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**Original Research Article**

# Clinical characteristics, serum albumin and eosinophil levels as risk factors for drug induced hepatitis in tuberculosis patients receiving fixed-dose combination anti-tuberculosis drug

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## ABSTRACT

**Background:** Drug-induced hepatitis (DIH) is a side effect of the usage of anti-tuberculosis (TB) drugs, which can cause alteration in treatment regiments and prolonged treatment. This study aim is to identify the risk factors that can be used to predict the occurrence of DIH on tuberculosis (TB) patients.
**Methods:** This was a case-control study, conducted at Sanglah central general hospital in Denpasar from January to June 2021. Data collection was carried out through the medical records of inpatients and outpatients who received fixed-dose combination anti-TB drug.
**Results:** There were 62 research samples which were divided into 31 samples in the case group and 31 samples in the control group. The clinical manifestations of DIH were vomiting (32.8%), nausea (15.7%), abdominal pain (13.1%), and hepatic encephalopathy (1.3%). Median time to onset of DIH was 18 (Interquartile range: 19) days. Low BMI was a significant risk factor for DIH (AOR=22.4; 95% CI 4.147-121.575; p<0.001). Other clinical characteristic variables such as age, female, extrapulmonary TB, positive HIV status, diabetes mellitus, hypoalbuminemia, and eosinophilia were not proven risk factors for DIH-TB.
**Conclusions:** Low BMI was a significant risk factor for DIH. Other variables such as age, female, extrapulmonary TB, positive HIV status, diabetes mellitus, hypoalbuminemia, and eosinophilia were not risk factors for DIH in TB patients.

**Keywords:** DIH, TB, Anti-TB drugs

## INTRODUCTION

Worldwide, tuberculosis (TB) is one of the top 10 causes of death and is the leading cause of infectious agents. In 2017, TB caused approximately 1.3 million deaths among HIV negative and an additional 300,000 deaths among HIV positive. Overall, 90% of patients are adults (aged 15 years), in which Indonesia ranks 3rd in the highest incidence of TB worldwide after India and China.[1]

Drug-induced hepatitis (DIH) is a side effect of the usage of anti-tuberculosis drugs, which can cause alteration in treatment regiments and prolonged treatment.[2] The incidence of DIH-TB shows a number that varies in each country. Incidence in America is reported as 3%, UK 4%, Germany 11%, Hong Kong 13%, Taiwan 26%, Japan 36%, and India 8-36%.[3]

The metabolism of anti-tuberculosis drugs is mainly by the liver, so it is potentially to cause hepatotoxicity. In DIH, there is an increase in liver enzymes, such as aspartate amino transaminase (AST), alanine transaminase (ALT), and total bilirubin three times the normal value.[4] Hepatotoxicity starts from a transient elevation of liver

enzymes without any symptoms to acute liver failure.[5] DIH-TB is generally unpredictable and occurs in a minority of patients despite receiving standard doses.[5] Several risk factors for hepatotoxicity such as age, sex, body mass index (BMI) and genetics have been investigated in previous studies, but in fact sometimes these risk factors are not proven to be associated with the incidence of DIH after receiving treatment with a standard regimen.[2] Based on those backgrounds, this study aimed to determine the risk factors that can be used to predict the occurrence of TB DIH in patients who received fixed-dose combination of anti-tuberculosis drugs.

## METHODS

This was an analytical observational study with case control study design located at Sanglah general hospital, Denpasar. All data obtained from medical records of the patients, either inpatient or outpatient. Data collected from January 2021 through June 2021. Research subjects were all patients with TB who received fixed dose combination of anti-TB drugs. Samples collected with consecutive sampling method at inpatient and outpatient. The case group was TB patients with DIH and the control group was patients without DIH during treatment.

The sample size calculated with Zα of 1.96, Zβ of 0.84, P1 obtained from literature and P2 was based on the judgment. Based on those requirements, minimal samples for each group were 31 subjects. This research has been approved by institutional review board of faculty of medicine Udayana university/ Sanglah hospital with ethical clearance number 1393/UN14.2.2.VII.14/LT/2021.

