



THE ASEAN JOURNAL OF MILITARY AND PREVENTIVE MEDICINE

ISSN (e): 3031-870X  
ISSN (p): 3031-9447

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Volume 1 No.1, January 2024

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Published by:  
  
**Faculty of Military Medicine**  
Republic of Indonesia Defense University

Editorial Contact:  
Kawasan IPSC Sentul, Sukahati, Kec. Citeureup, Kabupaten Bogor, Jawa Barat 16810  
Email: admin@ajmpm.net | WhatsApp: +62 813-1486-7994



Volume 1 No.1, January 2024



  
**Faculty of Military Medicine**  
Republic of Indonesia Defense University



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Republic of Indonesia Defense University

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Volume 1 No.1 (2024)

JOURNAL OF MILITARY  
AND PREVENTIVE  
MEDICINE

THE ASEAN

Faculty of Military Medicine  
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Jakarta, 17 Januari 2024

Nomor : 3031870X/IL7.4/SK.ISSN/01/2024  
Hal. : SK Penerbitan ISSN No. 3031-870X

Kepada Yth,  
Pengelola/Pimpinan Redaksi  
"The ASEAN Journal of Military and Preventive Medicine"  
Universitas Pertahanan Republik Indonesia  
Kawasan IPSC Sentul, Sukahati, Kec. Citeureup, Kab. Bogor, Jawa Barat 16810  
Telp : -  
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**BADAN RISET DAN INOVASI NASIONAL**  
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**Judul** : The ASEAN Journal of Military and Preventive Medicine  
**ISSN** : 3031-870X (media online)  
Mula edisi Volume 1 Nomor 1, Januari 2024  
**Penerbit** : Universitas Pertahanan Republik Indonesia

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Jakarta, 19 Januari 2024

Nomor : 30319447/IL7.4/SK.ISSN/01/2024  
Hal. : SK Penerbitan ISSN No. 3031-9447

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Universitas Pertahanan Republik Indonesia  
Kawasan IPSC Sentul, Sukahati, Kec. Citeureup, Kab. Bogor, Jawa Barat 16810  
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**BADAN RISET DAN INOVASI NASIONAL**  
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Pusat Nasional ISSN (*International Standard Serial Number*) untuk Indonesia yang berpusat di Paris, dengan ini memberikan ISSN (*International Standard Serial Number*) kepada terbitan berkala di bawah ini :

**Judul** : Asean Journal of Military and Preventive Medicine  
**ISSN** : 3031-9447 (media cetak)  
Mula edisi Volume 1 Nomor 1, Januari 2024  
**Penerbit** : Universitas Pertahanan Republik Indonesia

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Volume 1 No.1 (2024)  
THE ASEAN JOURNAL OF MILITARY AND PREVENTIVE MEDICINE

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Email: [admin@ajpm.net](mailto:admin@ajpm.net) | WhatsApp: +62 813-1466-7994



ISSN 3031-870X



9 773031 870003

ISSN 3031-9447



9 773031 944001



# AJMPM

## JOURNAL INFORMATION

The ASEAN Journal of Military and Preventive Medicine is an open-access, peer-reviewed publication dedicated to the advancement of knowledge in the disciplines of military medicine, biodefense, global health, emergency medicine, and associated preventive medicine.

Our journal, as the foremost platform in ASEAN, provides an indispensable arena for researchers, practitioners, and academics to publish their most recent research findings, cutting-edge technology, and interdisciplinary ideas. While military medicine is our core emphasis, we encourage contributions from allied disciplines that hold translational potential and promise impact on medical practices, humanitarian aid, and other military operations.

### Peer-Review Policy

The ASEAN Journal of Military and Preventive Medicine has a strict peer-review mechanism in place. Expert reviewers with peer-review certification and knowledge in relevant academic fields assess submitted publications for originality, validity, and novelty. This procedure assists editors in assessing if a submission is suitable for publication, while maintaining the highest standards of scientific rigor and professional excellence.

Manuscripts are thoroughly reviewed by two or more professional reviewers to ensure scientific rigor, coherence, and originality. The peer-review process encourages objective evaluation and constructive criticism, which eventually improves the quality of published work.

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### Editorial Policies

Our renowned Editorial Board collaborates to develop the editorial policies of the ASEAN Journal of Military and Preventive Medicine. Manuscripts submitted to our journal are required to conform with the journal's editorial rules unless otherwise noted, in accordance with Indonesian legal and regulatory standards.

We invite researchers and scholars to submit their impactful research to the ASEAN Journal of Military and Preventive Medicine, contributing to the advancement of military medicine and preventive healthcare.



## — *Guide for Authors*

Our journal offers various article categories to cater to diverse research and clinical experiences:

### Review Articles

These encompass narrative, scoping, and systematic reviews, meticulously summarizing and integrating existing literature. The aim is to guide future policy and practice based on an in-depth understanding of current research. The Methods section should clearly outline the search strategy and inclusion/exclusion criteria. These articles should not exceed 5,000 words, accompanied by a structured 300-word summary.

### Case Reports

Describing noteworthy clinical cases, typically focusing on a single case, although occasionally presenting 2-3 similar cases. These reports should be limited to 2,000 words, with appropriate references based on the paper's length, capped at 20 references.

### Brief Reports

Presenting new research findings, pilot study data, replication studies, or innovative therapeutic interventions. These reports should encompass 3,000 words, up to 4 tables/figures, and a structured 300-word summary.

### Commentaries

A special category offering a platform for addressing vital and often controversial topics. Combining literature review, original data, and speculative synthesis, these articles should be insightful and not exceed 2,500 words. A thoughtful commentary can be enhanced with limited, pertinent references, typically not exceeding 30.



### Manuscript Format Guidelines

Font: Calibri

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Indentation: None

Titles/Subsections: Clear and Bold

Title Page: Include title, authors, affiliations, and corresponding author contact

Tables/Figures: Clear, labeled, and appropriately numbered

References: Follow the AMA citation style

### Ethics and Standards

We hold ourselves to high ethical and publication standards, aligning with the guidelines set by the Commission on Publication Ethics (COPE) and the International Committee of Medical Journal Editors (ICMJE). Our ethos mandates originality, transparency, and responsible conduct, ensuring the trustworthiness and integrity of the scholarly work published in our journal.

### Authorship and Originality

Authors should affirm that the manuscript is original, unpublished, and not under consideration elsewhere. Designating a corresponding author, who will act as the guarantor and primary correspondent with our editorial office, is vital. The corresponding author plays a crucial role in manuscript review, editing, and release of information.

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Transparency regarding any potential conflicts of interest, financial relationships, or affiliations that could influence the work or manuscript is paramount. Authors are required to provide full disclosure, enabling an informed editorial decision.

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Authors for whom English is not their native language are encouraged to seek language assistance to enhance the clarity and quality of their manuscript. Options include having a native English-speaking colleague review the manuscript or reaching out to our editors for language services.

Join us at the ASEAN Journal of Military and Preventive Medicine in advancing the understanding and practice of military medicine and preventive healthcare. We look forward to your contributions and the impactful discussions that will shape our field.



## Foreword



Dear Esteemed Colleagues and Contributors,

It is with great pleasure and anticipation that I extend my warmest greetings to each of you as we embark on a significant and transformative journey with the inaugural volume of the ASEAN Journal of Military and Preventive Medicine.

As we stand on the precipice of a new era, our collective consciousness has been irrevocably shaped by the profound impact of the global COVID-19 pandemic. The harsh reality we faced has illuminated the inadequacies in our preparedness and underscored the imperative for a united front in fortifying our defenses against

unforeseen threats. The experience has been a clarion call, compelling us, as nations within the ASEAN community, to reassess our strategies and fortify our collective resilience in the face of evolving challenges.

In response to this urgent need, the Faculty of Medicine at the Republic of Indonesia Defense University was established under the visionary leadership of our Defense Minister, Mr. Prabowo Subianto. The primary objective is to elevate the standard of healthcare in Indonesia and to proactively equip our nation with the knowledge and skills necessary to confront future pandemics. Our commitment is resolute: to position our university as a preeminent academic center dedicated to training future doctors who not only serve our nation but contribute meaningfully to the global pursuit of health and well-being.

The inception of the ASEAN Journal of Military and Preventive Medicine stands as a pivotal milestone in our journey. This publication represents a proactive measure to disseminate the latest advancements in military medicine and healthcare at large. We recognize the intrinsic value of education and knowledge as catalysts for progress, and through this platform, we aspire to foster a dynamic exchange of ideas that transcends borders and disciplines.



Our vision for this journal is ambitious yet rooted in the belief that collaboration is the cornerstone of progress. We envision the ASEAN Journal of Military and Preventive Medicine as a distinguished repository of cutting-edge research, facilitating dialogue and collaboration among researchers and healthcare professionals from both the civilian and military sectors across ASEAN countries. By forging strong partnerships, we aim to cultivate a sense of community that transcends geographical boundaries, fostering a shared commitment to advancing medical knowledge and practice.

As we embark on this intellectual voyage, I extend my heartfelt gratitude to all contributors and collaborators who share our vision. Your commitment to advancing the field of military and preventive medicine is integral to the success of this journal and, more importantly, to the well-being of our communities.

I am confident that the ASEAN Journal of Military and Preventive Medicine will emerge as a beacon of scholarly excellence, illuminating the path toward a future where the collective wisdom of our region contributes significantly to global health security.

Thank you for your dedication, and I eagerly anticipate the rich and impactful contributions that will shape the future volumes of this esteemed journal.

Sincerely,

**Lieutenant General Jonni Mahroza, PhD**

Rector of Republic of Indonesia Defense University



# Foreword

It is with great pleasure and a profound sense of accomplishment that I extend my heartfelt greetings to the esteemed readership of the ASEAN Journal of Military and Preventive Medicine. As the Dean of the Faculty of Medicine at the Republic of Indonesia Defense University, it is my distinct honor to introduce this inaugural edition, a testament to the collective effort of our dedicated faculty members.

In the pursuit of academic excellence and a commitment to advancing the field of military medicine, our faculty has taken a significant stride by establishing the ASEAN Journal of Military and Preventive Medicine. This endeavor reflects our unwavering dedication to fostering a platform for rigorous research and knowledge dissemination in the specialized domains of military healthcare.

As a practicing cardiologist and an active member of the Indonesian military armed forces, I am acutely aware of the importance of knowledge sharing cannot be overstated, and the imperative to constantly update our understanding of military medicine is paramount. This journal stands as a testament to our commitment to these principles. The ASEAN region has witnessed commendable advancements, not only in economic spheres but also in the healthcare sector, earning international recognition. It is our sincere hope that this journal serves as a portal, facilitating the exchange of groundbreaking research, innovative ideas, and best practices in military and preventive medicine. By fostering collaboration among ASEAN nations, we aim to contribute to the collective enhancement of healthcare capabilities and outcomes in the region.

I extend my deepest gratitude to all contributors, reviewers, and supporters who have played pivotal roles in the realization of this journal. Your dedication to advancing the knowledge frontier in military medicine is invaluable, and we look forward to the continued success of the ASEAN Journal of Military and Preventive Medicine. Together, let us strive for the continual improvement of healthcare and knowledge. May this journal be a beacon guiding us towards new horizons in military and preventive medicine.

**Major General Prihati Pujowaskito, MD, PhD, Cardiologist**

Dean of the Faculty of Military Medicine, Republic of Indonesia Defense University





## Editor Preface

We are delighted to inform you about the launch of an open-access journal, ASEAN Journal Military and Preventive Medicine. Our Journal will discuss about all in life in military medicine. From promotive, preventive, curative include rehabilitative in all phases. Various training must be undertaken to achieve becoming a perfect soldier and ready to combat. Life in the military entails numerous risks, from mild injuries to severe disabilities, and possibly casualties in the line of duty. To attain the readiness for combat and prevent injuries, one must maintain good physical and mental health.



We hope that this journal can serve as a platform for the works of researchers and authors in the fields of medicine and health, from genetic and molecular systems to the holistic development of individuals. All facilities that can support health, leading to the creation of resilient warriors, are open for consideration.

As the Editor-in-Chief, I hope that this journal can become a reference and be embraced by scholars, researchers, authors, warriors, and clinicians in the field of health sciences.

Best regards,  
Editor in chief

**Lieutenant Colonel Endang Ernandini, MD (Medical Rehabilitation), PhD**



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## Human PPARG Gene Mutation as Risk Factor for Type 2 Diabetes Melitus: In Silico Analysis

Naufal Yafi Rais Wiguna<sup>1\*</sup>, Taufik Hidayat B<sup>1</sup>, Putrya Hawa<sup>1</sup>, Jonny<sup>1,2,3</sup>

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### Abstract

**Introduction:** Type 2 diabetes (T2DM) involves genetic and environmental factors. PPARG, encoding peroxisome proliferator-activated receptor gamma, is one of the key gene in T2DM development. Our study investigates PPARG variants' role as risk factor for T2DM by in silico analysis.

**Methods:** We identified Single Nucleotide Polymorphisms (SNPs) within the PPARG gene via UniProt and analyzed their effects using Ensembl Variant Effect Predictor (VEP). The VEP analysis provided us four important indicators: impact assessment, Sorting Intolerant from Tolerant (SIFT) score, PolyPhen score, and clinical significance. We also investigated PPARG's interactions with other T2DM-related genes using StringDB.

