"Assessment of Pharmacotherapy and Clinical Outcomes of Treatment for the Development of Cardiovascular Disease among Tuberculosis Patients"

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Abstract

Background: Tuberculosis (TB) continues to impose a substantial morbidity and mortality burden globally, particularly in developing countries. Growing evidence suggests an epidemiological and pathological interplay between TB and cardiovascular disease (CVD). Beyond conventional cardiovascular risk factors such as diabetes mellitus, hypertension, and dyslipidemia, there are other factors, including chronic inflammation, immune activation, and metabolic disruption, that are caused by *Mycobacterium tuberculosis* and may also contribute to cardiovascular complications. Chronic immune activation involving monocytes, macrophages, lymphocytes, and cytokines, which are crucial for TB defense, may also contribute to atherogenesis and cardiovascular dysfunction.

Objective: The main objective of this study was to evaluate anti-tuberculosis pharmacotherapy patterns and clinical outcomes among patients without cardiovascular disease (CVD).

Methodology: This retrospective cohort study with an observational analytic design, was

conducted at Penang General Hospital, Malaysia, from January 2023 to August 2023 using medical records from January 2015 to December 2022, evaluated 402 TB patients without pre-existing CVD. The study assessed the association between anti-tuberculosis pharmacotherapy patterns, adverse drug reactions, drug-resistant TB, clinical treatment outcomes, and the development of CVD during TB therapy using chi-square tests.

Results: The predominant anti-tuberculosis regimen was 2HRZE/4HR, commonly administered as fixed-dose combinations. Adverse drug reactions were observed, including transaminitis (8.3%), skin rashes (6.3%), nausea/vomiting (4.7%), hyperbilirubinemia (4.2%), blurred vision (2.3%), thrombocytopenia (2.1%), and drug-induced hepatitis (2.6%). Drug-resistant TB constituted 6.5% of cases, comprising mono-drug resistance (3.4%), MDR-TB (1.4%), and poly-drug resistance (0.9%). Regarding clinical outcomes, 41.5% of patients were cured, 21.9% completed treatment, 15.2% died, and 5.5% were lost to follow-up, with a treatment failure rate of 0.7%. A significant association was found between the type of TB case and clinical outcomes ($\chi^2 = 15.826$, $p < 0.05$). New TB cases showed higher cure and completion rates. Cardiovascular disease developed in 41 patients and was associated with markedly increased mortality (28/41) and significantly poorer treatment outcomes ($p < 0.001$). Comorbidities, including diabetes mellitus ($\chi^2 = 14.720$, $p = 0.012$), HIV infection ($\chi^2 = 28.727$, $p = 0.001$), acute kidney injury ($\chi^2 = 22.156$, $p < 0.001$), and anaemia ($\chi^2 = 16.872$, $p = 0.005$), were significantly linked to adverse clinical outcomes.

Conclusions: TB patients who developed cardiovascular disease exhibited significantly higher mortality and reduced treatment success. Comorbidities such as diabetes, HIV, acute kidney injury, and anaemia further compromised clinical outcomes. These findings highlight the need for routine cardiovascular risk assessment during TB therapy. Early identification of high-risk patients and integrated, multidisciplinary management approaches are essential. Strengthening combined care for infectious and non-communicable diseases may improve survival in resource-limited settings.

Keywords: tuberculosis, cardiovascular disease, anti-tubercular pharmacotherapy, drug-resistant tuberculosis, treatment outcomes

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)

Human Research Ethics Committee USM (HREC)

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17th October 2022

Mr. Bheesham Ram
School of Pharmaceutical Sciences
Universiti Sains Malaysia
11800 Gelugor, Pulau Pinang

JEPeM Code: USM/JEPeM/22080554
Protocol Title: Prevalence and Incidence of Cardiovascular Diseases among Tuberculosis Patients and Treatment Outcomes

Dear Mr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/22080554,** which should be used for all communications to JEPeM-USM in relation to this study. This ethical approval is valid from **17th October 2022** until **16th October 2023.**

Study Site: General Hospital, Pulau Pinang

The following researchers are also involved in this study:
1. Dr. Amer Hayat Khan
2. Dr. Sabariah Noor Harun
3. Dr. Irfan Ali Haider Ali

The following document has been approved for use in the study:
1. Research Proposal

In addition to the abovementioned document, the following technical documents were included in the review on which this approval is based:
1. Data Collection Form
2. Laboratory Investigation Sheet

While the study is in progress, we request that you submit to us the following documents:

1. Application for renewal of ethical approval 60 days before the expiration date of this approval through submission of **JEPeM-USM FORM 3(B) 2019: Continuing Review Application Form.**
2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial, including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form.**
3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form.**
4. Reports of adverse events from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2019: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2019.**

6. Any event that may have ethical significance.

7. Any information that is needed by the JEPeM-USM to do an ongoing review.
8. Notice of time of completion of the study using **JEPeM-USM FORM 3(C) 2019: Final Report Form.**

Please note that forms may be downloaded from the JEPeM-USM website: **www.jepem.kk.usm.my**

JEPeM-USM complies with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.

