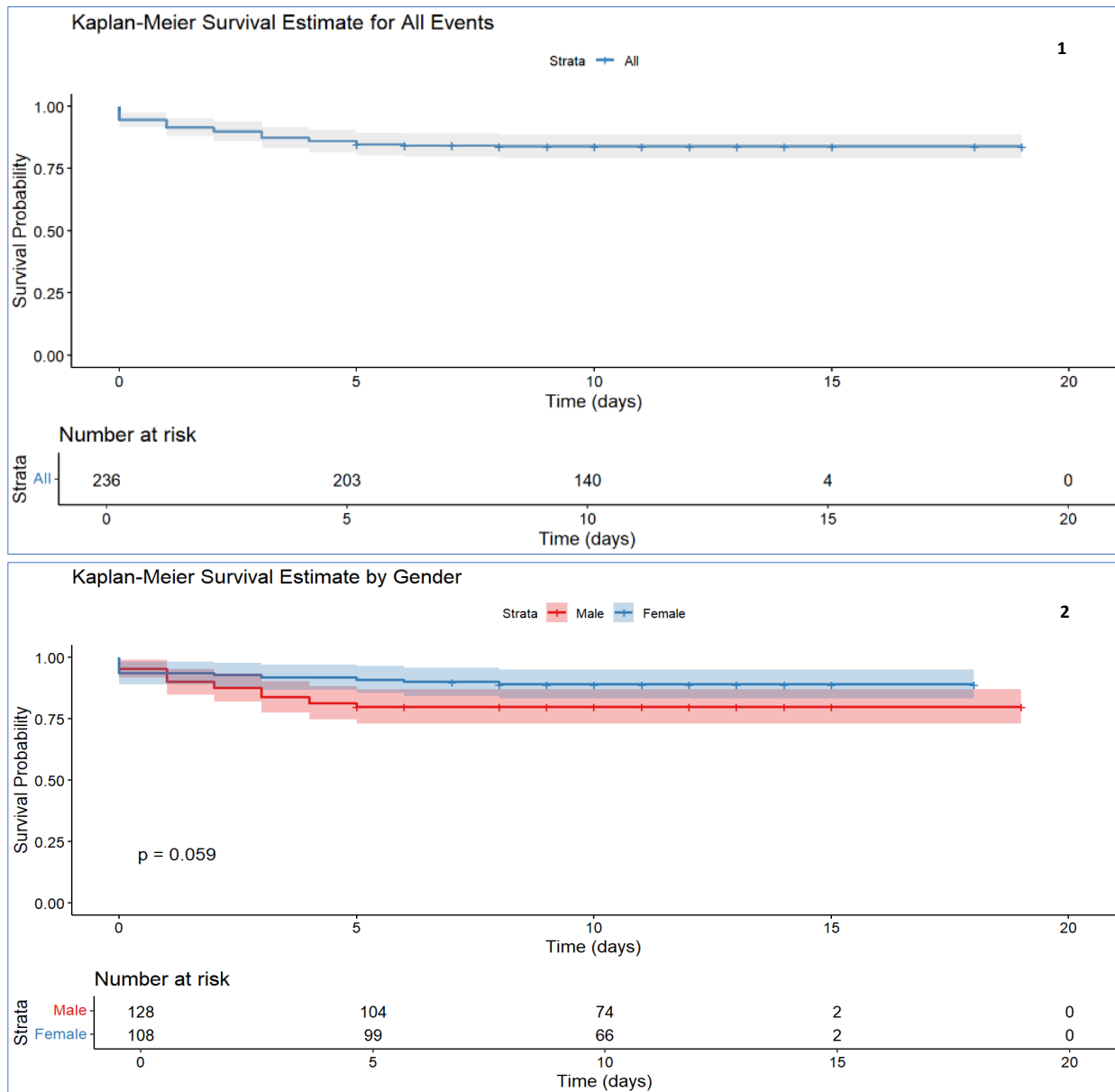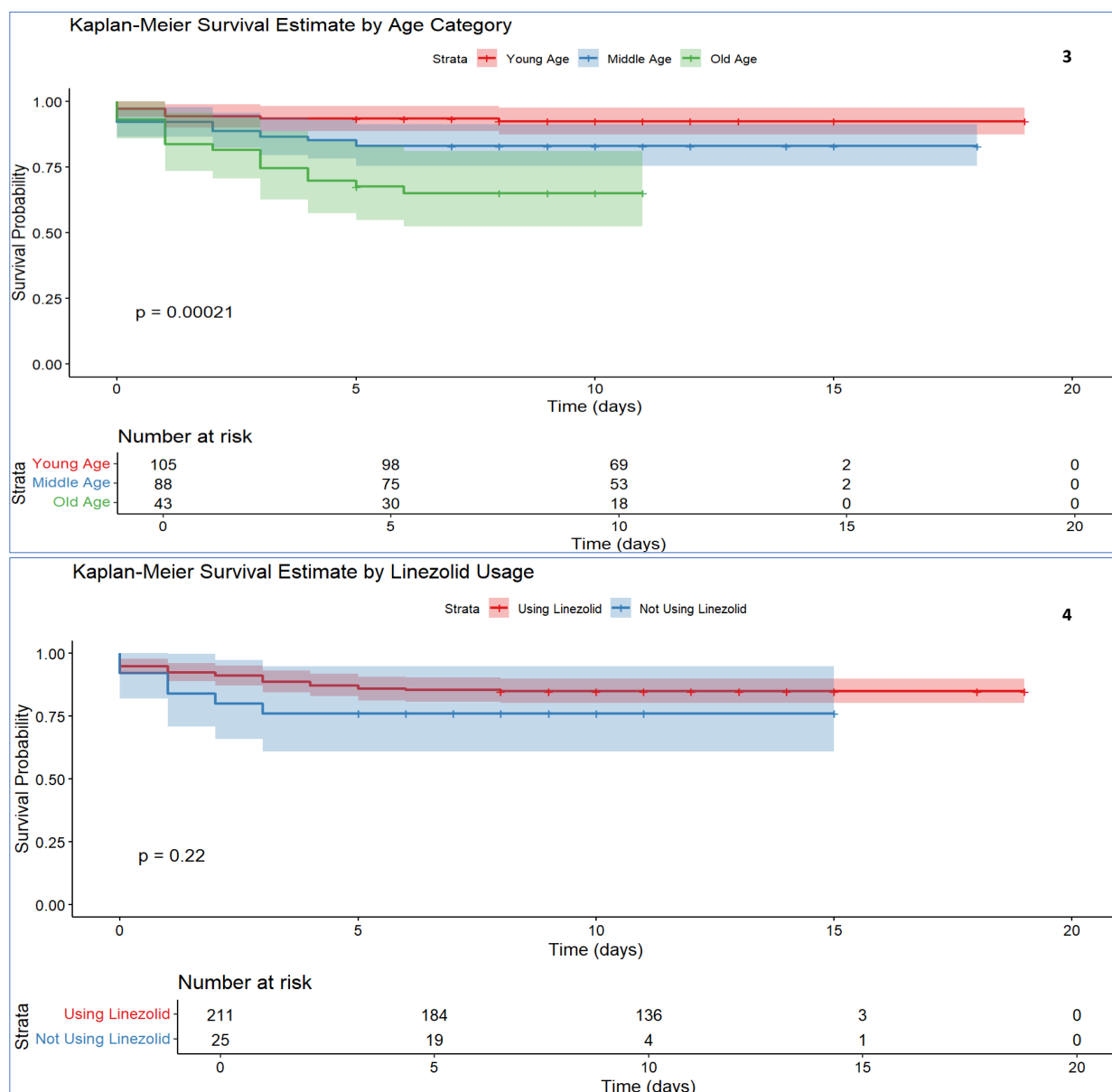
Figure 3. Kaplan-Meier Survival Estimate overall (1), age category (2), gender (3), linezolid usage (4).