**Results:** In our analysis of 35 UniProt-sourced SNPs, 32 underwent successful VEP analysis. The SIFT indicators identified 23 of SNPs as deleterious, The PolyPhen identified 18 of SNPs as probably damaging. Impact assessments revealed that 27 had a moderate impact on gene function. Clinically, 8 of the SNPs were considered pathogenic and rs1805192 emerged as a notable risk factor for T2DM. Additionally, StringDB analysis confirmed PPARG's role in the T2DM-associated gene network, from the 25 proteins involved in T2DM, 21 of them exhibit correlations with PPARG.

**Discussion:** PPARG SNPs variant has a significant impact on T2DM as a risk factor. However, SNPs associated with T2DM vary across different populations.

**Conclusion:** Analysis of PPARG genetic variations highlights their significant association with T2DM susceptibility in specific populations. Bioinformatics tools are useful for investigating genetic mutations but require additional research, such as functional studies, to improve reliability as their outcomes are primarily predictions.

**Keywords:** Type 2 Diabetes Melitus, PPARG, Bioinformatics, In Silico, SNPs

### Introduction

Diabetes melitus, particularly Type 2 Diabetes Melitus (T2DM), represents a significant global health challenge. Globally, diabetes affects an estimated 462 million individuals,<sup>1,2</sup> posing a substantial burden on healthcare systems and communities worldwide. In addition to its prevalence, diabetes-related complications contribute significantly to morbidity and mortality rates globally, warranting continuous research and intervention strategies.<sup>2-4</sup>

At a national level, Indonesia faces a burgeoning diabetes crisis, with approximately 19 millions adults have T2DM.<sup>3</sup> The rising prevalence of diabetes in Indonesia is a grave concern, accentuated by various socioeconomic factors, lifestyle changes, and limited access to adequate healthcare, making it a pressing national health issue.<sup>5-8</sup> Understanding the

intricate dynamics of diabetes within the Indonesian context is imperative to devise effective preventive measures and treatment strategies.

Peroxisome proliferator-activated receptor gamma (PPARG), a pivotal gene involved in metabolic regulation, has garnered attention in diabetes research due to its significant role in T2DM pathogenesis.<sup>9-13</sup> PPARG's impact on the Insulin Resistance pathway, as revealed by Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway analysis, underscores its relevance in understanding the molecular mechanisms underlying T2DM development. Furthermore, the strong association highlighted by Malacard between PPARG and T2DM reinforces the importance of investigating PPARG variants in elucidating T2DM susceptibility and progression.

The rationale behind this manuscript stems from the dearth of comprehensive reviews examining the entirety of PPARG single nucleotide polymorphisms (SNPs) and mutations correlated with T2DM. This review aims to consolidate existing knowledge on PPARG variations and their intricate associations with T2DM, providing a comprehensive resource for researchers and clinicians. By synthesizing available data and exploring the uncharted landscape of PPARG variants in the context of T2DM, this manuscript strives to offer novel insights that could potentially impact future research directions and clinical management strategies for this prevalent metabolic disorder.

## Methods

### Searching the database for Single Nucleotide Polymorphisms (SNPs)

We obtained the SNPs database from Uniprot (<https://www.uniprot.org/>) and conducted a search using "PPARG" as our query term. To refine our results, we applied the Clinical Variant filter. We selected this gene due to its relevance to T2DM and its potential as a treatment target.

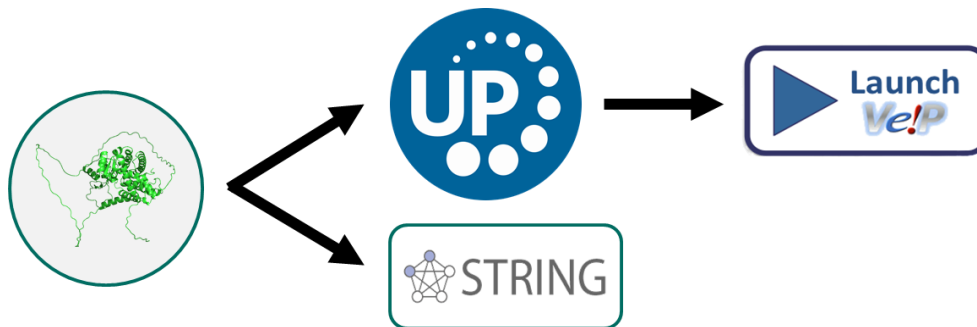
### Evaluating of coding SNPs

We uploaded the reference sequences of all the SNPs into VEP (<http://asia.ensembl.org/Tools/VEP>) and concentrated on four key indicators: impact assessment, Sorting Intolerant from Tolerant (SIFT) score, PolyPhen score, and clinical significance. Our objective was to assess and predict the potential impact of these SNPs.

### Outline gene-gene interactions

We conducted an analysis of gene-gene interactions to identify potential genes associated with T2DM for future research. For this purpose, we used Stringdb (<https://string-db.org/>), a tool that identifies genes related to a specific disease by utilizing an extensive dataset of functional associations. We entered T2DM as our query disease and the website generated a network of genes along with their gene-gene interactions, according to gene

ontology terms.



## Results

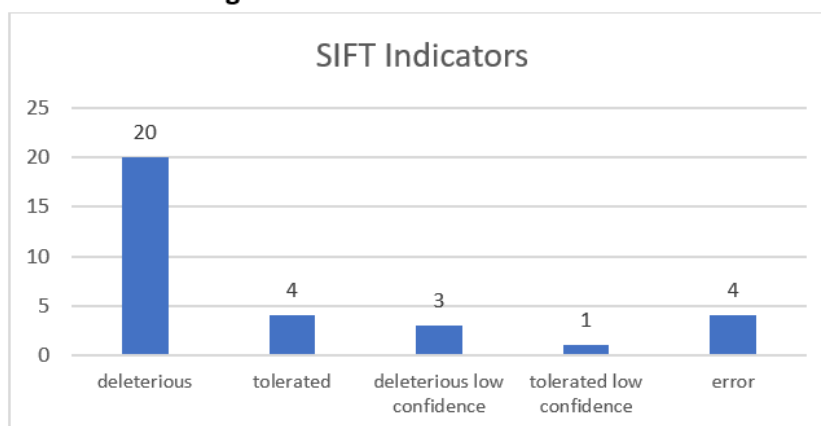
### VEP

In our analysis of 35 UniProt-sourced SNPs, 32 underwent successful VEP analysis. In SIFT indicators, there are 23 SNPs identified having a SIFT score less than 0.05. These SNPs are categorized as deleterious. Meanwhile, there are 5 SNPs categorized as tolerated which means the SNPs have a score above 0.05. Of all of the SNPs, there are at least 4 of the SNPs have low confidence, which means the median info of the SNPs is higher than 3.25. Also, there are at least 4 SNPs categorized as errors.

**Table 1. SIFT Score categorization**

SIFT Value	Qualitative Prediction
Less than 0.05	“Deleterious”
	“Deleterious – low confidence”
More than 0.05	“Tolerated”
	“Tolerated – low confidence”

**Figure 1. Results of SIFT Indicators**

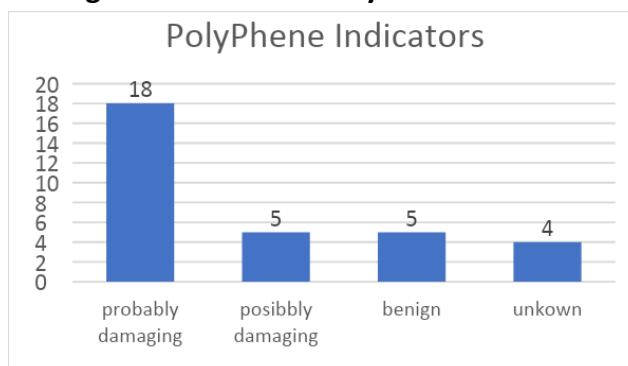


In PolyPhen indicators, 18 SNPs are categorized as probably damaging, which means the SNPs have PolyPhen values greater than 0.908. Then, there are 5 of the SNPs that are categorized as possibly damaging—the PolyPhen value is greater than 0.446 and less than or equal to 0.908. There are also 5 SNPs categorized as benign (PolyPhen value less than or equal to 0.446). From all 32 SNPs, there are 4 SNPs identified as unknown or error.

**Table 2. PolyPhen value categorization**

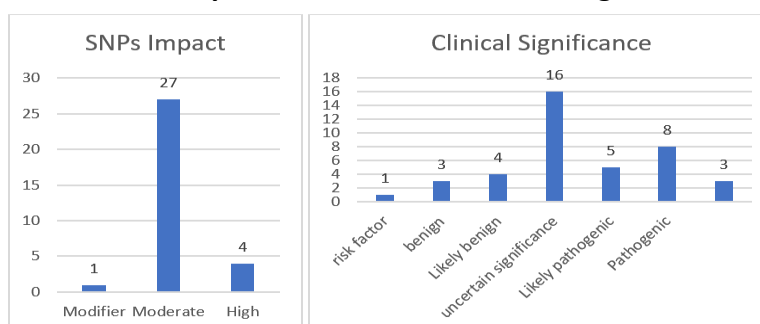
PolyPhen Value	Qualitative Prediction
Greater than 0.908	“Probably Damaging”
Greater than 0.446 and less than or equal to 0.908	“Possibly Damaging”
Lees than or equal to 0.446	“Benign”
Unknown	“Unknown”

**Figure 2. Results of PolyPhen Indicators**



Impact assessments revealed that there are at least 4 of SNPs that had a high impact, 27 of SNPs had a moderate impact, and 1 of SNPs had a modifier impact on gene function and structure. Clinically, 8 of the SNPs were considered pathogenic, and at least 5 of the SNPs are considered to be likely pathogenic. Around 3 of the SNPs are benign, and 4 of the SNPs are likely to be benign. Still, there are 16 of the SNPs that has uncertain significance. One of the SNP that has a high correlation with T2DM is rs1800571.

**Figure 3. Results of Impact Indicators and Clinical Significance Indicators**



**Table 3. Result of the PPARG's SNPs analysis using VEP**

PPARG Variant	Consequence	Position(s)	Change	IMPACT	SIFT	PolyPhen	Clinical Significance
rs1801282	intron variant	12	P>A	MODIFIER	deleterious low confidence	benign (0)	benign, likely benign
rs1805192	missense variant	40	P>A	MODERATE	deleterious low confidence (0.02)	benign (0.131)	risk factor
rs762280243	missense variant	47	S>Missing	MODERATE	deleterious low confidence (0)	possibly damaging (0.893)	uncertain significance, likely benign
rs777334819	missense variant	49	D>A	MODERATE	tolerated low confidence (0.17)	benign (0.039)	uncertain significance, likely benign
rs1800571	missense variant	79	E>K	MODERATE	deleterious (0)	probably damaging (0.999)	pathogenic
rs1553643326	missense variant	113	P>Q	MODERATE	deleterious (0)	probably damaging (1)	likely pathogenic
rs1553645235	missense variant	157	E>G	MODERATE	deleterious (0.02)	probably damaging (1)	uncertain significance
rs1211829538	missense variant	161	G>V	MODERATE	deleterious (0.01)	probably damaging (0.969)	uncertain significance
rs587776687	frameshift variant	174	D>G	HIGH	-	-	-
rs121909245	missense variant	186	S>Missing	MODERATE	deleterious (0.02)	probably damaging (1)	pathogenic
rs148195788	missense variant	190	C>S	MODERATE	deleterious (0)	probably damaging (1)	likely pathogenic
rs1553647989	missense variant	194	R>Q	MODERATE	deleterious (0)	probably damaging (0.996)	likely pathogenic
rs150296212	missense variant	240	R>Q	MODERATE	tolerated (0.07)	probably damaging (0.974)	uncertain significance, likely benign
rs1176746892	missense variant	308	R>C	MODERATE	deleterious (0.02)	benign (0.328)	uncertain significance
rs2051075084	missense variant	310	F>S	MODERATE	deleterious (0)	probably damaging (0.994)	uncertain significance
rs121909242	missense variant	314	Q>P	MODERATE	deleterious (0.01)	probably damaging (0.995)	pathogenic
rs28936407	missense variant	316	R>H	MODERATE	deleterious (0)	probably damaging (0.958)	pathogenic