Inclusion criteria included tuberculosis patients receiving fixed-dose combination of anti-TB drugs with symptoms of DIH accompanied by an increase in ALT >3 times the upper limit of normal or an increase in ALP >2 times the upper limit of normal or an increase in bilirubin >1 times the upper limit of normal, at least 5 days after initiation of therapy. The patient's liver function was also normal before starting fixed dose combination anti-tuberculosis drugs and was over 18 years of age. The exclusion criteria included incomplete medical record data, history of atopy, history of alcohol use at least 10 days before starting anti-TB drugs, acute and chronic liver disease, gallbladder, and cirrhosis before starting therapy, routine consumption of potentially hepatotoxic drugs and drugs that metabolized to cytochrome P450 concurrently with anti-TB therapy.

The risk factors analyzed including age, sex, BMI, location of tuberculosis, HIV status, comorbid of diabetes mellitus, albumin and serum eosinophils at the time of treatment. Age and gender data were obtained from the patient's identity card. Body mass index is calculated by dividing the patient's weight (in kilograms) by the patient's height (in meters) squared. The location of TB is categorized as the anatomical location of the disease, pulmonary TB and extrapulmonary tuberculosis. The patient's HIV status is known through HIV test, divided into positive and negative status HIV. Comorbid diabetes mellitus was obtained from medical records, as diabetes mellitus and without diabetes mellitus. Hypoalbuminemia defined as serum albumin <3.4 g/dL. Eosinophilia was defined as relative eosinophil levels >5% or absolute eosinophils exceeding $0.5\times10^3/\mu$l as measured from blood serum.

Descriptive statistical analysis aimed to describe the characteristics of research subjects based on case and control groups. Numerical data presented in mean and standard deviation and categorical data displayed in frequencies and percentages. The results of descriptive statistical analysis are presented in the form of a cross-distribution table so that the comparability of subjects between groups can be assessed. Risk factor assessment analysis aimed to assess the relationship of each risk factor with the occurrence of DIH. The statistical analysis used to examine the difference in proportions in the cross-distribution table was Chi-Square test, with the result of crude odds ratio (COR). Analysis continued with multiple logistic regressions to obtain adjusted odds ratio (AOR). The process of inference or drawing conclusions is done using 95% CI and p. All analyzes were performed using the statistical package for the social sciences (SPSS) 24.0.

## RESULTS

The majority of patients in case and control group was > 35 years old with dominant of male. Most of the patients in the case group had low BMI, while in the control group was normal. The difference in BMI was considered significant (p<0.001). No difference observed for TB location, HIV status, diabetes mellitus status, baseline AST, baseline ALT, serum eosinophil and blood glucose. However, the serum albumin of the case group was lower than control group with 3.10 (0.80) g/dL vs 3.46 (1.00) g/dL, respectively (p<0.004) (Table 1).

In the case group, the clinical manifestations DIH was varied and the most had more than one clinical manifestation. Vomiting, nausea, abdominal pain, jaundice, weakness, anorexia, diarrhea, headache, joint pain and hepatic encephalopathy were clinical manifestations that occurred in the case group. Vomiting was the most common clinical manifestation (32.8%), followed by nausea (15.7%). Joint pain and hepatic encephalopathy occurred in 1.3% of the subjects (Table 2).

The onset of DIH, AST, ALT and bilirubin values during the event depicted in Table 3. Median time to onset of DIH was 18 (Interquartile range: 19) days. The AST values at the event was 158.7 (291.50) U/L and ALT values was 148.6 (194.50) U/L (Table 3).

The risk factor analysis presented in Table 4. From the analysis it was found that BMI and hypoalbuminemia were risk factors for DIH. The OR value of BMI was 26.36 (5.266-131.99), with p<0.001. The OR value of hypoalbuminemia was 3.3 (1.168-9.357) with p=0.022.

