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Article

Correlation of Skin Pigmentation Changes as a Side Effect of Clofazimine Treatment with Anxiety Level in MDR-TB Patients at Dr. Soebandi Hospital

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Abstract: Clofazimine, used to treat Multidrug-resistant tuberculosis (MDR-TB), often causes skin pigmentation changes, potentially impacting patients' self-esteem and anxiety. Anxiety represents a common but often underrecognized comorbidity in MDR-TB patients, who are challenged by lengthy treatment regimens, social stigma, and distressing adverse effects. This study aimed to examine this correlation at Dr. Soebandi Hospital. The study utilized an observational analytic method with a cross-sectional design. The population was all MDR-TB patients in Dr. Soebandi hospital, presented from April to May 2024. We recruited 67 patients using a total sampling technique. We analyzed the primary data from the respondents: 1) Respondents' self-rating of skin pigmentation change; 2) Hamilton Anxiety Rating Scale (HARS) score. We also checked the medical records to analyze the respondents' treatment history. The data were analyzed using the chi-square test. Most respondents were male and in a productive age. The chi-square test results show a p-value of 0.822, indicating no significant correlation between skin pigmentation changes and anxiety levels in MDR-TB patients. Clofazimine-induced skin pigmentation changes had no significant correlation with the anxiety levels among MDR-TB Patients at Dr. Soebandi Hospital. Further studies should consider methodological improvements, including prospective design, larger sample size, mixed method, and involvement of dermatology experts in assessing the skin changes induced by clofazimine. Recognizing individual differences in psychological response highlights the need to offer reassurance, counseling, and psychosocial support for MDR-TB patients.

Keywords: Skin Pigmentation, Level of Anxiety, Clofazimine, MDR-TB

1. Introduction

Tuberculosis (TB), particularly multidrug-resistant strains (MDR-TB), remains a significant global health concern. MDR-TB, characterized by resistance to isoniazid and rifampicin, requires prolonged and complex treatment regimens, often involving second-line drugs like clofazimine [1]. Indonesia faces a high burden of MDR-TB, with an estimated 28,000 cases in 2021 [2]. Clofazimine, a key component of MDR-TB treatment, is associated with notable side effects, particularly skin pigmentation changes occurring in 75-100% of patients [3]. The discoloration results from the accumulation of clofazimine's phenazine pigment in subcutaneous fat, appearing as reddish-brown to black and may persisting long after treatment ends [4], [5].

While effective against MDR-TB, the visible nature of clofazimine-induced skin pigmentation can lead to psychosocial distress in patients, potentially impacting self-esteem, body image, and social interactions [6]. Moreover, MDR-TB itself needs a long-time treatment up to 18-24 months [7]. Hence, MDR-TB patients who has medication-induced pigmentation disorders may also experience anxiety and depression, adding to the existing stigma faced by MDR-TB patients ([8], [9]). Anxiety represents a common but often underrecognized comorbidity in MDR-TB patients, who are challenged by lengthy treatment regimens, social stigma, and distressing adverse effects. Unlike depression,

which is primarily linked to persistent low mood, anxiety arises as a psychological response to stressors or unfamiliar circumstances [10], [11].

Despite the known psychosocial impact of skin changes, limited research has specifically addressed the effect of clofazimine-induced pigmentation on the mental health of MDR-TB patients. Previous study only stated amount of MDR-TB experienced darkening skin due to clofazimine without clearly addressing the mental health morbidity caused by the skin condition [12]. In a meta-analysis, Sutar et al. reported a high prevalence of anxiety, with a pooled estimate of 32.5%, associated with factors such as primary TB infection, immunocompromised status, socioeconomic challenges, malnutrition, stigma, and poor adherence to treatment. Elevated anxiety levels were also observed in patients with HIV coinfection, largely attributed to social stigma, the severe disease trajectory, and related stressors. However, none of these studies specifically addressed the relationship between clofazimine-induced skin changes and anxiety in MDR-TB patients [13]. Research on anxiety comorbidity among TB patients in Indonesia has primarily reported prevalence rates, with limited exploration of the underlying causes [14].

This study aims to investigate the correlation between changes in skin pigmentation due to clofazimine and the level of anxiety in patients with MDR-TB at Dr. Soebandi General Hospital, Jember, Indonesia, to inform the development of more comprehensive patient care strategies.

2. Materials and Methods

This study employed a cross-sectional observational analytic design to investigate the relationship between clofazimine-induced skin pigmentation changes and anxiety levels in patients with TB-MDR. The study was conducted at the Dr. Soebandi Regional Hospital in Jember, Indonesia, from April 16 to May 16, 2024.