## Human PPARG Gene Mutation as Risk Factor for Type 2 Diabetes Melitus: In Silico Analysis

Naufal Yafi Rais Wiguna, Taufik Hidayat B, Putrya Hawa, Jonny

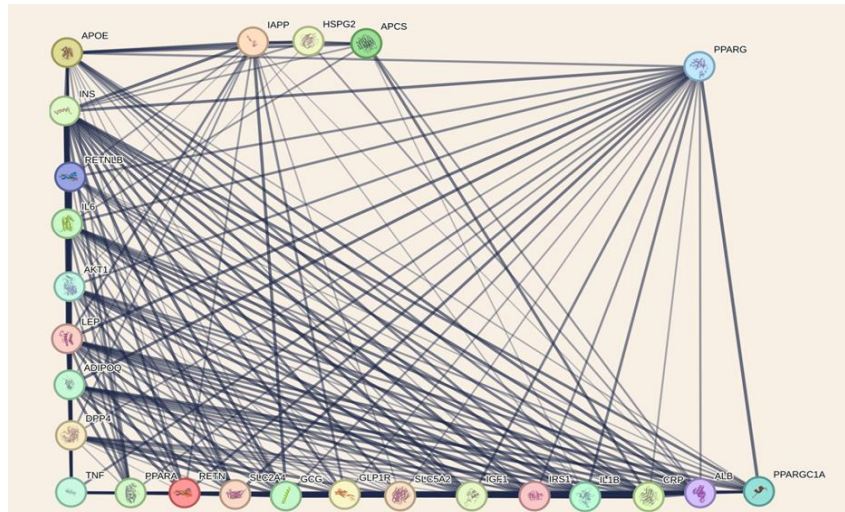
rs72551362	missense variant	318	V>M	MODERATE	deleterious (0)	possibly damaging (0.854)	pathogenic
rs1378972597	missense variant	324	I>T	MODERATE	deleterious (0)	probably damaging (0.988)	benign, uncertain significance
rs139894525	missense variant	335	V>L	MODERATE	tolerated (0.09)	benign (0.015)	benign, uncertain significance
rs1553650477	frameshift variant, 3 prime UTR variant	338	D>Missing	HIGH	-	-	-
rs121909243	stop gained variant	347	K>*	HIGH	-	-	pathogenic
rs530007199	missense variant	352	E>K	MODERATE	deleterious (0)	probably damaging (0.997)	uncertain significance
rs1553650533	missense variant	379	E>K	MODERATE	deleterious (0)	probably damaging (0.986)	uncertain significance
rs72551363	missense variant	388	F>L	MODERATE	deleterious (0)	probably damaging (0.976)	pathogenic
rs886057902	missense variant	402	F>L	MODERATE	deleterious (0)	possibly damaging (0.76)	uncertain significance
rs1437186245	missense variant	432	K>N	MODERATE	deleterious (0.01)	possibly damaging (0.451)	uncertain significance
rs587780424	missense variant	450	K>Q	MODERATE	tolerated (0.58)	possibly damaging (0.835)	uncertain significance
rs1553653993	missense variant	451	L>P	MODERATE	tolerated (0.09)	probably damaging (0.996)	likely pathogenic
rs770557781	frameshift variant	454	P>Missing	HIGH	-	-	-
rs756523051	missense variant	462	K>R	MODERATE	deleterious (0.03)	probably damaging (0.995)	uncertain significance
rs121909244	missense variant	495	P>L	MODERATE	deleterious (0)	probably damaging (0.997)	uncertain significance, pathogenic, likely pathogenic

### StringDB

Additionally, StringDB analysis found from the 25 proteins involved with PPARG, 21 of them exhibit direct correlations with PPARG. Notably, the highest correlation scores were found between PPARG with Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 Alpha PPARGC1A (0.9999) and adiponectin ADIPOQ (0.965). Whereas the protein with the

lowest correlation with PPARG is Solute Carrier Family 5 Member 2 SLC5A2.

**Figure 4. StringDB analysis of PPARG**



**Table 4. Correlation score of protein correlated with PPARG**

No.	Corellation	Score
1.	PPARGC1A	0,999
2.	ADIPOQ	0,965
3.	LEP	0,948
4.	INS	0,944
5.	SLC2A4	0,934
6.	RETN	0,858
7.	IL1B	0,858
8.	IGF1	0,828
9.	IL6	0,82
10.	TNF	0,807
11.	AKT11	0,79
12.	RETNLB	0,782
13.	APOE	0,74
14.	IRS1	0,726
15.	GCG	0,687
16.	ALB	0,682
17.	PPARA	0,647
18.	DPP4	0,623
19.	GLP1R	0,58
20.	CRP	0,578
21.	SLC5A2	0,546

## Discussions

The results indicate that genetic variations in PPARG can have consequences on T2DM susceptibility. PPARG is a gene that encodes the peroxisome proliferator-activated receptor gamma, which plays a role in regulating the expression of genes involved in glucose metabolism and lipid homeostasis. Genetic variations in PPARG can affect its normal function, leading to imbalances in metabolic regulation.<sup>14</sup> PPARG is also plays a crucial role in adipocyte differentiation, maintenance, and function. Genetic elements significantly impact an individual's vulnerability to the onset of Type 2 Diabetes (T2D). Variations in genetic polymorphisms can heighten or diminish the risk of developing this condition.<sup>15</sup>

We are focusing in 4 indicators include, sift analysis, polyphen analysis, impact and clinical significance. SIFT provides a method to assess the potential impact of amino acid substitutions on protein function by analyzing sequence conservation and diversity. Positions predicted as deleterious are likely to be functionally important, while tolerated positions may have more flexibility in terms of sequence variation.<sup>16,17</sup>

In our analysis, Pro115Gln (rs1800571, G>T), One mutation leads to translation of a Glutamine instead of an proline at position 115, and the mutant residue is predicted as deleterious in SIFT analysis .The rs1800571 mutation is a gain-of-function mutation associated with morbid obesity. It has been primarily identified in a small number of cases within the German population, and there appears to be an association with type 2 diabetes in some affected individuals.<sup>18</sup> However, the rarity of the mutation and its absence in certain populations suggest that its prevalence vary among different ethnic groups or regions.<sup>19</sup>

PolyPhen-2 is a comprehensive tool that utilizes machine learning and various biological data sources to predict the impact of amino acid substitutions on human protein stability and function. The prediction outcomes and scores provide valuable information for assessing the potential damaging effects of genetic variations.<sup>20</sup> Our polyphen analysis identified rs121909244 as probably damaging (0,997) . The rs12190924,4 variant led to the replacement of a Proline (wild type) with Leucine (mutant) at positions 467 and 473. The mutant Leucine residue, being larger than the wild-type Proline, disrupts the unique backbone conformation induced by Prolines, potentially affecting the required structural integrity at this position. This mutation may disturb the specific conformation due to the rigid nature of Prolines. Furthermore, as the larger Leucine is situated on the protein's surface, its mutation could interfere with interactions with other molecules or different regions of the protein.<sup>21</sup>

Identifying rs1805192 as a risk factor could present opportunities for developing targeted therapies or prevention strategies for individuals with this variant. Understanding the specific impact of this genetic variant in rs1805192 can aid in designing more effective approaches to manage or prevent Type 2 Diabetes (T2DM). In a study Chinese Han population, *Xiaohui Lv et.al* revealed a significant association between the risk of type 2 diabetes (T2DM) and the rs1805192-G allele in individuals. Individuals carrying the rs1805192-G allele exhibited a significantly higher risk of developing T2DM compared to those

with other alleles.<sup>22</sup> Moreover, *Purabi et.al* suggested that no involvement of the rs1805192 variant (PPAR $\gamma$ 2) in conferring susceptibility to type 2 diabetes (T2D) in the North East Indian population.<sup>23</sup>

Our results from StringDB showed that PPARG interacts with a lot of genes (Figure 2), mainly functioning to control gluconeogenesis and maintain glucose homeostasis. PPARG, alongside PPARGC1A, also correlated with T2DM.<sup>24</sup> These results were also proved by text-mining ([DOI:9352](#)), which showed that mutations in PPARG lead to T2DM.

### Conclusion

The analysis of PPARG genetic variations revealed significant insights into their association with T2DM susceptibility in specific populations. The use of bioinformatics tools can be powerful, particularly in investigating genetic mutations. However, the outcomes of these bioinformatics tools are mostly limited to only predictions and, therefore need further research, such as functional studies, to enhance its reliability.

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## Introducing the Camry Electronic Hand Dynamometer EH101 as a Functional Strength Measurement Tool among Healthy Teenagers in Jakarta, Indonesia

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### Abstract

Hand grip strength (HGS) is correlated with activities of daily living (ADL) and is intricately related to lung function. The American College of Sports Medicine recommends incorporating hand grip strength tests as a component of musculoskeletal fitness assessment for children. The hydraulic Jamar dynamometer, developed by Bechtol in 1954, is the most widely used tool among clinicians for measuring HGS. Currently, the widely available HGS measurement tool in Indonesia is the Camry electronic hand dynamometer EH101. This study aimed to introduce a new tool, known for its easy accessibility and affordability. An analytical observational design with a cross-sectional method. 19 males and 19 females, aged between 12–18 years, in one junior high school and one senior high school in Central Jakarta, who find inclusion criterias. There were differences of the results between both tools for all parameters. However, we detected consistency in term of the values of measurements. When the Jamar<sup>®</sup> measured a lower result than the other parameter, the Camry<sup>®</sup> would measure the same. A significant correlation between both values, as measured by Camry<sup>®</sup> and Jamar<sup>®</sup> (>0.7) that might be interpreted as a strong correlation of statistical significance. Camry EH101 had a significant correlation with Jamar, indicating consistency in measurements despite observed value gaps. While the Camry holds promise for use in Indonesia due to its affordability and accessibility, further investigation is warranted. It is recommended to calculate sensitivity and specificity of the Camry, considering its unique cut-off points for clinical application.

**Keywords:** Camry Electronic, Hand Dynamometer EH101, Measurement Tool, Healthy Teenagers

### Introduction

Physical medicine and rehabilitation constitute medical disciplines that evaluates function.<sup>1</sup> Among the parameters assessed, hand function, specifically hand grip strength (HGS), holds clinical significance.<sup>2</sup> HGS is correlated with activities of daily living (ADL) and is intricately related to lung function.<sup>3</sup> Its predictive power and simplicity make it a suitable choice for preventive measures and therapeutic interventions.<sup>4</sup> Several previously published articles advocate the use of HGS as a crucial test for examinations, often deemed a significant indicator for screening purposes.<sup>5</sup>

The hydraulic Jamar dynamometer, developed by Bechtol in 1954, is the most widely used tool among clinicians for measuring hand grip strength.<sup>6</sup> The measurement of grip

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strength using Jamar has high reliability with a correlation coefficient of 0.80 or higher. Various studies have reported re-test reliability values, with coefficients ranging around  $r = 0.90$ .<sup>7,8</sup>

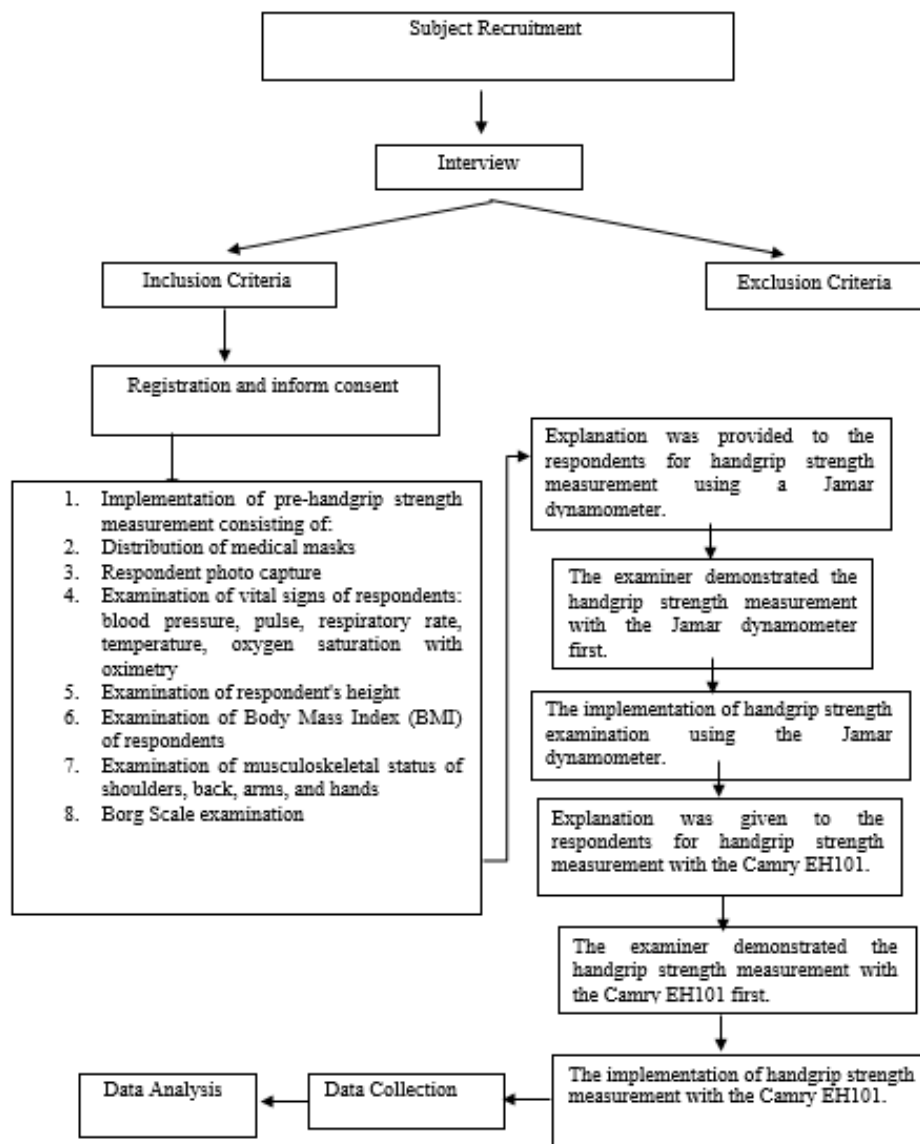
Currently, the widely available HGS measurement tool in Indonesia is the Camry electronic hand dynamometer EH101. The manual specifies a tolerance accuracy of  $\pm 0.5$  kg/1 lb. However, the reliability and validity of this tool for measuring HGS have not been examined in Indonesia. This study aims to examine the reliability and validity of the Camry electronic hand dynamometer EH101 compared to the internationally accepted Jamar hydraulic dynamometer. The objective is to popularize HGS measurements in Indonesia, owing to the tool's affordability and accessibility while upholding satisfactory reliability.