The analysis continued with multiple logistic regression tests to determine risk factors for DIH. Logistic regression test was performed on variables with p<0.25 in bivariate analysis, namely BMI, HIV status and hypo-albuminemia using backward LR method. In initial step, the AOR for low BMI variable was 22.4, 95% CI 4.147-121.575, p<0.001. AOR for positive HIV status variable was 2.5, 95% CI 0.436-14.430, p=0.303 and hypoalbuminemia variable was 1.2, 95% CI 0.312-4.655, p=0.787. HIV status and hypo-albuminemia were not significant as risk factors for DIH. In final step after eliminating confounding variables as risk factors for DIH, it was found that low BMI was risk factor for DIH in TB patients with treatment (AOR 26.4, 95% CI 5.266-131.990, p<0.001) (Table 5).

**Table 1: Characteristic of subjects.**

| Variables | Group | | P value |
|---|---|---|---|
| | Case, (n=31) (%) | Control, (n=31) (%) | |
| **Age (Years)** | | | |
| ≤ 35 | 11 (35.5) | 13 (41.9) | 0.602 |
| >35 | 20 (64.5) | 18 (58.1) | |
| **Gender** | | | |
| Male | 23 (74.2) | 26 (83.9) | 0.349 |
| Female | 8 (25.8) | 5 (16.1) | |
| **BMI (kg/m$^2$)** | | | |
| Low | 20 (64.5) | 2 (6.5) | <0.001 |
| Normal/overweight | 11 (35.5) | 29 (93.5) | |
| **TB location** | | | |
| Pulmonary | 26 (83.9) | 23 (74.2) | 0.349 |
| Extrapulmonary | 5 (16.1) | 8 (25.8) | |
| **HIV status** | | | |
| Positive | 9 (29.0) | 3 (9.7) | 0.054 |
| Negative | 22 (71.0) | 28 (90.3) | |
| **Diabetes mellitus** | | | |
| Yes | 6 (19.4) | 6 (19.4) | 1.000 |
| No | 25 (80.6) | 25 (80.6) | |
| **Baseline AST (U/L), (mean ± SD)** | 26.6±12.1 | 24.1±11.0 | 0.393 |
| **Baseline ALT (U/L), (mean ± SD)** | 21.22±10.17 | 18.47±10.16 | 0.291 |
| **Serum albumin (g/dl), median (IQR)** | 3.10 (0.80) | 3.46 (1.00) | 0.004 |
| **#Serum eosinofil ($10^3/\mu l$), median (IQR)** | 0.05 (0.19) | 0.12 (0.17) | 0.385 |
| **RBG (mg/dl), (mean ± SD)** | 88±62 | 72±38 | 0.391 |

BMI-body mass index; HIV-Human Immunodeficiency virus; AST-aspartate amino transaminase; ALT-alanine transaminase; RBG-random blood glucose; SD-standard deviation; IQR-interquartile range.

**Table 2: Clinical manifestation of DIH.**

| Symptoms | N (%) |
|---|---|
| **Vomiting** | 25 (32.8) |
| **Nausea** | 12 (15.7) |
| **Abdominal pain** | 10 (13.1) |
| **Icteric** | 9 (11.8) |
| **Weakness** | 8 (10.5) |
| **Anorexia** | 4 (5.2) |
| **Diarrhea** | 4 (5.2) |
| **Headache** | 2 (2.6) |
| **Joint pain** | 1 (1.3) |
| **Hepatic encephalopathy** | 1 (1.3) |

**Table 3: Onset of DIH, AST value, ALT value, and bilirubin value at the time of DIH occur.**

| Values | N=31 (%) |
|---|---|
| **Onset of DIH (days), median (IQR)** | 18 (19) |
| **AST (U/L), median (IQR)** | 158.7 (291.50) |
| **ALT (U/L), median (IQR)** | 148.6 (194.50) |
| **Bilirubin (mg/dl), median (IQR)** | 2.17 (4.92) |

AST, aspartate amino transaminase; ALT, alanine transaminase; IQR, interquartile range.