2.1. Participants

The study population comprised all patients diagnosed with TB-MDR who were registered and actively receiving treatment at the Dr. Soebandi Regional Hospital during the study period. A total of 76 patients with TB-MDR were identified. The inclusion criteria for this study were: (1) confirmed diagnosis of TB-MDR based on medical records; (2) currently undergoing treatment with a regimen containing clofazimine for at least one month; (3) willingness to participate in the study and provide informed consent; (4) accompanied by a family member or close companion who could help confirm changes in skin pigmentation and (5) ability to communicate effectively for the interview. Exclusion criteria were: (1) a diagnosis of a psychiatric disorder documented in the medical records prior to starting TB-MDR treatment, (2) the presence of visual impairment that could affect the ability to assess skin pigmentation, (3) HIV-AIDS, (4) refusal to participate or withdrawal from the study, and (5) incomplete questionnaire responses. After applying the inclusion and exclusion criteria, a total of 67 patients were included in the final analysis.

2.2. Data Collection

Data were collected using a combination of primary and secondary data collection methods. Primary data were obtained through structured interviews with the patients and their accompanying family member or close companion. Secondary data were extracted from the patients' medical records.

2.2.1. Assessment of Skin Pigmentation Changes

A standardized questionnaire was used to assess changes in skin pigmentation. Participants were asked to rate their skin color changes compared to their skin tone before starting clofazimine treatment. The questionnaire included the question: "Have you

experienced skin color changes since starting your TB-MDR treatment?". The participants' responses were confirmed by their accompanying family member or close companion, who was also asked to assess the changes. To further aid in the assessment, a printed color palette based on the Fitzpatrick scale was shown to the participants and their companions. The participants were asked to identify the color on the palette that most closely resembled their skin tone before and after starting clofazimine treatment. It is important to note that the Fitzpatrick scale was used here only as a visual aid for color comparison and not for its original purpose of classifying skin types based on sun sensitivity. Dermatological consultation or photographic validation was not feasible due to resource limitations and the clinical setting, where standardized photographic equipment and controlled lighting were unavailable. To ensure the reliability of data collection, assessments were conducted by two trained researchers independently. Inter-rater consistency was maintained by using predefined criteria for pigmentation grading, and discrepancies were resolved through consensus discussions.

A minimum treatment duration of one month was selected because clofazimine-induced pigmentation typically becomes clinically apparent within the first few weeks of therapy. Previous clinical observations have shown that discoloration of the skin, conjunctiva, or bodily secretions usually develops after 2–4 weeks of continuous use, making one month a sufficient threshold to detect visible pigmentation changes [15], [16].

2.2.2. Assessment of Anxiety Levels

Anxiety levels were measured using the Indonesian version of the Hamilton Anxiety Rating Scale (HARS), a widely used and validated instrument for assessing anxiety severity [17]. The HARS consists of 14 items, each rated on a 5-point Likert scale (0 = not present, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe). The total score ranges from 0 to 56, with higher scores indicating greater anxiety severity. The severity of anxiety was categorized as follows: no anxiety (score < 14), mild anxiety (score 14-20), moderate anxiety (score 21-27), severe anxiety (score 28-41), and very severe anxiety (score > 41) [18]. The HARS was administered by trained research assistants through face-to-face interviews.

2.2.3. Medical Record Review

Medical records were reviewed to obtain data on the following: (1) demographic characteristics (age, sex); (2) duration of clofazimine treatment; (3) history of psychiatric disorders; and (4) HIV status. This was to ensure that the participants met the inclusion and exclusion criteria.

2.3. Ethical Considerations

This study was approved by the Ethics Committee of the Faculty of Medicine, University of Jember (Ethical Clearance No. 3832/UN25.1.10.2/KE/2024) and the Dr. Soebandi Regional Hospital. Written informed consent was obtained from all participants before data collection. Confidentiality and anonymity were maintained throughout the study.

2.4. Data Analysis

Data were analyzed using IBM SPSS Statistics version 25. Descriptive statistics were used to summarize the demographic characteristics of the participants, the prevalence of skin pigmentation changes, and the distribution of anxiety levels. The chi-square test was used to examine the association between skin pigmentation changes and anxiety levels. A p-value of less than 0.05 was considered statistically significant.