## **Method**

This study employs an analytical observational design with a cross-sectional method. The study was conducted in one junior high school and one senior high school in Central Jakarta. The sample size required for the study was determined to be 38, evenly distributed into two groups of 19 males and 19 females. Inclusion criteria encompassed individuals aged between 12–18 years, absence of musculoskeletal disorders in the shoulders, back, arms, and hands, normal body mass index (BMI), and overall good health. Exclusion criteria include inability to understand research technical instructions, complaints related to muscle or joint pain, including history of fractures, muscle pain, muscle weakness, shortness of breath, fever, or any subjective or objective complaints before the test. The tools and materials used in this study include: (1) an explanation and consent form for participation in the research; (2) research status form; (3) body weight scale; (4) stethoscope; (5) blood pressure monitor; (6) Jamar hydraulic hand dynamometer; (7) Camry electric hand dynamometer EH101; (8) Goniometer.

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Hand grip strength was measured using the Jamar hydraulic hand dynamometer and Camry electric hand dynamometer EH101. Subjects were instructed to sit upright on a chair with back support, utilizing the chair's armrests with both feet flat on the floor. Shoulders were adducted and in a neutral position, elbows flexed at 90 degrees, the forearm placed on the armrest with the wrist at the edge of the armrest in a neutral position, and the wrist in extension between 0-30 degrees. Subjects were instructed to clean their hands with hand sanitizer and then grip the dynamometer with fingers encircling the handle comfortably. Subjects were instructed to exert a maximum isometric effort held for 3 seconds. During the measurement, the researcher and subject maintain a distance of 1 meter. Measurements are taken on the dominant hand, and repeated three times with a 1-minute rest between measurements. After completion, the patient cleaned their hands with hand sanitizer, and

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the hand grip tool was sanitized using alcohol. The best measurement value obtained was utilized for statistical analysis, HGS measurements were evaluated with values adjusted for gender and BMI.

Ethical clearance for this study was obtained from the Research Ethics Committee of University of Indonesia affiliated Cipto Mangunkusumo Hospital with approval number: KET-1421/UN2.F1/ETIK/PPM.00.02/2020.

All data are processed using the IBM SPSS for Windows version 20 computer program. Data analysis involved assessing the basic characteristics of research subjects, instrument validity, and reliability. Univariate analysis was performed to observe the uniformity of research subjects. Validation tests were conducted by examining the consistency of items and scales measured through Spearman correlation tests. Correlation involved measuring twice, during inspiration and expiration using the Camry electric hand dynamometer EH101. Inter-rater testing involved the same measurement but using the Jamar hydraulic hand dynamometer.

## Results

Data collection took place in 2020 during the COVID 19 pandemic, necessitating a meeting point in a residency. Invitations to be included in the study were extended to all students from both schools, resulting in response from 61 students, all of whom met the inclusion criteria, and did not meet the exclusion criteria. Consequently, they were all accepted to participate after signing the informed consent. Further details regarding the subjects are provided in Table 1. All data were presented as mean and range of the collected variables.

**Table 1. Subjects' Characteristics**

Variables	Subjects (n=61)
Age (years)	15 (12-18)
Gender, n (%)	
- Female	31 (50.8%)
- Male	30 (49.2%)
Body weight (kg)	51.8 (39.9-69.7)
Body height (cm)	158 (145-178)
Body mass index (kg/m <sup>2</sup> )	20 (17.9-22.8)

Male and female participants had approximately similar proportions with average BMI which is considered as normal.

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**Table 2. Hand grip strength value**

Variable	Value
Jamar <sup>®</sup> dynamometer	
Dominant hand, Inspiration (kg)	20 (8-48)
Dominant hand, Expiration (kg)	20 (8-46)
Non-Dominant hand, Inspiration (kg)	20 (6-46)
Non-Dominant, Expiration (kg)	19 (6-48)
Camry EH101 <sup>®</sup>	
Dominant hand, Inspiration (kg)	14.6 (6,4-26,5)
Dominant hand, Expiration (kg)	14.6 (6.4-26.5)
Non-Dominant hand, Inspiration (kg)	12.7 (5.7-24.1)
Non-Dominant, Expiration (kg)	11.7 (5.7-24.4)

There were differences of the results between both tools for all parameters. However, we detected consistency in term of the values of measurements. When the Jamar<sup>®</sup> measured a lower result than the other parameter, the Camry<sup>®</sup> would measure the same.

**Table 3. Correlation of Hand grip strength measurement between using Camry and Jamar<sup>®</sup>**

Variable	Correlation coefficient (r)	P value
Jamar <sup>®</sup> dynamometer		
Camry EH101 <sup>®</sup>		
Dominant hand, Inspiration (kg)	0.772	<0.001
Dominant hand, Expiration (kg)	0.776	<0.001
Non-Dominant hand, Inspiration (kg)	0.835	<0.001
Non-Dominant, Expiration (kg)	0.797	<0.001

Table 3 demonstrates a significant correlation between both values, as measured by Camry<sup>®</sup> and Jamar<sup>®</sup> (>0.7) that might be interpreted as a strong correlation of statistical significance.

## Discussion

This study aimed to introduce a new tool, known for its easy accessibility and affordability. The findings demonstrated a significant correlation, between the standard Jamar dynamometer and the new Camry tool. However, disparities in values were observed, prompting consideration of potential internal mechanisms within the measurement tools or variations arising from subjects, potentially influenced by fatigue during consecutive measurements.

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Muscle strength plays a pivotal role in adolescent development, forming the foundation for social development. Concerns about declining muscle strength in adolescents nowadays have been raised, attributed to reduced physical activity and increased engagement in indoor activities involving electronic devices, leading to diminished utilization of muscle mass.<sup>9</sup>

HGS involves the coordinated movement of several hand and forearm muscles, forming maximal flexion of all finger joints.<sup>10</sup> This serves as an indicator of hand and forearm muscle performance, muscle mass, overall physical performance, and a functional index of nutritional status.<sup>10,11</sup> Recognizing its importance, the American College of Sports Medicine recommends incorporating hand grip strength tests as a component of musculoskeletal fitness assessment for children.<sup>12</sup> Variability in HGS among individuals is influenced by factors such as gender, age, and body size, including weight, height, and anthropometrics of the five fingers.<sup>10,11,13</sup> Moreover, all flexor muscles of the hand and forearm are closely anatomically, physiologically, and biomechanically related to each other in performing tasks.<sup>10</sup>

There are two types of gripping activities: power grip, relying on strength, and precision grip, relying on accuracy. Power grip is used when an object needs to be held with full force while in motion (e.g., holding a hammer or a doorknob). At this point, isometric contraction occurs, and fingers flex around the object in the same direction as the thumb but in the opposite direction. The flexor and extensor muscles of the fingers grip in a neutral or slightly extended position. When the gripping process involves the thumb, it causes adduction movement. Precision grip is used when holding an object with smooth movements, such as holding a pen or sewing with a needle.<sup>14</sup>

Hand grip strength can be measured using static hand strength that can grip a dynamometer. This force is commonly measured in kilograms and pounds but can also use mercury milliliters and Newtons. Various methods determine patient positioning during measurement and calculate grip strength results from repeated measurements, prompting the American Society for Surgery of Hand and the American Society of Hand Therapists to establish standards for positioning, instructions, and grip strength calculations.<sup>15</sup>

Hand grip strength provides an objective overview of upper limb functional integrity. Additionally, hand grip strength has long been used to measure muscle strength and has shown a correlation with physical fitness, including body composition, energy expenditure, aerobic strength, lower limb strength, speed, flexibility, agility, and sit-up performance.<sup>16</sup>

Low muscle strength, as determined by a dynamometer, is a marker of poor health during adolescence and is associated with diseases and adult mortality. Epidemiological studies indicate that muscle weakness is linked to a higher risk of adverse health conditions, including obesity, systemic inflammation, and insulin resistance. A recent meta-analysis highlights the importance of improving muscle strength in youth for health-related benefits in the young population.<sup>17</sup>

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Analysis of hand grip strength by gender shows higher grip strength in males at all ages, with peak grip strength occurring in the fourth decade, followed by a gradual decline for both genders. This trend persists even when some studies categorize subjects by gender, age, and then by right and left hands, while a small number of studies categorize subjects by gender, age, and then by dominant and non-dominant hands.<sup>15</sup> Andrade Fernandes et al in 2014 emphasized the importance of obtaining grip strength reference values from different countries, as different ethnicities have been shown to have different grip strengths. In another study by Woo et al in 2014, significant variations in average grip strength were found between Asian ethnic groups and among the same ethnic groups living in various geographic locations.<sup>18</sup>

Hand grip strength measurements using the Camry dynamometer displayed high level of agreement with Jamar® in all conditions (r values greater than 0.7).

A test can be said to have high validity if the test performs its measurement function or provides accurate and precise measurement results according to the intended purpose of the test. The testing technique often used by researchers for validity tests is using Pearson Bivariate correlation (Pearson Product-Moment)

In this study, it can be seen that the results of hand grip strength measurements using the Jamar tool compared to the Camry tool showed a gap of the values from the measurements. This is however, remaining the limitation of this study, since we did not give sufficient resting time in between two measurements. Further, the study did not calculate sensitivity and specificity of the new tool. Each tool has its own cut-off point, necessitating further investigation.

### **Conclusion**

Camry EH101 had a significant correlation with Jamar, indicating consistency in measurements despite observed value gaps. While the Camry holds promise for use in Indonesia due to its affordability and accessibility, further investigation is warranted. It is recommended to calculate sensitivity and specificity of the Camry, considering its unique cut-off points for clinical application.

### **Disclaimer**

The study had no conflict of interest. The authors did not receive sponsors from any of both brands.

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## Heat Therapy Intervention and Pulse Dose Itraconazole as Combination Treatment for Chromoblastomycosis: An Unusual Case Report

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### Abstract

Chromoblastomycosis (CBM) is a rare chronic fungal infection caused by dematiaceous fungi, presenting a significant challenge in Indonesia. This case involves a 54-year-old man who reported a lump on his right leg persisting for 10 years. Examination revealed multiple erythematous nodules with well-defined borders and a verrucous surface, forming a linear pattern around the ankle, some covered by brownish crusts. The patient denied itching and pain in the lesions. The initial diagnosis of chromoblastomycosis was confirmed through culture and histopathology. Treatment involved pulsed doses of itraconazole and heat therapy. Remarkably, lesions significantly improved after one month, underscoring the efficacy of combination therapy for chromoblastomycosis. Pulsed dose itraconazole enhances treatment compliance with its cost-effectiveness, while heat therapy, as a physical intervention, proves to be an easily administered option with promising efficacy. Considering the prolonged management required for CBM, it is imperative to factor in the patient's socioeconomic condition during treatment planning.

**Keywords:** chromoblastomycosis, heat therapy, itraconazole pulse dose, case report

### Introduction

Chromoblastomycosis, a chronic fungal infection affecting the skin and subcutaneous tissue, is primarily attributed to pigmented dematiaceous fungi introduced into the dermis from environmental sources.<sup>1,2</sup> Fungi within the Dermateaceae family are the main culprits behind these infections.<sup>3,4</sup> Notably, this disease exhibits a prevalence exceeding 70% in tropical and subtropical regions, with Madagascar recording the highest prevalence. Additionally, observed cases are notable in Latin America, Asia, Oceania, and select European countries.<sup>5,6,7</sup>

Clinically, the onset of chromoblastomycosis often follows trauma, leading to the inoculation of the causative fungus.<sup>3,8</sup> Manifesting with diverse features, the initial lesion typically presents as a slowly spreading verrucous papule. A definitive diagnosis relies on the presence of muriform cells in the tissue and the isolation of the causative agent through culture examination.<sup>1,2,5,6,7</sup>

Managing chromoblastomycosis poses challenges for clinicians, particularly in severe and recalcitrant cases. Treatment modalities include physical therapy, chemotherapy, and

combination therapy.<sup>7</sup> Notably, heat therapy emerges as a conventional yet effective alternative among physical therapies, frequently employed as an adjuvant therapy in chromoblastomycosis.

This paper presents a compelling case of chromoblastomycosis treated with pulsed dose itraconazole in combination with heat therapy. The case not only outlines the diagnostic approach but also underscores the significance of employing appropriate and affordable treatment modalities in managing this challenging fungal infection.

### **Case Presentation**

A 54-year-old Southeast Asian male presented to the outpatient clinic with a chief complaint of a lump on his right leg, a condition persisting for approximately 10 years. Throughout his adolescence and adult life, the patient worked as a farmer in an outdoor setting, often without wearing footwear. Initially attributing his skin condition to minor injuries caused by grass or wood branches during garden work, the patient noted that these scratches would heal but gradually transformed into painless, persistent, small nodules. These nodules progressed in size, thickness, and surface alterations. Notably, the patient denied experiencing significant weight loss, prolonged cough, night sweats, or any other systemic diseases.

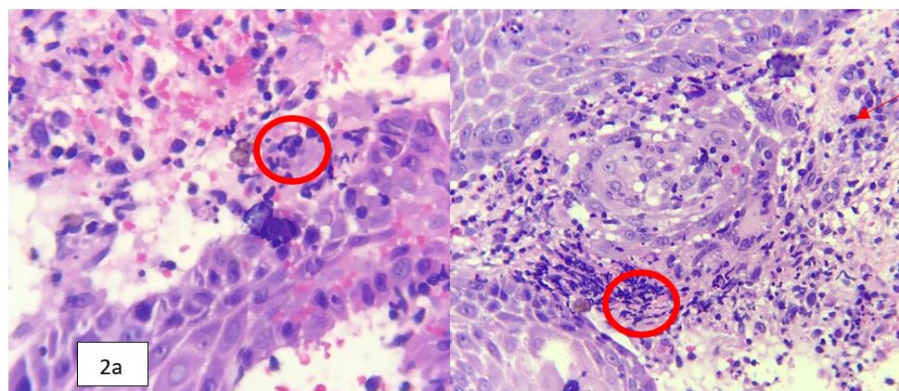
Dermatological evaluation of the distal right leg revealed multiple erythematous nodules with well-defined borders, oval to round in shape, measuring 1.5 to 2.5 cm in diameter. The nodules' surface exhibited a verrucous appearance, and several lesions demonstrated a linear pattern around the patient's ankle, as illustrated in Figures 1a-1d. Additionally, scattered dry erosions covered with brownish and dark crusts, measuring 0.1 to 0.3 cm in diameter, were observed in some areas, as depicted in Figures 1b and 1d.