**Table 4: Bivariate analysis for risk factors of DIH.**

| Variables | Groups | | OR | 95% CI | P value |
|---|---|---|---|---|---|
| | Case, (n=31) (%) | Control, (n=31) (%) | | | |
| **BMI (Kg/m$^2$)** | | | | | |
| Low | 20 (64.5) | 2 (6.5) | 26.36 | 5.266-131.99 | <0.001 |
| Normal/overweight | 11 (35.5) | 29 (93.5) | | | |
| **TB location** | | | | | |
| Pulmonary | 26 (83.9) | 23 (74.2) | 1.80 | 0.518-6.315 | 0.349 |
| Extrapulmonary | 5 (16.1) | 8 (25.8) | | | |
| **HIV status** | | | | | |
| Positive | 9 (29) | 3 (9.7) | 3.81 | 0.922-15.811 | 0.054 |
| Negative | 22 (71) | 28 (90.3) | | | |
| **Diabetes mellitus** | | | | | |
| Yes | 6 (19.4) | 6 (19.4) | 1.00 | 0.284-3.526 | 1.000 |
| No | 25 (80.6) | 25 (80.6) | | | |
| **Hypoalbuminemia** | | | | | |
| Yes | 20 (64.5) | 11 (35.5) | 3.30 | 1.168-9.357 | 0.022 |
| No | 11 (35.5) | 20 (64.5) | | | |
| **Eosinophilia** | | | | | |
| Yes | 4 (12.9) | 3 (9.7) | 1.38 | 0.283-6.764 | 1.000 |
| No | 27 (87.1) | 28 (90.3) | | | |

BMI, body mass index; TB, tuberculosis; HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval

**Table 5: Multiple logistic regression of clinical characteristics and laboratory as risk factors of DIH.**

| Variables | First step | | | Final step* | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P value | OR | 95% CI | P value |
| **Low BMI (Kg/m$^2$)** | 22.4 | 4.147-121.575 | <0.001 | 26.4 | 5.266-131.990 | <0.001 |
| **HIV status of positive** | 2.5 | 0.436-14.43 | 0.303 | - | - | - |
| **Hypoalbuminemia** | 1.2 | 0.312-4.655 | 0.787 | - | - | - |

*With backward LR method OR, odds ratio; CI, confidence interval; BMI, body mass index; HIV, human immunodeficiency virus

## DISCUSSION

Anti-TB drugs cause hepatotoxicity, from an asymptomatic transient increase in liver enzymes to acute liver failure.[5,6] In this study, vomiting was the most common clinical manifestation for DIH (32.8%). This result similar to a study in India from with a total of 244 TB patients receiving anti-TB drugs, in which 14.3% had DIH with symptoms including vomiting (80%), nausea (65.7%), anorexia (31.4%), abdominal pain (17.1%) and jaundice (2.8%).[12]

The onset of DIH was varied. In this study, the onset of the DIH reaction was with the median of 18 days from the start of anti-TB drugs fixed dose combination. In a 7-year study conducted in US which evaluated the hepatotoxicity effect of 3377 anti-TB DIH patients, clinical manifestations appeared within 4 weeks of starting treatment.[7,8]

Although anti-TB drugs have been used for decades and are used worldwide, the pathogenesis underlying hepatotoxicity still not fully understood.[6] Several studies reported the risk factors that can cause DIH in patients receiving anti-TB drugs. Identification of patients at high risk will be useful for early detection of hepatotoxicity and reducing morbidity and mortality.[5]

Old age, as a risk factor for DIH, still varies in existing studies. A study by Soedarsono et al which classified the age groups to <35 years and ≥35 years old showed that age ≥35 years old group was not associated with the incidence of DIH with p value of 0.176.[2] In this study, the age of >35 years was not proven as a risk factor for DIH-TB. As for gender, in this study female gender was not proven as a risk factor for DIH-TB with p value of 0.349, although several other studies showed significant results. The higher risk odds for the development of DIH in women may be due to variations in pharmacokinetics and slower acetylation patterns and lower BMI in women.[9]