DISCUSSION

Earlier research investigating the impact of demographic factors on the survival of MDR-TB patients identified a weak negative correlation between age and survival outcomes. While older age was linked to lower survival rates, this relationship did not reach statistical significance (p = 0.052).[16] While this value approaches the threshold for statistical significance, it cannot yet be regarded as statistically significant. The findings from this study, which demonstrate that age has a significant impact on survival among patients receiving short-term MDR-TB treatment, align with earlier research that identified older age as a factor linked to poorer prognosis—likely due to immunosenescence and the resulting decline in immune function associated with aging.[18] MDR-TB contributes to the acceleration of age-related physiological decline, resulting in reduced drug

absorption and metabolism alongside weakened immune function. This combination worsens disease progression by hastening immunosenescence, increasing the likelihood of drug toxicity, and diminishing the overall effectiveness of treatment. [19–22]

Studies examining short-term treatment outcomes in MDR-TB patients indicate that these regimens generally achieve success rates above 50%, with several reports noting rates exceeding 80% among younger patients.[23] The most successful treatment regimens involve combinations of multiple drugs and tend to yield higher success rates among younger patients. A prospective cohort study found that younger individuals (average age 34.16 years) undergoing short-term treatment achieved a success rate of 86.31%, while older patients (average age 41.71 years) receiving long-term treatment had a lower success rate of 79.51%. Additionally, the mortality rate was notably lower in the short-term treatment group (4.21%) compared to the long-term treatment group (9.63%).[24]

A comparable study examining the link between demographic and clinical factors and survival in MDR-TB patients undergoing short-term treatment found that both employment status and age were significantly associated with survival outcomes, whereas gender did not emerge as a significant predictor.[16] The absence of a significant association between gender and MDR-TB treatment outcomes may be due to biological factors,[25,26] access to treatment, similar adherence, dominance of other risk factors, as well as data limitations that make gender differences not statistically apparent.[25–28]

Employment status plays a crucial role during the treatment of MDR-TB. Patients with stable financial situations are more likely to access proper nutrition, which is essential for supporting recovery.