**Figures 1a-1d.** The lesion on the right ankle appears to form a linear growth pattern towards the patient's healthy skin with a verrucous surface nodule.

The KOH examination of skin scrapings did not reveal sclerotic, muriform cells, or fungal elements. Nevertheless, histopathological examination of the skin biopsy tissue, utilizing hematoxylin and eosin (HE) staining, indicated the presence of golden-brown, thick-walled round cells around the granuloma and abscess area, as illustrated in Figure 2. No evidence of tuberculoid granuloma, characteristic of mycobacterial lesions, or squamous cell carcinoma was found, leading to the exclusion of these possibilities. Consequently, the histological morphological features of the lesions on the patient's right ankle were consistent with the diagnosis of chromoblastomycosis.

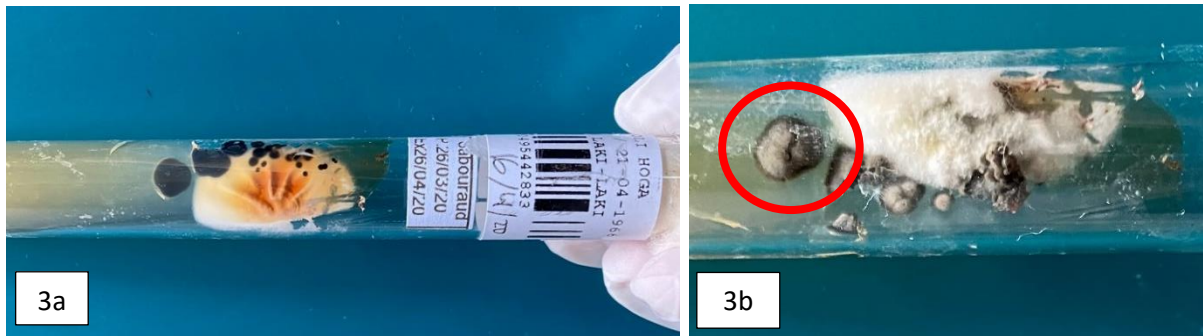


**Figure 2a.** Showing different magnifications, showing medular bodies

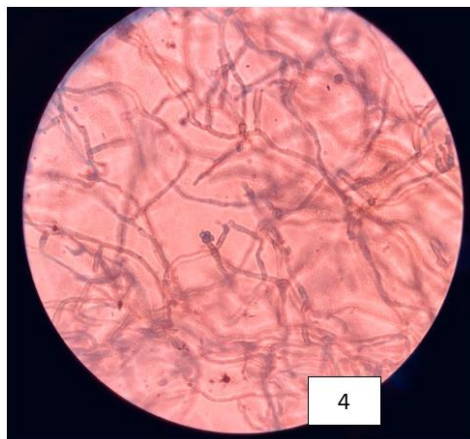
Subsequent culture on SDA media revealed the growth of black fungal colonies with a slightly irregular surface and a velvety greyish layer, as depicted in Figures 3. Microscopic examination using lactophenol cotton blue staining of the colony culture exhibited long, branched hyphae and conidia with a flask shape, known as thin-walled and long phialides, as seen in Figure 4. The suspected causative species was identified as *Fonsecaea pedrosoi*.

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**Figures 3a,b.** Fungal colonies. Figure 3b shows a blackish colony covered with a velvety greyish surface.



**Figure 4.** Samples taken from cultures on media

In light of the patient's history, physical examination, and supporting investigations, the working diagnosis was confirmed as chromoblastomycosis. The patient was managed on an outpatient basis with itraconazole 400 mg every 24 hours. Warm compress therapy was advised for home use. Remarkable improvement was observed after one month of this therapeutic regimen, as depicted in Figures 5a-5d.





**Figure 5a-d.** Shows improvement of the lesion in the form of a smoother nodule surface and reduced black dots.

## Discussion

Chromoblastomycosis, a chronic fungal infection affecting the skin and subcutaneous tissue, is primarily caused by pigmented fungi forming sclerotic, muriform bodies within the tissue.<sup>2,5,6</sup> The predominant causative agent is a saprophytic fungus found in soil, wood, and plants.<sup>8</sup> *Fonsecaea pedrosoi* being the most common, followed by *Phialophora verrucosa*, *Cladosporium carrionii*, *Fonsecaea compacta*, and *Rhinocladiella aquaspersa*. In Indonesia, reported cases are notably rare, with only 13 documented from 1930 to 2019, showing a higher prevalence in males aged 30 to 60, possibly linked to occupational factors and a higher risk of inoculation trauma, particularly in agriculture and forestry workers.<sup>9</sup> The primary mode of infection involves traumatic inoculation of the causative agent into the host tissue, often stemming from unnoticed injuries like thorn or wood splinter punctures. In this case, the patient's occupation, involving daily garden work and walking barefoot, likely exposed him to such trauma. Other potential risk factors include age, low socioeconomic status, poor nutrition, and inadequate personal hygiene.

Chromoblastomycosis's pathogenesis is intricate, dependent on factors such as the host's immune response, fungal virulence, and exposure level to the causative agent. Skin lesions are variable, typically initiating at the site of traumatic inoculation, with slow, asymptomatic growth over several years to decades. Lesion types include nodular, tumorous, verrucous, plaque, and cicatricial. In our case, the patient initially presented with a blister that progressed into a persistent nodular lesion spreading to surrounding healthy skin, characterized by nodules with uneven surfaces or reddish-colored verrucose with black dots.<sup>10</sup>

Supporting examinations, including potassium hydroxide (KOH 10%) examination, culture on SDA medium at 25 to 30°C, and histopathological examination, are crucial for a correct chromoblastomycosis diagnosis. Specific identification relies on culture examination, but in our case, the KOH examination did not reveal muriform bodies, potentially due to improper sampling.<sup>2,5,6,7,11</sup>

Therapeutic approaches encompass physical therapy, chemotherapy, and combination therapy. Physical therapy options include surgery, frozen surgery, and

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thermotherapy, while common chemotherapy modalities are indicated for extensive and long-standing lesions. First-line therapies are itraconazole (200-400mg/day) and terbinafine (250-500 mg/day) for 6 to 12 months, with posaconazole for refractory cases. Pulse dose itraconazole, with its advantages of high cure rates, minimal side effects, and improved compliance, has shown success in reported cases.<sup>12</sup> Pulse dose itraconazole, with its advantages of high cure rates, minimal side effects, and improved compliance, has shown success in reported cases.<sup>13</sup>

Combination therapy, an option for refractory or severe cases, can involve physical therapy and chemotherapy or systemic therapy. Reports on the combination of heat therapy, such as warm compress with itraconazole, have shown promising results. Heat therapy inhibits fungal development by restraining pathogen growth at temperatures over 42 to 46°C, making it a favorable consideration for combination therapy. Its application in Japan resulted in clinical improvement and negative microscopic examination and culture results. This cost-effective combination alternative allows patients to administer it themselves.<sup>14</sup>

In our case, the patient received pulsed dose itraconazole (400 mg/day) alongside heat therapy. The therapy choice considered the lesion extent requiring systemic treatment, drug availability, patient compliance, and economic ability. Combining itraconazole with heat therapy aimed to reduce drug side effects and additional costs. The planned therapy duration ranged from 8 to 12 months, aligning with chromoblastomycosis cure criteria. Despite the limitation of a lack of follow-up information after one month due to the patient not returning, the case exhibited improvement characterized by a smoother nodule surface and reduced black dots.

### **Conclusion**

This case represents a rare occurrence in Indonesia. The diagnosis relied on thorough anamnesis, physical examination, and additional investigations. The patient fulfilled the epidemiological, clinical, and supporting criteria for chromoblastomycosis. Treatment involved a pulse dose of itraconazole and daily heat therapy, offering a cost-effective and patient-friendly combination that can be self-administered at home. However, to comprehensively assess clinical and mycological cure, monitor therapy side effects, and evaluate potential disease complications, follow-up observations are essential. Further research and long-term observations will contribute valuable insights into the efficacy and outcomes of this combined therapeutic approach for chromoblastomycosis.

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## The Significance of Entrepreneurial Leadership in Armed Forces Hospitals

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### Abstract

**Background:** Currently, merely possessing leadership or entrepreneurial qualities is insufficient for assuming the role of a hospital head in the armed forces. Successful hospital leadership necessitates the embodiment of Entrepreneurial Leadership (EL), a contemporary model combining leadership excellence with an entrepreneurial spirit. The capacity of a hospital to advance is profoundly shaped by its economic acumen, and to thrive, leaders surpassing EL standards are imperative.

**Methods:** A scoping review was conducted utilizing the Google Scholar database and PubMed, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines. A total of 136 articles from various studies conducted between 2018 and 2023, spanning diverse countries, were reviewed. Extraction focused on 5 studies from 4 countries that implemented leadership interventions among doctors, dentists, and hospitals.

**Discussion:** In light of the global impact of the COVID-19 pandemic, the landscape of hospital management is undergoing rapid transformation. Internet-based technologies are becoming essential for hospitals to address service requirements and enhance efficiency, thereby increasing overall effectiveness. Only leaders possessing EL can ensure the survival, development, and competitiveness of hospitals amidst these evolving challenges.

**Conclusion:** The characteristics of EL exhibited by hospital leaders significantly influence the performance, continuity, effectiveness, and productivity of competitive hospital enterprises. The application of EL enables hospitals to attain superiority, professionalism, resilience, innovation, and adaptability to various changing conditions.

**Keywords:** Entrepreneurial leadership, hospital, military, army

### Introduction

In accordance with Indonesia Constitutional Law No. 34 of 2004, Article 50, Paragraph 2, Letter d, it is stipulated that soldiers and student soldiers are entitled to official care and services, encompassing health care.<sup>1</sup>

Article 51, Paragraphs 1 and 2, further elaborate that soldiers honorably discharged receive post-service treatment and services, including pensions, retirement benefits, allowances or severance pay, and health care.

Article 57 outlines that the rights of soldiers with severe, moderate, or mild disabilities resulting from military operations or non-military operations during military service are regulated by Government Regulations. These provisions underscore the comprehensive protection of armed forces soldiers' health through various health service facilities. Such

facilities include national insurance, specific health services as per Presidential Regulation 107 of 2013, and policies set by armed forces hospital leadership.

Armed forces hospitals, in addition to serving the general public, bear the responsibility of providing heightened attention to soldiers, as their existence is intertwined with the armed forces. To ensure continued competitiveness for better healthcare services, Indonesian hospitals must focus on three critical aspects.<sup>2</sup> (1) Quality: Mandatory certification for all Indonesian hospitals is a pivotal step in enhancing quality; (2) Safety: The implementation of a patient safety program is imperative for delivering safer hospital services; (3) Equity: Establishing a public health insurance program is the first stride toward providing impoverished populations with improved access.

The Ministry of Defence and the police of the Republic of Indonesia oversee a network of hospitals and primary-level health facilities distributed as follows: (1) Ministry of Defense: 1 Hospital; (2) Army: 68 Hospitals and 438 Primary Level Health Facilities; (3) Navy: 34 Hospitals, 25 Health Units, and 140 Primary Level Health Facilities; (4) Air Force: 23 Hospitals and 57 Primary Level Health Facilities; (5) Indonesian National Police: 53 Hospitals and 564 Primary Level Health Facilities.

The provision of healthcare services by hospitals is increasingly influenced by rising public awareness of health value. Hospitals are expanding medical offerings to emphasize rehabilitation and healing, with a keen focus on patient comfort. Scientific and technological advancements have empowered individuals to demand high-quality healthcare, positioning it as a benchmark for the success of hospital managers and leaders.<sup>3</sup> Overcoming the challenges posed by Health Minister Budi Gunadi's mandated health system overhaul is a formidable obstacle faced by Indonesian hospitals.<sup>4</sup>

In the contemporary hospital management landscape, possessing leadership qualities alone is insufficient to sustain and advance business development, especially in the face of fierce competition and rapid changes post-COVID-19. Leaders must now demonstrate innovation, seize opportunities, and embrace risks. The key lies in possessing the character of EL.<sup>5</sup>

Success in EL necessitates the ability to face risks, exploit opportunities, develop strategies, pursue innovation, and be both innovative and productive. EL leaders excel in identifying new opportunities that create value for the business and benefit subordinates and society at large.<sup>6</sup> Each EL leadership style is unique, with its own method of direction and guidance. EL leaders are continual learners, adept at experimentation and persistent until success is achieved. Unlike conventional leaders, ELs thrive in turbulent, fast-moving, and unpredictable organizational contexts.<sup>7</sup> To overcome formidable obstacles, EL prioritizes others and leverages the power of relationships. President Stephen Spinelli Jr. of Babson College asserts that EL is a mindset generating social and commercial value, transforming challenges into opportunities while keeping the organization in mind.<sup>8</sup>

EL, driven by a relentless pursuit of improvement, harbors an optimistic outlook on the future. EL exhibits exceptional adaptability and optimism regarding global business prospects. A crucial attribute of ELs, as highlighted by Professor Nan Langowitz, is their

openness to learning. ELs are not born but created, continually trainable, akin to entrepreneurs. Professor Langowitz emphasizes, "The best chiefs are students," underlining the significance of fostering a learning mindset for optimal decision-making.<sup>8</sup>

In light of the preceding discussion, the author will provide a brief review of the increasingly pivotal concept of EL in the business world, particularly in the context of hospital management in armed forces hospitals

## **Method**

### **Search Strategy**

This study conducts a scoping of the literature using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Figure 1).