Malnutrition is common in tuberculosis patients and contributes to an increased incidence of DIH after taking anti-TB drugs.[2,3,10] In this study, low BMI was a risk factor for DIH in TB patients receiving fixed dose combination of anti-TB drugs, consistent with several previous studies. Malnutrition causes depletion of glutathione storage, that is a cofactor in glutathione s-transferase (GST). This is a detoxifying enzyme causing patients to become more susceptible to oxidative injury, slower drug metabolism in the liver, and reduced drug detoxification ability.[2,9,11] Malnutrition conditions also lead to reduced xenobiotic clearance and higher plasma levels.[2,5]

Controversies still exist regarding cause of hepatotoxicity in tuberculosis patients accompanied by HIV infection.[5,6] Deficiency of immune status in patients with HIV can be served as one of the causes of hepatotoxicity.[12] Viral replication or immunocompromised conditions that occur in HIV patients are prone to malnutrition, including hypoalbuminemia.[13] The use of antifungals such as fluconazole and anti-retroviral therapy in HIV conjunction with anti-TB drugs patients increase in development of DIH in TB patients.[5,14] Research by Ambreen et al in India found that positive HIV status was significant for the occurrence of DIH (p=0.02).[12] In a study in the UK, HIV infection had a four times higher risk of developing DIH and was statistically significant (p=0.04).[15]

Albumin transports various substances including bilirubin, fatty acids, metals, ions, hormones, and drugs. One of the consequences of hypoalbuminemia is that drugs, which are generally protein-bound, become free in plasma, causing higher drug levels, faster liver metabolism, or both. Pro-inflammatory cytokines such as TNF and IL-6 in chronic inflammation such as tuberculosis can reduce serum albumin levels by increasing vascular permeability (causing albumin to diffuse into the extravascular space), increasing degradation, and decreased synthesis (activation of TNF-α causing reduced albumin gene transcription).[16] In a study by Gaude et al hypoalbuminemia led to three times higher likelihood for DIH (p=0.002).[10] The study by Marzuki et al showed that low serum albumin levels were associated with a higher risk of anti-TB DIH (p=0.023) although in this study the results were not significant in multivariate analysis.[13] In the current study, there was a higher tendency for DIH to occur in patients with hypoalbuminemia, but not statistically significant.

Limited studies still become a problem for the evidence of eosinophilia as a risk factor for DIH in patients with anti-TB drugs therapy. A study by An et al in Beijing with 267 patients with anti-TB DIH, a total of 12.4% showed allergic manifestations such as fever, rash, and increased serum eosinophils that occurred before the event of DIH occur, although statistically not significant.[17] This is similar to the study by Yin et al which reported that 1.7% of patients with anti-TB DIH had elevated blood eosinophils.[18] In this study, eosinophilia was found in 12.9% of the subjects in the case group and there is not enough evidence to state eosinophilia as a risk factor for DIH.

Several limitations exist in this research. This study used medical records that rely on the completeness of documented data; therefore, incomplete data will be excluded from the study. Furthermore, there is a potential for information bias due to variations in weight and height measurements by different people and variations in measurement tools that may affect BMI values. Another point to note is that there is a potential for selection bias in the form of calibration and differences in laboratory equipment used during blood tests, because before treatment, some patients took blood test in another laboratory. To reduce the potential of limitation, the hospital has already accredited and has a proper protocol. In this study data were only taken from one center, so the scope was limited to TB patients who were hospitalized.

Despite all the limitations, this study evaluates risk factors for DIH in TB patients receiving fixed dose combination of anti-TB drugs with normal baseline liver function before starting therapy. This can be considered as the strength of the current research.

## CONCLUSION

In conclusion, the clinical characteristics which served as a risk factor for the occurrence of DIH is low BMI. The risk of DIH in TB patients with low BMI was 22.4 times compared to normal BMI. Other variables such as age, female, extrapulmonary tuberculosis, HIV status, diabetes mellitus, hypoalbuminemia, and eosinophilia were not proven as a risk factor for DIH-TB in this study.

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