"WAWASAN KEMAKMURAN BERSAMA 2030"

"BERKHIDMAT UNTUK NEGARA"

Sincerely,

Narazah

PROF. DR. NARAZAH MOHD YUSOFF
Advisor
Jawatankuasa Etika Penyelidikan (Manusia) JEPeM
Universiti Sains Malaysia

CONFLICT OF INTEREST DECLARATION FORM FOR INVESTIGATORS

SECTION 1.0: GENERAL INFORMATION

Research ID:	RSCH ID-22-02959-USV	**Protocol Number: (if any):**	
Research Title:	PREVALENCE AND INCIDENCE OF CARDIOVASCULAR DISEASES AMONG PATIENTS WITH TUBERCULOSIS & TREATMENT OUTCOMES		
Study Type: Observational	☒ **IIR (Investigator Initiated Research)** ☐ **ISR (Industry Sponsored Research)**		
Principal Investigator's Name:	Amer Hayat Khan		
Sponsor/Funding (if any):	School of Pharmaceutical Sciences Universiti Sains Malaysia (USM)		

Study Team Members:

Note:

1. *Please list all the research team members (Principal/ Lead Investigator, Principal Investigator at the Site, and Sub Investigator at the Site) involved in this study.*

Investigator Name	**Site Conducted**	**Investigator's Role** *(Principal/ Lead Investigator, Principal Investigator at the Site or Sub Investigator at the Site)*
Amer Hayat Khan	HOSPITAL PULAU PINANG	Principal / Coordinating Investigator
BHEESHAM RAM	HOSPITAL PULAU PINANG	Co / Sub Investigator at the site
Sabariah Noor Harun	HOSPITAL PULAU PINANG	Co / Sub Investigator at the site
Irfhan Ali Bin Hyder Ali	HOSPITAL PULAU PINANG	Co / Sub Investigator at the site
Azfar Athar Ishaqi	HOSPITAL PULAU PINANG	Co / Sub Investigator at the site
Irfanullah Khan	HOSPITAL PULAU PINANG	Co / Sub Investigator at the site

SECTION 2.0: CONFLICT OF INTEREST INFORMATION

2.1 **Instruction**: Please read each of the statements below and mark/tick (√) in the appropriate column
Please note that the statements below are relevant to/applicable to include your study team members (Principal/ Coordinating Investigator, Principal Investigator at the Site and Co/Sub Investigator at the Site), your spouse and each dependent child.

Nature of Interest	**YES**	**NO**	**If YES, please describe/ explain your plan for reducing or eliminating the potential conflict of interest : *(note: MREC may recommend other conditions if such condition will eliminate, reduce or manage the conflict of interest/s)***
Financial arrangement / anticipated compensation/ employment by the sponsor or product manufacturer		✓	
Proprietary interest *(e.g. trademark, copyright, licensing agreement, royalty payment or compensation tied to sales of the product)*		✓	
Equity interest in the product manufacturer/ any commercial organisation being involved in this research *(e.g. ownership interest, stock options or other financial interest)*		✓	
Any significant payment of other sorts from the sponsor or product manufacturer to support activities of the investigators (exclusive of the cost of conducting the clinical study/research)		✓	

SECTION 3.0 DECLARATION BY PRINCIPAL/ COORDINATING INVESTIGATOR

I certify that the responses to the statements above are accurate and complete and that my responses constitute a full disclosure of any conflicting interest/s and activities that may affect the integrity of the research or the rights, safety and welfare of human subjects.

I will promptly disclose to MREC any significant new information which would cause the answers to the above statements to change during the course of the study.