### **Inclusion Criteria**

Study Design: Randomized Controlled Trials (RCTs) and Non-Randomized Controlled Trials (Non-RCT) published between 2018 and 2023.

Participants: Doctors, dentists, and healthcare workers working in hospital setting

Intervention: Leadership training and completion of questionnaires related to leadership.

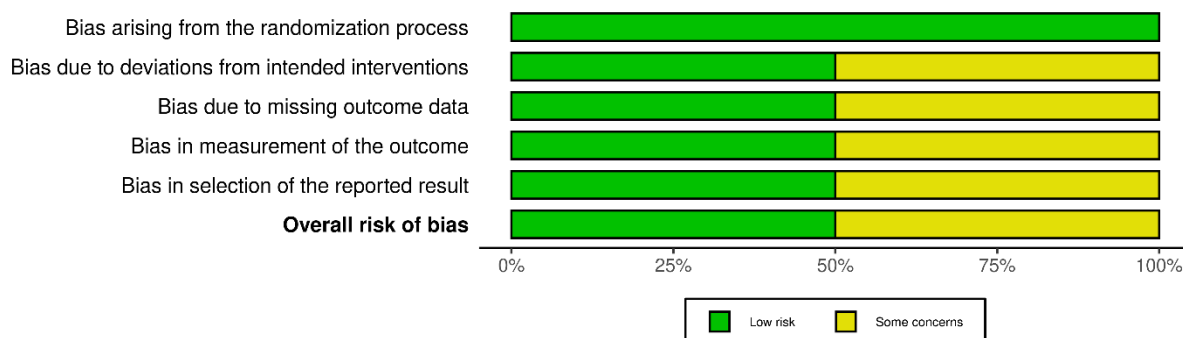
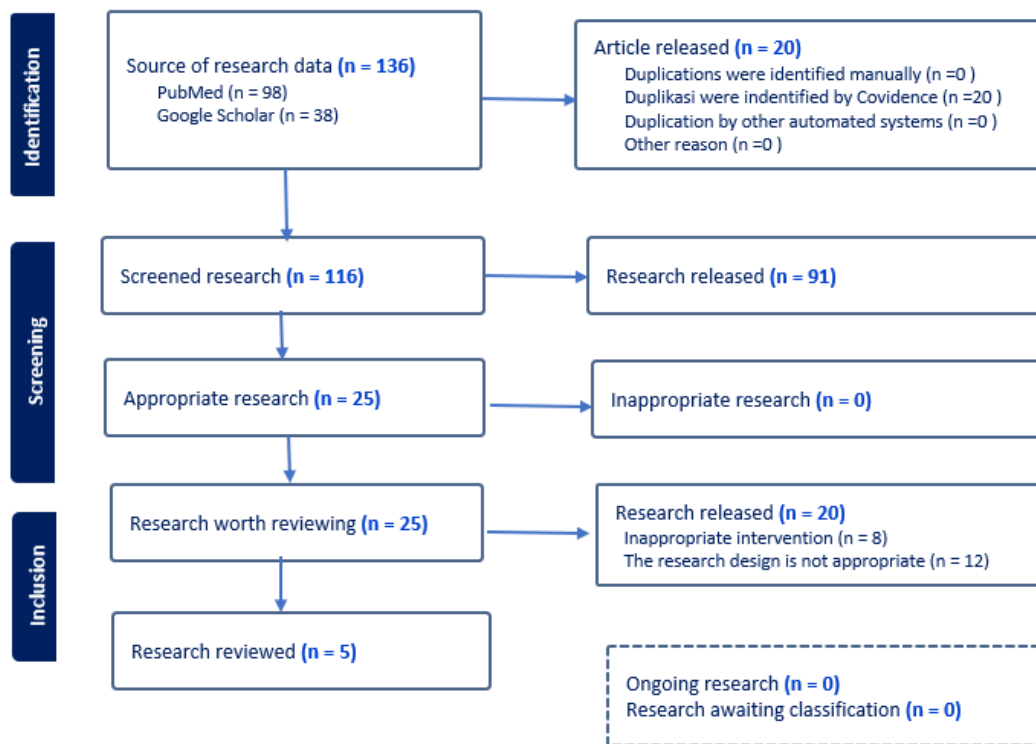
Outcome: Increased performance supporting the sustainability of relevant health services.

Articles undergo a screening process, starting with a review of the title and abstract according to the inclusion criteria. After removing duplicate articles, a comprehensive review of the full text is conducted.

### **Data Extraction**

Inclusion criteria are applied based on the title and abstract of the publication. Subsequently, each article is thoroughly read to ensure alignment with inclusion conditions. For evaluation, two reviewers (NW and DD) independently extract and discuss the data, resolving any discrepancies. Extracted data includes the study's title, the year and nation of conduct, the research intervention, total participant count, and the study's conclusions. Table 1 presents the findings of the data extraction process.

**Figure 1. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis**



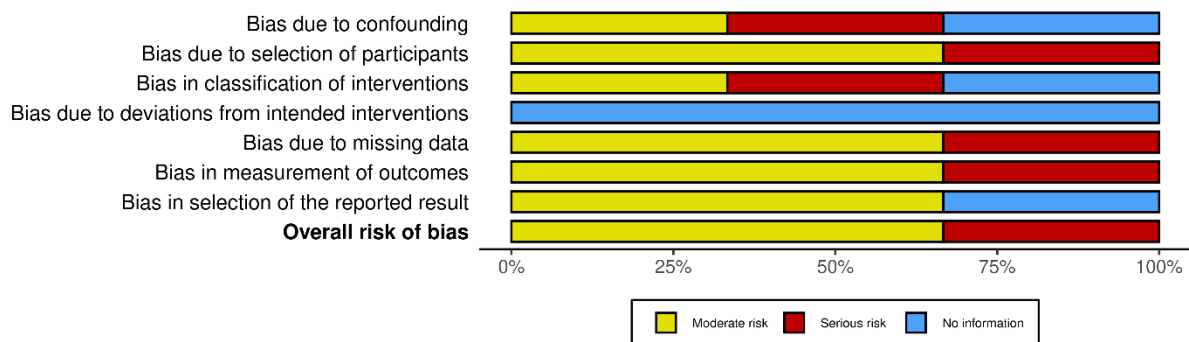
**Risk of bias domains**

	D1	D2	D3	D4	D5	Overall
Study Kim (2023)	+	+	+	+	+	+
Study Lucas (2022)	+	-	-	-	-	-

**Domains:**  
 D1: Bias arising from the randomization process.  
 D2: Bias due to deviations from intended intervention.  
 D3: Bias due to missing outcome data.  
 D4: Bias in measurement of the outcome.  
 D5: Bias in selection of the reported result.

**Judgement**  
 - Some concerns  
 + Low

In this study there are two RCT articles, the first article was by Kim et al., in 2023 with the overall risk of bias being low risk. In the second article by Lucas et al., 2022, the risk of bias in the article is of some concern.



Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Hardeep (2019)	?	-	?	?	-	-	-	-
Jiabi (2020)	-	-	-	?	-	-	-	-
Phatthranit (2023)	X	X	X	?	X	X	?	X

Domains:  
 D1: Bias due to confounding.  
 D2: Bias due to selection of participants.  
 D3: Bias in classification of interventions.  
 D4: Bias due to deviations from intended interventions.  
 D5: Bias due to missing data.  
 D6: Bias in measurement of outcomes.  
 D7: Bias in selection of the reported result.

Judgement  
 X Serious  
 - Moderate  
 ? No information

In this study, three non-Randomized Controlled Trials (non-RCT) articles were utilized. The initial article by Hardeep et al. (2019) is assessed as having an overall moderate risk. The second article by Jiabi et al. (2020) is also categorized as having a moderate overall risk. The final article by Phatthranit et al. (2023) is deemed to pose a serious overall risk.

**Table 1. Summary of Study Characteristics Included in Inclusion Criteria**

No.	Author (Country where research was conducted, year)	Title	Research purposes	Population and intervention	Number of participants	Result
1.	Degen Lucas, <i>et al</i> (German, 2022)	Leadership program with skills training for general practitioners was highly accepted without improving job	This article's goal is to optimize work satisfaction through leadership intervention. Examine work-related variables such as general	There are two groups (control group=139, intervention group=129), each of which consists of the following	268 participants	Twelve primary physicians, 1 attending physician, and ten physician assistants made up 23 out of the 11 physicians who

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No.	Author (Country where research was conducted, year)	Title	Research purposes	Population and intervention	Number of participants	Result
		satisfaction: the cluster randomized IMPROVE job study. <sup>9</sup>	practitioners' workload, weariness and stress from patient care support teams, recognition, bureaucracy, and revenue. A wide range of treatments, including seminars, group work, mentoring, multi-source feedback, and action research, were examined.	roles: assistant doctors (182), leaders (70), and general practitioners (16). Physicians who took part were chosen from North Rhine Westphalia, Germany.		completed the brief questionnaire (8.6%). Leaders typically have longer tenure in their practice and work full-time. Throughout the study, 51.4% of women reported feeling together, and this feeling significantly influenced changes in job satisfaction (t=2.67, b=0.14).
2.	Kim C. Brimhall, Chou-Yu Tsai, Eckardt R, Dionne SL, Biying Yang, Sharp A. (US, 2023)	The effects of leadership for self-worth, inclusion, trust, and psychological safety on medical error reporting <sup>10</sup>	Examining how leadership may promote psychological safety, which can lower medical errors and boost cooperation by building self-esteem and trust.	The participants' average age was 49 years old. Eleven percent are men. Of the total, 26%, or 97 of them, are licensed nurses. Of the total number of employees, 21% are coordinators or administrative staff (78), 19% are medical laboratory technicians or scientists (68), 13% are supervisors or managers (47), and the remaining individuals	318 participants	According to a leadership study, the negative binomial path model directly affects how people report medical errors when it comes to self-esteem, inclusion, trust, and psychological safety. about psychological stability, trust, and self-worth. The number of medical errors that are reported declines with increased confidence. This indicates that medical errors are not

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No.	Author (Country where research was conducted, year)	Title	Research purposes	Population and intervention	Number of participants	Result
				hold a variety of other professions. 4% were social workers (15 or medical assistants), 3% were directors of 12 companies, 2% were pharmacists (8 or data analysts), and 6% were other occupations with 25 workers.		immediately decreased by policy.
3.	Phattharapornjaroen P, Eric C, Atiksawedparit P, Holmqvist LD, Pitidhamabhorn D, Sittichanbuncha Y and Manesh AK (Thailand, 2023)	The impact of the three-level collaboration exercise on collaboration and leadership during scenario-based hospital evacuation exercises using flexible surge capacity concept: a mixed method cross-sectional study <sup>11</sup>	Exercises that center on hospital leadership and cooperation during emergencies and disasters. This study used the idea of flexible capacity and collaboration tools to simulate hospital support in order to demonstrate how well a three-level collaboration (3LC) exercise can foster leadership and collaboration in Thai districts.	74% of the participants, ages 23 to 58, were employed directly by hospital groups or province or local governments. In total, hospitals from four different nations made up 58% of the sample.	40 participants	3LC training significantly improved participants' abilities at the collaboration level (P<0.001).
4.	Chahala H, Guptab M, Lonialc S, Raina S (US, 2019)	Operational flexibility-entrepreneurial orientation relationship: Effects and consequences <sup>12</sup>	The purpose of this study is to explore the relationship between internal performance in hospital companies and entrepreneurial	A questionnaire that might be utilized for data analysis was completed by 152 hospitals.	152 hospitals	Risk, proactivity, and innovation all have dimensions. Proactiveness is the most significant and vital of these

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No.	Author (Country where research was conducted, year)	Title	Research purposes	Population and intervention	Number of participants	Result
			<p>orientation. Additionally, the operational significance of Moderation will be examined. Envisioning is a relatively new multidimensional construct that is based on operations management theory.</p>	<p>The questionnaire asks about the hospital's nature, how many services it offers that set it apart from other hospitals, and how many beds it has.</p>		<p>three dimensions. Proactive behavior yields outcomes that are more valuable to total performance, both in terms of money and non-money. Hospital performance is impacted by proactive hospitals that create improvements in operational and service processes. The fierce competition in the US healthcare industry is the reason for the interest in initiative and creativity. The hospital gives potential patients the chance to get timely, efficient care tailored to their needs. Hospitals work hard to promptly adapt to the demands and preferences of the modern market in order to satisfactorily serve their patients.</p>
5.	Wang J, Peng B, Zhou H and Zhang JH	Dentists' entrepreneurial	The purpose of this study is to	Women made up 70.83% of	336 participants	According to the study's

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No.	Author (Country where research was conducted, year)	Title	Research purposes	Population and intervention	Number of participants	Result
	(China, 2022)	intention (EI) and associated factors in public hospitals in major cities in Guangdong (South China): a cross-sectional study <sup>13</sup>	ascertain the degree of entrepreneurship among dentists working in Chinese hospitals, taking into account several criteria such as their education, experience in the field, leadership and entrepreneurial abilities, family history, and risk aversion.	the responses. Just 11.01% of the population was 46 years of age or older, and ¾ were under 35. Only 10.71% of dentists hold a PhD, compared to nearly half who have a degree. Approximately 78% of those surveyed have a relative or family member who owns or operates a dental business.		findings, 35.71% of dentist respondents used EI. Dentists with 10 and 11 years of professional experience, respectively, had odds ratios of 0.133 (p=0.014) and 0.015 (p<0.0001), indicating better emotional intelligence. Dentists were substantially more likely to report emotional intelligence (EI) if they had entrepreneurial family members (OR=3.672, p=0.003) or higher levels of entrepreneurial conduct (OR=3.602, p<0.0001). Nonetheless, the likelihood of reporting EI was lower for dentists who had higher risk aversion (OR=0.702, p=0.007).