3. Results and Discussion

This study investigated the relationship between clofazimine-induced skin pigmentation changes and anxiety levels in patients with TB-MDR undergoing treatment

at Dr. Soebandi Regional Hospital, Jember. A total of 67 patients with TB-MDR were included in the study

3.1. Characteristics of Respondents

The demographic and clinical characteristics of the participants are presented in Table 1. Most of the respondents were male (61.2%, n = 41), which is consistent with the higher prevalence of TB-MDR reported among men globally. This male predominance in our study might be attributed to factors such as higher rates of smoking and alcohol consumption among men, which are known risk factors for TB ([19], [20]). Also, most of the respondents were in the productive age, which is in line with Mehari et al. (2019) research. The mean age was within the productive age range (80.6% were in the adult age between ≥18 years old, n=54), aligning with previous studies that have shown a higher incidence of TB-MDR in this age group [21]. This could be due to increased mobility, social interactions, and potential occupational exposures in this demographic.

The most frequent level of anxiety experienced by participants was "no anxiety" (62.7%, n = 42), followed by mild anxiety (22.4%, n = 15), moderate anxiety (7.5%, n = 5), severe anxiety (4.5%, n = 3), and very severe anxiety (3%, n = 2). Most participants reported experiencing skin pigmentation changes (91%, n = 61), while 9% (n = 6) reported no changes.

Table 1. Distribution of Respondent Characteristics (n=67)

Characteristic	Frequency (n)	Percentage (%)
Sex		
Male	41	61.2
Female	26	38.8
Age		
Remaja (<18 tahun)	5	7.5
Dewasa (≥18 tahun)	54	80.6
Lansia (≥60 tahun)	8	11.9
Anxiety Level (HARS)		
No anxiety	42	62.7
Mild	15	22.4
Moderate	5	7.5
Severe	3	4.5
Very Severe	2	3.0
Skin Pigmentation Changes		
Yes	61	91.0
No	6	9.0

3.2. Association Between Skin Pigmentation Changes and Anxiety Levels

Table 2 presents the distribution of anxiety levels among participants with and without skin pigmentation changes. Among the 61 participants who experienced skin pigmentation changes, 37 (60.7%) had no anxiety, 14 (23%) had mild anxiety, 5 (8.2%) had moderate anxiety, 3 (4.9%) had severe anxiety, and 2 (3.2%) had very severe anxiety. Of the 6 participants who did not experience skin pigmentation changes, 5 (83.3%) had no anxiety and 1 (16.7%) had mild anxiety. The chi-square test revealed no statistically significant association between skin pigmentation changes and anxiety levels ($\chi^2 = 1.53$, $p = 0.822$). The effect size was small (Cramer's V = 0.15, 95% CI: −0.09 to 0.38), indicating a negligible association between skin pigmentation changes and anxiety levels.

Table 2. Distribution and Analysis of the Association between Skin Pigmentation Changes and Anxiety Levels (n=67)

Skin Pigmentation Changes	Anxiety Level						*p-value*
	No Anxiety	Mild	Moderate	Severe	Very Severe	Total	
Yes	37 (60.7%)	14 (23.0%)	5 (8.2%)	3 (4.9%)	2 (3.2%)	61 (91.0%)	0.822
No	5 (83.3%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (9.0%)	
Total	42 (62.7%)	15 (22.4%)	5 (7.5%)	3 (4.5%)	2 (3.0%)	67 (100.0%)	

3.3 Discussion

The high prevalence of skin pigmentation changes (91%) observed in this study is consistent with previous research, which has reported that 75-100% of patients treated with clofazimine experience this side effect [3]. The mechanism underlying clofazimine-induced pigmentation involves the accumulation of clofazimine crystals in the subcutaneous fat and the formation of pigmented macrophages (melanophages) in the skin ([4], [22]).

Despite the high prevalence of skin pigmentation changes, most of the participants in this study did not experience clinically significant levels of anxiety. This finding suggests that clofazimine-induced skin pigmentation may not be a major determinant of anxiety in this population. Several factors may contribute to this lack of association.

The study population consisted mostly of men (61.2%) of productive age. Studies have shown that men tend to have different coping mechanisms and may be less likely to express psychological distress compared to women [23]. Compared to females, males tended to perform better in information acquisition and processing, while females showed an advantage in communicative interaction. This might also relate to the cultural acceptance that may influence how patients, both men and women, perceive and report psychological distress [24]. Generally, with longer disease duration, men are likely to acquire greater knowledge about disease management and become more practiced in coping strategies. In contrast, as the illness advances, older women may face increasing difficulties in accessing, evaluating, and applying health information, which can contribute to a decline in their health literacy. But, this statement more likely occurs among older women compared to productive women who also have coping mechanism. In addition, resilience developed through living with a chronic disease, where prolonged treatment and multiple side effects are common, might reduce the psychological impact [24], [25]. Additionally, individuals of productive age might prioritize economic and social responsibilities over the cosmetic concerns associated with skin pigmentation changes [26]. They might be more focused on completing their treatment and returning to their daily activities.