Adequate nutritional status strengthens the immune system and improves the body's ability to withstand the often prolonged and intense side effects of MDR-TB therapy. Evidence from regions like Shenzhen, China, where treatment and medical costs are subsidized by the government, shows a lower rate of patients lost to follow-up compared to areas lacking such support, contributing to better treatment outcomes. [29] Similarly, a study conducted in Peru found a notable increase in employment rates among patients, rising from 34% before treatment to 71% following the completion of MDR-TB therapy. This change highlights not only economic recovery but also enhanced social well-being as key benefits of successful treatment.[30]

The findings of this study align with those of a cohort study involving 664 MDR-TB patients, which identified age and HIV status as significant factors influencing survival. In contrast, gender was not found to have a statistically significant impact. Notably, older MDR-TB patients, particularly those living with HIV/AIDS or other comorbid conditions, exhibited reduced survival rates.[31,32] These findings imply that clinical variables and the overall health status of patients play a more significant role in the survival of MDR-TB patients than demographic characteristics like gender. Supporting this, a study conducted in Pakistan found that short-term treatment success rates were comparable between males and females, indicating that gender is not a key factor influencing treatment outcomes or survival in MDR-TB therapy.[24]

A retrospective study conducted at Shanghai Pulmonary Hospital involving 18 MDR-TB patients found that the use of linezolid was strongly associated with treatment success. Specifically, half of the patients (9 out of 18) achieved successful TB treatment, with a median culture

conversion time of seven weeks.[33] Additional studies have demonstrated that regimens containing linezolid can enhance survival outcomes. Patients treated with linezolid are more likely to achieve recovery and experience lower rates of treatment failure compared to those who do not receive the medication.[34]

Side effects of linezolid, including myelosuppression, neurotoxicity, and gastrointestinal issues, present significant challenges to successful treatment in MDR-TB patients. One study found that 17 of 18 patients experienced such adverse effects, frequently necessitating dose modifications or temporary interruptions in therapy. [33,35] Adjusting the dosage has emerged as a key approach to managing these toxicities. Evidence indicates that using lower doses or intermittent dosing schedules can minimize side effects while maintaining treatment effectiveness.[34,36,37]

Research indicates that linezolid holds significant promise in enhancing treatment outcomes for MDR-TB, particularly in patients needing more intensive therapy. Its effectiveness positions linezolid as a valuable alternative to standard treatment options. Several studies have demonstrated that linezolid-containing regimens achieved culture conversion rates of 93.5% and smear negativity rates of 92.5% in MDR-TB cases, surpassing many other second-line drugs. Additionally, for extensively drug-resistant TB (XDR-TB), incorporating linezolid has shown success in achieving culture conversion within six months.[38] A meta-analysis reported treatment success rates ranging from 68% to 73% for regimens based on linezolid. These outcomes are similar to overall MDR-TB treatment success rates but demonstrate improved effectiveness in more complicated cases.[39] Furthermore, a retrospective study revealed that 80% of MDR-TB patients treated with linezolid experienced favorable treatment outcomes,

even in the face of initially high resistance rates. [40]

Analysis using the Cox Proportional Hazards Model further identified HIV status as a key factor influencing mortality in MDR-TB patients. Being HIV positive was associated with a significantly higher risk of death. According to the World Health Organization, the co-infection of HIV and TB elevates the risk of mortality by compromising the immune system.[5] Previous research has indicated that mortality among HIV-positive patients undergoing MDR-TB treatment is linked to factors such as immunosuppression, delayed diagnosis, and difficulties in managing coexisting infections.[41,42] The lack of significant effects from factors like gender, employment status, and treatment history suggests that these variables might not directly impact the risk of death among MDR-TB patients receiving short-term treatment. However, additional research is necessary to better understand their potential role in patient survival during this treatment period. To enhance survival rates within this population, it is essential to develop treatment strategies that specifically address the needs of older adults and individuals living with HIV.

CONCLUSION

The findings revealed that age plays a crucial role in the survival outcomes of patients undergoing short-term treatment for MDR-TB. Specifically, younger patients aged 19 to 35 demonstrated better survival rates compared to older individuals, with those aged 56 and above facing the greatest risk of mortality. These results highlight the critical role of age in shaping treatment approaches for MDR-TB, underscoring the necessity for tailored interventions for vulnerable populations, particularly older adults and individuals with coexisting health conditions.

AUTHOR CONTRIBUTIONS

M.Z.S. contributed to the conceptualization, methodology design, project administration, and overall supervision of the study. I.H.A. and I.Z. were responsible for data curation, including applying for data access and managing ethical approvals. A.A. led the original draft preparation, including writing and critical manuscript revisions to ensure clarity and coherence. All authors read and approved the final version of the manuscript.

ETHICAL CONSIDERATION

Ethical approval for the study was obtained from the Health Research Ethics Commission of the Faculty of Health Sciences at Jenderal Soedirman University. Ethical approval for this study was granted under reference number 1481/EC/KEPK/VI/2024. Since the study involved secondary data analysis, no further ethical approval was necessary.

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