## **Results**

In the contemporary business landscape, a leader must possess a blend of managerial and leadership skills to facilitate the expansion, improvement, and sustainability of their company. Additionally, leaders should stay abreast of the latest developments, take calculated risks, and seize opportunities as they arise. Such a leader is characterized by possessing both an entrepreneurial attitude and leadership principles.<sup>14</sup>

The advent of COVID-19 has brought about transformative changes in the hospital business, catalysing numerous ideas for future advancements and reshaping the health industry. Consequently, hospital management must adapt, particularly with the increasing importance of adopting virtual health innovations. Examples of these innovations include electronic visits, screening, and observation. The COVID-19 pandemic has provided valuable insights into potential applications of virtual health technology.<sup>15</sup>

### **1. Future Hospital Business**

The Deloitte Center for Health Solutions conducted a survey of health futurists in mid-January 2020 to gather predictions about future hospitals. Post-epidemic, perspectives on the sustainability of hospitals have evolved. The discussion anticipates that value-based reimbursement, technological advancements in clinical care, and breakthroughs in treatments such as DNA sequencing, genomics, and personalized medicine will significantly influence hospital administration in 2040. The future business strategy of hospitals is expected to shift towards high-acuity, technologically advanced, complex case- and data-driven virtual products, moving away from a traditional brick-and-mortar approach. The emergence of "smart hospitals" capable of digital activation based on customer demand is foreseen.<sup>16</sup>

Hospitals cannot revert to their earlier business strategies, and hospital executives must consider how to sustain and position their companies for growth during the post-pandemic economic recovery. The trend in therapy is gradually shifting from intrusive procedures to non-invasive interventional procedures, with virtual visits and long-distance monitoring gaining popularity in technology. Patients express a preference to avoid hospitals or minimize their visits.<sup>17</sup>

In envisioning the changes that hospitals will undergo in 2040, three major themes emerge, each supported by specialist doctors with various objectives, including cost reduction, customer service enhancement, physician education, and competition with other emergency hospitals.<sup>18</sup>

### **Transformation of Hospital Business Models**

Anticipated changes by 2040 include a drastic reduction in hospital bed counts, with a focus on operations for complex, specialist, and critical care patients.<sup>19</sup>

The primary focus of hospitals will shift towards epidemic and or pandemic, trauma and critical care, and specialized services like transplantation, emergency, trauma service, intensive care unit and neonatal intensive care unit, infectious disease prevention unit, lastly, specialized procedures for complex patients.

Hospital structures will integrate medical facilities with retail, virtual care, and outpatient services, offering diagnostic and outpatient surgical procedures. The environment will be more laid-back, providing comprehensive services. Virtual technology-enabled hospitals or hospitals at home will emerge, allowing remote patient treatment and monitoring. Some medical facilities are pioneering "bed-less hospitals."

### **Data and Technology-Based Service Delivery Models**

Hospitals operate with interconnected data and systems, facilitating streamlined operations and efficient delivery of clinical care. Technology plays a pivotal role in monitoring and providing care, with the integration of Artificial Intelligence (AI) into clinical services and hospital operations. A prominent example is the establishment of a central health department entirely based on digital reality.<sup>20</sup>

### **Smart Spaces and Digitally Enabled Hospitals**

The future hospital will feature smart rooms, integrating digital technology throughout the facility, reshaping the physical layout to resemble a sophisticated hotel. Measured areas in the clinic layout will be crucial to allow for adjustments in services based on demand. The ability to synchronize virtual services with in-person services must be considered, acknowledging potential variations in physical space and the hospital's preference for a seamless blend of virtual and in-person offerings.<sup>21</sup> Virtual contributions will be integral to the patient experience, ensuring constant access to information, ease of specialist consultations, and continuous medication monitoring, whether within the hospital or at the patient's home. Future innovations will continue to prioritize bringing technology to patients, enabling clinical equipment to be portable, compact, and self-contained, thereby supporting care at home.<sup>20</sup>

### **Leadership Theory**

A contemporary leadership style gaining prominence is EL.

#### **(1) Leadership**

According to a scoping review by Fennel et al., on Conceptualizations of Leadership and Relevance to Health and Human Service Workforce Development, leadership remains a multifaceted and multi-contextual phenomenon with various definitions. Despite the abundant literature on leadership, no theory or approach has provided a comprehensive explanation for leadership in the health and human service sector.[29]

#### **(2) Entrepreneurship**

Entrepreneurship has recently emerged as a crucial factor in social welfare and economic prosperity, ranking alongside capital, labor, and natural resources. As a multifaceted activity involving labor, capital, technology, goods, services, and production, entrepreneurship is now recognized as the primary factor in production. Entrepreneurs are individuals who assess market prospects, assuming both profit and loss risks.[30]

Hospital organizations desperately need a leadership style that emphasizes innovation and the introduction of new opportunities. When it comes to encouraging creativity and change among healthcare providers, EL is a powerful approach. By adopting this leadership style, leaders can effectively handle significant changes and complex problems in the health services sector. According to a previous study, the characteristics of a practical business visionary include fearlessness, assurance, the ability to communicate and influence others, receptiveness to new ideas, having a dream, using drive, reliability, positive reasoning, adaptability, ability to face challenges, really putting in the work, hierarchical capacity, information, harmony with the climate, tirelessness, discernment, taking advantage of opportunities, and constant self-repair.<sup>22</sup>

EL encompasses the enterprising attributes of a leader—courage to face challenges, discernment of opportunities, and a creative and productive mindset. The impact of entrepreneurial leadership extends to fostering innovative work behavior in various competitive scenarios. Key elements that enhance EL include collaborative problem-solving, results-oriented action, faith in improvement, and the ability to lead and resolve diverse issues from any position.<sup>23</sup>

### **The Significance of EL in Armed Force Emergency Hospitals**

The Army Hospital association operates at the central and level-2, led by the Gatot Soebroto Army Central Hospital, functionally under the Military Head of Staff. Its primary task is to organize and conduct medical health functions at the central level, serving as the highest hospital within the Indonesian Public Armed Forces.

Implementing the core characteristics of EL across all Armed Forces hospitals, with a steadfast commitment to professionalism and innovation, ensures the resilience and adaptability of these hospitals, allowing them to survive and thrive under any conditions. Psychological safety (PS) is imperative for enhancing patient safety and reducing medical errors, but many struggle with its effective implementation. Brimhall et al. investigated how leadership indirectly influences self-esteem, participation, and trust, thereby increasing PS and ultimately reducing the number of reported medical errors. Trust fosters a culture where workers continuously learn from mistakes, improving services to prevent errors. Leadership instills confidence, active participation, and trust among healthcare workers in their work environment.[11]

Phattharapornjaroen et al. led a case-control study focusing on the effectiveness of the 3-level collaboration training (3LC) in fostering collaboration and leadership in Thailand.<sup>11</sup> With 40 participants from disaster response organizations, the study utilized flexible surge

capacity (FSC) and hospital evacuation simulation with collaboration tools. The data encompassed elements of Order and Control, Security, Communication, Emergency Assessment, Management, and Transportation. The results demonstrated that 3LC training significantly enhanced understanding, collaboration, leadership, and individual adaptability within the hospital setting.<sup>11</sup>

Chahala et al. conducted research to assess entrepreneurial orientation (EO) in the hospital industry and the role of operational flexibility (OF), a novel multi-dimensional construct in operational management theory. The findings indicated that the three-dimensional construct can induce innovative, proactive, and risk-ready behavior in hospital management. This research contributes to expanding the relationship between corporate entrepreneurship and field operational management.[13]

Wang et al. research (China 2022) delves into the entrepreneurial intentions of dentists in public hospitals in China's largest cities. Factors such as risk aversion level, work experience, education, professional background qualifications, entrepreneurial skills, and leadership are examined. The study reveals that dental professionals' development of abilities based on age, professional history, and initiative skills encourages entrepreneurial interest. Greater entrepreneurial inclination is found among dental specialists in medium-sized and smaller clinics than in larger, well-known medical facilities in China. Support is needed to encourage female dentists to enhance their entrepreneurial leadership skills, as leadership is acknowledged to foster a desire for business endeavours among dental professionals.[14]

## **Conclusion**

Entrepreneurial leadership is essential for hospitals to effectively achieve their business objectives. The entrepreneurial leadership traits of hospital leaders significantly impact the performance, continuity, efficacy, and productivity of hospital businesses. In a competitive environment, applying entrepreneurial leadership provides a competitive advantage. Beyond entrepreneurial qualities such as risk-taking, seizing opportunities, seeking innovation, and strategic thinking, entrepreneurial leadership encompasses vision, courage, inventiveness, and inspiring leadership. Entrepreneurial leaders have the ability to perceive the unseen or interpret possibilities in seemingly impossible situations.

Entrepreneurial leadership contributes to job creation in the business sector, ensuring that employment opportunities align with new ideas and developments. Through a collaborative approach, entrepreneurial leadership builds teams that complement each other, working towards shared goals. Entrepreneurial leaders are attuned to their surroundings and themselves, consistently identifying new opportunities for the benefit of stakeholders, the business, and the community. While uncertainty and resource constraints may deter conventional leaders, entrepreneurial leaders are motivated to seek innovative solutions to challenges. Entrepreneurial leadership thrives on practical thinking, examining and finding solutions to seemingly intractable problems, guiding society towards resolutions.

In military hospitals, entrepreneurial leadership anticipates the evolving needs of future hospitals within a broader local community.

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## Temperature and Cardiovascular Morbidity

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### Abstract

The negative influence of extreme heat on cardiovascular health has been observed across various geographical locations across the world. In the state of New York, discovered a significant increase in cardiovascular disease (CVD) related emergency department, following an extremely hot day. Increase in 3-day delayed CVD hospital admissions with every 1°C above the temperature-health effect curve (29°C–36°C). Another study conducted in China, estimated that the cumulative relative risk of having an out-of-hospital cardiac arrest (OHCA) following a day with extreme heat. Analogous impacts of extreme heat on cardiovascular morbidity have also been observed in Australia and Korea. Data from Thai Nguyen province in Vietnam with the daily weather, observed no statistically significant association between hot temperatures and CVD-related hospital admission over the course of lag days 0–30. Contradictory evidence was also found in epidemiological studies conducted across Europe. A systematic review and meta-analysis of twenty-one studies also failed to detect a significant association between cardiovascular morbidity and ambient temperature.

**Keywords:** extreme heat, cardiovascular health, cardiovascular morbidity

This section summarizes the impacts of temperature on cardiovascular morbidity (degree of cardiovascular illness) with respect to heat exposure, based on a search of peer-reviewed literature through 2019 (see appendix for literature search methodology).

The negative influence of extreme heat on cardiovascular health has been observed across various geographical locations. In the state of New York, utilizing the definition of “extremely hot day” as a daily mean temperature of >95th percentile of regional monthly mean temperature, researchers discovered a significant increase in cardiovascular disease (CVD) related emergency department (ED) visits on day 5 and 6 (odds ratio (OR) = 1.02, 95% confidence interval (CI): 1.01-1.04, and OR = 1.01, 95% CI: 1.00-1.03 respectively) in older adults (≥ 65 years old) following an extremely hot day during the months of April – October, 2005-2013.<sup>1</sup>

A similar lag effect of extreme heat was observed by Li et al. on the hospitalizations due to CVDs in New York City throughout June, July and August of 1991–2004. This study reported an 1.4%–3.6% increase in 3-day delayed CVD hospital admissions with every 1°C above the temperature-health effect curve (29°C–36°C).<sup>2</sup> Aggregated county-level ED visits from six regions of California from July 15th, 2006 to August 1st, 2006 showed a significant increase (relative risk (RR) = 1.05, 95% CI: 1.02–1.09) in CVD visits due to the 2006 California

heat wave compared to a reference period (July 8th–14th, 2006 and August 12th–22nd, 2006).<sup>3</sup>

The above three studies considered CVD ED visits and hospital admissions that included the following International Classification of Disease 9th version (ICD-9) principal diagnoses: hypertension (401–405), ischemic heart diseases (410–414), cardiac dysrhythmias (427), heart failure (428), cerebrovascular diseases (430–434, 436–438) and chronic rheumatic heart diseases (393–396).