Important note: Please note that the terms "I" and "my" include your study team members (Principal/Coordinating Investigator, Principal Investigator at the Site and Co/Sub Investigator at the Site), your spouse and each dependent child

Signature: 	Date: 08-09-2022
Name: Amer Hayat Khan	Designation: Principal Investigator

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(*Medical Research & Ethics Committee*)
KEMENTERIAN KESIHATAN MALAYSIA
d/a Kompleks Institut Kesihatan Negara
Blok A, No 1, Jalan Setia Murni U13/52,
Seksyen U13, Bandar Setia Alam,
40170 Shah Alam, Selangor.
Tel: 03-3362 8888/8205

Ruj.Kami: 22-02255-60W (1)
Tarikh **: 11-Januari-2023**

DR AMER HAYAT KHAN
SCHOOL OF PHARMACEUTICAL SCIENCES, USM

Dato'/ Tuan/ Puan,

SURAT KELULUSAN ETIKA: NMRR ID-22-02255-60W (IIR)
PREVALENCE OF CARDIOVASCULAR DISEASES AMONG PATIENTS WITH TUBERCULOSIS & TREATMENT OUTCOMES

Dengan hormatnya perkara di atas adalah dirujuk.

2. Bersama dengan surat ini dilampirkan surat kelulusan saintifik dan etika bagi projek ini. Segala rekod dan data subjek adalah **SULIT** dan hanya digunakan untuk tujuan kajian dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi. Kebenaran daripada Pengarah Hospital / Institusi di mana kajian akan dijalankan mesti diperolehi terlebih dahulu sebelum kajian dijalankan. Dato' / Tuan / Puan perlu akur dan mematuhi keputusan tersebut dan undang-undang lain yang berkaitan, termasuklah Akta Akses Kepada Sumber Biologi dan Perkongsian Faedah 2017.

3. Penyelidik- penyelidik dan lokasi kajian yang terlibat ialah:

   HOSPITAL PULAU PINANG
   Amer Hayat Khan (Penyelidik Utama)
   Bheesham Ram
   Sabariah Noor Bt Harun
   Irfhan Ali Bin Hyder Ali

4. Adalah dimaklumkan bahawa kelulusan ini adalah sah sehingga **10-Januari-2024.** Tuan/Puan perlu menghantar dokumen-dokumen seperti berikut selepas mendapat kelulusan etika. Borang-borang berkaitan boleh dimuat turun daripada laman web *National Medical Research Register (NMRR).*

   i. ***Continuing Review Form*** selewat-lewatnya dalam tempoh 2 bulan (60 hari) sebelum tamat tempoh kelulusan ini bagi memperbaharui kelulusan etika.
   ii. ***Study Final Report*** pada penghujung kajian.
   iii. Mendapat kelulusan etika sekiranya terdapat pindaan ke atas sebarang dokumen kajian / lokasi kajian / penyelidik. Pihak JEPP mempunyai hak untuk menarik balik kelulusan etika sekiranya terdapat perubahan dokumen kajian yang tidak diisytiharkan.

5. Kajian tersebut hanya melibatkan pengumpulan data melalui:

   i. Retrospektif
   ii. Rekod Perubatan

6. Sila ambil maklum bahawa sebarang urusan surat-menyurat berkaitan dengan penyelidikan ini haruslah dinyatakan **nombor rujukan surat** ini untuk melicinkan urusan yang berkaitan.

Sekian terima kasih.

Komen (Jika ada) : NIL

Ruj.Kami: 22-02255-60W (1)

Lokasi Kajian:
HOSPITAL PULAU PINANG

Keputusan Jawatankuasa Etika dan Penyelidikan Perubatan:
(√) Lulus
( ) Tidak Lulus

Tarikh kelulusan etika : **11-Januari-2023**

"BERKHIDMAT UNTUK NEGARA"

Saya yang menjalankan amanah,

.....
DR NURAIN MOHD NOOR
Pengerusi
Jawatankuasa Etika & Penyelidikan Perubatan
Kementerian Kesihatan Malaysia
No. MPM: 31576

ICMJE DISCLOSURE FORM

Date: 6/15/2025

Your Name: BHEESHAM RAM

Manuscript Title: "Cardiovascular Mortality Among Tuberculosis Patients"

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	**Specifications/Comments (e.g., if payments were made to you or to your institution)**
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ None	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
3	Royalties or licenses	☒ **None**	
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board,	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
	society, committee or advocacy group, paid or unpaid		
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Click or tap here to enter text.

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
1		☒ None	
Time frame: past 36 months			
2		☒	
3		☒ **None**	
4		☒ **None**	
5		☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
6		☒ **None**	
7		☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid		
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
	or other services		
13	Other financial or non-financial interests		

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.