The strong social support observed among the participants, as evidenced by the presence of family members or companions during hospital visits, might have mitigated the psychological impact of skin pigmentation changes. Social support has been shown to be a protective factor against anxiety and depression in various populations [27], including patients with chronic illnesses. Specifically, in the context of TB treatment, social support plays a crucial role in improving patients' well-being and treatment adherence. Research by Handayani & Suryana (2024) found that support from family, friends, and the community can enhance the quality of life for TB patients [28]. Similarly, Muna & Soleha (2018) reported that social and family support were associated with higher medication adherence [29]. The collectivist culture prevalent in Indonesia, where family and community ties are highly valued, might also contribute to greater acceptance and tolerance of physical changes.

The study found that older individuals (adult and elderly) experienced more pigmentation, but they did not experience anxiety. This can be attributed to coping mechanisms that are better than younger age, according to research by Mahoney et al.,

(2015) [30]. Also, the coping mechanism for the elderly is to focus more on non-physical aspects, such as mental health and well-being [31].

Furthermore, the study participants were already undergoing treatment for TB-MDR, which is a serious and potentially life-threatening condition. It is possible that their concerns about the disease itself and the challenges of treatment overshadowed the distress caused by skin pigmentation changes. Research has indicated that patients with TB-MDR often experience a range of physical and psychological symptoms, including pain, fatigue, and social isolation, which may be more distressing than cosmetic changes. The study by Walker et al., (2019) showed a significant correlation between anxiety and physical symptoms such as headaches, joint and limb problems, fatigue, digestive issues, and hearing problems [32].

Although this study did not find a statistically significant correlation between clofazimine-induced pigmentation and anxiety, the clinical implications remain relevant. Skin changes are visible and potentially distressing. Healthcare workers should acknowledge patient concerns, provide reassurance, and offer counseling when needed. Integrating psychosocial support into MDR-TB care could strengthen adherence and improve overall treatment outcomes, regardless of statistical associations. To overcame it, a stepped care approach may be applied, such as incorporating universal education, targeted depression screening, counseling for those affected, and peer support groups. Successful integration depends on a patient-centered model that addresses the emotional and social challenges of long-term therapy, ultimately enhancing adherence, alleviating psychological distress, and improving treatment outcomes [33].

It is important to acknowledge the limitations of this study. The cross-sectional design does not allow for the establishment of causality; a longitudinal approach would better capture changes in anxiety over the course of treatment. Additionally, the assessment of skin pigmentation changes relied on subjective reports and visual comparison using the Fitzpatrick scale as a reference, rather than objective measurements which may introduce recall bias and subjective variability. Future research could benefit from using a prospective design, and objective measures of skin pigmentation. Next, anxiety was measured through a self-reported questionnaire, which is prone to underreporting or overreporting depending on the patient's openness and social desirability. Hence, using mixed methods will enhance the result of the study, for exploring the cause of anxiety. Moreover, the study population was limited to patients at a single hospital in Indonesia, and the findings may not be generalizable to other populations with different cultural backgrounds and healthcare systems. Further studies involving larger and more diverse populations are needed to confirm these findings.

4. Conclusions

In conclusion, there was no statistically significant association between clofazimine-induced skin pigmentation changes and anxiety levels among MDR-TB patients. The findings suggest that while skin pigmentation changes are a common side effect of clofazimine treatment, they may not be a major source of psychological distress for all patients. However, individual differences in psychological responses should not be overlooked, as visible treatment side effects may still carry a personal impact on self-confidence and emotional well-being. Further research is needed to explore the factors that may influence individual responses to clofazimine-induced skin pigmentation changes and to develop strategies for addressing the psychological needs of patients with TB-MDR. Therefore, psychosocial support should be integrated into MDR-TB management to address patient concerns, provide reassurance, and strengthen treatment adherence, even in the absence of a demonstrated statistical association.

Supplementary Materials: There are no supplementary materials provided in this study.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical and privacy concerns related to patient information.

Conflicts of Interest: The authors declare no conflict of interest.

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