Additionally, conditions such as hypertrophic cardiomyopathy (HC), an illness in which the muscle of the heart (myocardium) becomes abnormally thick (hypertrophied), are also affected by heat exposure. A telephone survey of HC patients (n=173) evaluated at Mayo Clinic (Rochester, MN) found that 72 respondents observed a deterioration of their baseline HC symptoms (shortness of breath, chest pain, loss of consciousness) due to a change in ambient temperature. 21% (n=17) of those patients reported an exacerbation with an increase or decrease in ambient temperature. More notably, the other 79% (n=57) attributed their symptom exacerbations to heat alone.<sup>4</sup>

In Ontario, Canada, an analysis of all those who were hospitalized for CHD from 1996 to 2013, found a 6% (95% CI: 1%–11%) increase in CHD related admissions on days with high temperatures (daily mean temperature >99th percentile) relative to the optimal temperature (noted in the study as daily mean temperature that is at the 79th percentile). Overall, out of the 1.4 million CHD admissions included in the study, 1.20% (16,000) were attributable to heat.<sup>5</sup> Consistent data was also revealed in an investigation into the relationship between daily mean temperature and rheumatic heart disease (RHD) hospital admissions in Shanghai, China from 2013–2015. Following a day with moderate (>28°C, 90th percentile regional mean temperature) or extreme regional temperatures (>33.5 °C, 99th percentile regional mean temperature) the cumulative relative risks for RHD hospital admissions were 2.55 (95% CI: 1.14–5.73) and 3.22 (95% CI: 1.36–7.61) over lag 0–5 days correspondingly, when compared to the reference temperature of 0°C.<sup>6</sup>

Another study conducted in China, estimated that the cumulative relative risk of having an out-of-hospital cardiac arrest (OHCA) following a day with extreme heat (>99th percentile daily mean temperature) in Guangzhou from 2008-2015 was 2.45 (95% CI: 1.15–5.33) over lag days 0–21, compared with the reference temperature (28°C).<sup>7</sup> Analogous impacts of extreme heat on cardiovascular morbidity have also been observed in Australia and Korea.<sup>8,9</sup>

Some research indicates that temperature variability (large changes in mean temperature for a given region for a particular period of time) can also have an impact on cardiovascular morbidity. A nation-wide study in China that included 184 cities found that cardiovascular hospital admission rates increased 0.44% (95% CI: 0.32%–0.55%) for CVDs, 0.31% (95% CI: 0.20%–0.43%) for IHD, 0.48% (95% CI: 0.01%–0.96%) for HF and 0.34% (95% CI: 0.01%–0.67%) for heart rhythm disturbances for every 1°C increase in temperature variability at 0–1 days.<sup>10</sup>

Additional investigations into the impact of temperature variability on cardiovascular morbidity are highly warranted as scientific evidence on this relationship remains inadequate. Its critical to note that some peer-reviewed work found no statistically significant links between heat and cardiovascular morbidity. For example, after merging the daily CVD admissions (acute myocardial infarction, angina pectoris, congestive heart failure, hypertension, and stroke) data from four different hospitals in Thai Nguyen province in Vietnam with the daily weather, Giang et. al. observed no statistically significant association between hot temperatures and CVD-related hospital admission over the course of lag days 0–30.<sup>11</sup>

A systematic review and meta-analysis of twenty-one studies also failed to detect a significant association between cardiovascular morbidity and ambient temperature (-0.5% (95% CI: -3.0%–10.1%)).<sup>12</sup> Contradictory evidence was also found in epidemiological studies conducted across Europe.<sup>13,14</sup>

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# Biological Threats as Emerging Challenges in Modern Military Biodefense

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## Abstract

A biological threat refers to an infectious disease with the potential to spread and cause an outbreak. The challenges posed by rapidly changing and increasingly complex biological threats became apparent after the global COVID-19 pandemic, leading to a decline in the preparedness of nations and sluggish responses. Despite the potential severity of casualties, military readiness should be the first line of defense, emphasizing deep prevention. The role of the military in overcoming threats becomes an urgency that cannot be avoided and must be an integral part of the handling of biological threats nationally.

**Keywords:** Biological Threats, Emerging Challenges, Modern Military, Biodefense

## Introduction

A biological threat refers to an infectious disease with the potential to spread and cause an outbreak.<sup>1</sup> There are two types: natural outbreaks and man-made incidents. While most disease outbreaks and food contaminations generally occur naturally, there exists a real risk of diseases being transmitted to susceptible human or animal populations due to intentional or accidental releases of infectious agents or toxins. Unnatural biological threats pose particular risks, as pathogens can be engineered or released in ways that make them more dangerous. Although the likelihood of intentional or accidental releases may be relatively low, the impact can be catastrophic on a national and even global scale.<sup>2,3</sup> The challenges posed by rapidly changing and increasingly complex biological threats became apparent after the global COVID-19 pandemic, leading to a decline in the preparedness of nations and sluggish responses. Despite the potential severity of casualties, military readiness should be the first line of defense, emphasizing deep prevention.

## History

Biological threats have a long history, ranging from natural occurrences to man-made incidents. Notable natural outbreaks include the Black Death in the 14th century and the Spanish Flu in the early 19th century. In contrast, man-made incidents have been shrouded in secrecy, particularly in organized research programs. The policies guiding such research have been surrounded by even greater secrecy, with events and decisions often described without reference to their immediate or broader political context. Given these limitations, histories of biological threats seldom explore the varied ways in which scientists, the military,

and government officials perceived biological threats in the past.<sup>4</sup> Throughout the past 2000 years, historical records have mentioned the use of biological agents in the form of diseases, filth, and animal and human cadavers on numerous occasions.<sup>5</sup>

On the contrary, from a medical and biomedical standpoint military has done an extraordinarily good job over the past decades in preparing and planning for biological threats however there are several differences compared to protection for civilians. First, the civilian population is significantly more diverse than the military population in terms of age and health and, as such, poses unique challenges such as knowing which vaccinations and antibiotics should administered. Second, military preparedness emphasizes vaccine protection, however many biological agents it's neither feasible nor desirable to vaccinate entire civilians. Furthermore, the evolution of emerging and reemerging diseases in the last decade has become a real threat to entire civilians, although from an infectious disease perspective, the only difference between bioterrorism and any of these other naturally occurring diseases is that bioterrorism is deliberate.<sup>2</sup>

In civilian the era of openness to biological threats began on January 10, 2000 when the UN Security Council held an unprecedented event on threats to international peace and security. The purpose of the meeting was to assess the impact of HIV (Human Immunodeficiency Virus) and AIDS (acquired immunodeficiency syndrome) in Africa. UN Secretary-General Kofi Annan underlined that armed conflict in Africa kills 200.000 people per year while HIV/AIDS kills more than 2.2 million people in the same year. US Vice President Al Gore stated that the HIV/AIDS epidemic in Africa is not a humanitarian crisis but has become a security crisis. It is a security crisis because it threatens not only individual citizens but also the institutions that define and sustain the character of society. 6 months later the UN Security Council passed a resolution that the spread of HIV/AIDS could have uniquely devastating impacts on all sectors and levels of society and if not controlled, could pose a risk to stability and security.<sup>7</sup>

## **Covert Threat**

The international release or threat of releasing biologic agents (i.e., viruses, bacteria, fungi, or their toxins) with the intent to cause disease or death among the human population or harm food crops and livestock has become a tangible concern, particularly in terms of threatening government stability and security. Furthermore, the impact extends beyond a singular dimension, encompassing social, economic, and regional and international affairs.<sup>8</sup> Notably, the dangers posed by both natural occurrences and man-made biological threats, as exemplified by the pandemic outbreaks of SARS (Severe Acute Respiratory Syndrome) in 2003 and H5N1 avian influenza, underscore the urgency highlighted in national and international security reviews.<sup>7</sup> In 2004, a high-level UN panel advocated for intensified efforts to counter biological security challenges, encompassing infectious diseases and the specter of biological terrorism. In 2005, UN Secretary General Kofi Annan drew the attention of the Security Council to any outbreak of an extraordinary infectious disease that posed a threat to

international peace and security. Subsequently, in 2006, the United States National Security Strategy elevated pandemics to the status of a national security threat, ranking alongside nuclear, biological, and chemical weapons in the context of terrorist threats. The 2017 meeting of the United States Intelligence Community, in its quadrigeminal global threat report, warned that increased human mobility and inadequate health infrastructure will render the management of infectious diseases more challenging.<sup>9</sup>

A widely accepted framework for understanding biological threats is a spectrum that encompasses naturally occurring infectious diseases, accidental harm arising from research, and the intentional use of diseases as weapons, along with the taxonomy of biological threats.<sup>7,10</sup> Both the Centers for Disease Control and Prevention and the European Medicines Agency have categorized diseases into three groups.<sup>11</sup>

### **Biological Agents: Effect and Tactical Utility**

Biological agents can be broadly classified into three main groups: pathogenic microorganisms, viruses, and toxins. The first two groups comprise self-replicating living organisms, with viruses solely replicating within a host. Toxins, on the other hand, are toxic products produced by bacteria, plants, or fungi.<sup>13</sup>

Pathogenic microorganisms include protozoa, fungi, bacteria, and rickettsia. Protozoa are motile single-celled organisms, fungi are non-photosynthetic organisms capable of anaerobic growth, and obtain nutrients from decaying plant matter. Bacteria, considered the most likely type of biological warfare agent, are small, free-living organisms that can grow in solid or liquid cultures. Bacteria possess a structure comprising a nucleus, cytoplasm, and cell membrane, varying in shape and size from spherical cells and cocci (with a diameter of 0.5 to 1.0 microns) to bacilli (with a diameter of 1.0 to 5.0 microns). Certain bacteria can transform into spores in response to environmental changes, rendering them more resistant to cold, heat, drying, chemicals, and radiation than the bacteria themselves. The next biological agent, a virus, varies in diameter from 0.02 to 0.2 microns and must be cultivated within a host for reproduction. Rickettsia shares characteristics with both bacteria and viruses, resembling bacteria in cell membranes and metabolic enzymes, utilizing oxygen, and being susceptible to antibiotics. Similar to viruses, rickettsia requires a host for reproduction.

Another classification for biological agents is non-high-threats and high-threat biological agents. High-threat biological agents are pathogens that infect and cause serious illness in humans. While biological agents have not been used to cause mass casualties in modern times and are incapable of destroying physical infrastructure, there is an imminent threat in modern times related to biological agents, such as multidrug resistance in bacterial therapy. Many factors contribute to the development of bacterial resistance, with the common thread being the proliferation and misuse of antibiotics. The proliferation of biological threats has led to the emergence and re-emergence of infectious diseases.<sup>14</sup>

## **Infectious Diseases as Biological Threats**

The Global Burden of Disease Survey (GBD) has meticulously examined health status at global, national, and regional levels since 1990, providing insights into evolving health challenges across populations worldwide.<sup>15</sup> The 2017 data and reports underscore a deceleration in health-related progress towards achieving the Sustainable Development Goals (SDGs).<sup>16</sup> While most deaths from infectious diseases have declined due to improved healthcare, medications combating infections, and vaccines preventing diseases, the frequency and intensity of infectious disease outbreaks globally have not diminished over the past four decades. Analysis of over 10,000 outbreaks reveals bacteria and viruses as the predominant causes, with person-to-person, vector-borne, zoonotic, and human-specific diseases on the rise.<sup>16</sup>

In a groundbreaking 2008 paper, Kate Jones and colleagues in London demonstrated that emerging infectious disease events between 1940 and 2004 were distributed non-randomly worldwide.<sup>17</sup> Emerging Infectious Diseases are primarily driven by zoonotic pathogens and show an increasing trend over time. The paper also forewarns about antimicrobial resistance (AMR/Anti-Microbial Resistance) as a looming threat, predicting global emerging disease 'hotspots,' notably in India, South, and Southeast Asia.

Viruses constitute only 14 percent of known human pathogens but account for 44% of new and emerging pathogens.<sup>7</sup> Some of the most significant public health threats of the 20th century, such as influenza and HIV, originated from viruses of zoonotic origin. The first two decades of the twenty-first century witnessed two pandemics, the 2009 swine flu, and the ongoing COVID-19, as well as the SARS, MERS, and Ebola epidemics. While the latter posed significant threats, they lacked the geographical spread to become pandemics. All these outbreaks were caused by viruses transmitted from wild animals to humans, either directly or through intermediate animal hosts. The speed of new virus emergence has accelerated over the past 25 years, with the World Health Organization's list of 20 pandemic threats including 16 viruses.<sup>18</sup>

The intricate interplay of biological, environmental, socioeconomic, and political factors jeopardizes past achievements in infectious disease mortality and morbidity. Factors such as pathogen evolution, antimicrobial resistance, climate change, global warming, deforestation, vaccine skepticism, increased pollution and overcrowding, donor exhaustion, and geopolitical conflicts pose substantial threats. Simultaneously, life sciences, nanotechnology, communications, and space technology are providing new tools to detect, prevent, cure, and control infectious diseases based on scientific advancements.

Pandemics and catastrophic biological events differ from routine health threats. These events occur suddenly and are severe, emphasizing the necessity of prioritizing early detection and prevention. COVID-19 has underscored the global nature of the response required, even when many low-income countries lack the necessary technology or infrastructure. Therefore, ensuring prompt accessibility to protective equipment, diagnostics, therapeutics, medical devices, and clinical management protocols for all is imperative. The

technology needed to mitigate risks is expected to differ qualitatively from routine public health and clinical practice. A report from the Centre for Health Security at Johns Hopkins University, USA has outlined technologies that can better prepare the world to prevent infectious disease outbreaks from developing into catastrophic events.<sup>19</sup> Implemented technologies will require: (1) greater sensitivity to facilitate prevention, (2) capacity for early response and decision-making, (3) improved scale and access, (4) ability to be used in a variety of settings, and (5) rapid development, availability, and deployment in the field.

## Conclusion

Technological advancements and the progress of world civilization have transformed erstwhile threats into tangible realities. Historical biological threats, which led to the Black Death and Spanish flu pandemics, now pose a genuine risk to the contemporary global situation, especially in the aftermath of the COVID-19 pandemic. The role of the military in addressing these threats becomes an urgent and indispensable component of national biological threat management.

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