

**VITAMIN D DEFICIENCY IN COVID-19
PATIENT: AN ASSOCIATION TOWARDS
DISEASE PROGRESSION, MORBIDITY AND
MORTALITY**

DR UNG XIU MING

DISSERTATION SUBMITTED IN PARTIAL
FULFILLMENT OF THE REQUIREMENT FOR
DEGREE OF MASTER OF MEDICINE
(ANAESTHESIOLOGY AND CRITICAL CARE)



UNIVERSITI SAINS MALAYSIA

2022

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Many thanks from the bottom of my heart to Dr. Chin Ji Zhang for his continuous support and guidance. His kindness and compassion will forever be cherished. I would like to extend my sincere thanks to Dr. Huda bin Zainal Abidin and Dr. Eric Tang Boon Kiat for their editing help and moral support in manuscript writing. I am also grateful to Dr. Adlina Athilah Binti Abdullah for her data collection assistance, and she motivated me with her high spirit.

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Last but not least, I want to extend my sincere thanks to Adeline Wong Xueling, my family, and my housemates for their support, motivation, and companionship in times of darkness. Thank you for holding me together when it all felt like it was coming apart.

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LIST OF SYMBOLS AND ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ARDS	Acute respiratory distress syndrome
CD4	Cluster of differentiation 4
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CRP	C-Reactive Protein
EPI Updates	Epidemiological updates by World Health Organisation
Etc.	etcetera
HDU	High dependency unit
HFNC	High flow nasal cannula
ICU	Intensive care unit
IL-6	Interleukin-6
IQR	Interquartile range
JCEM	Journal of clinical endocrinology and metabolism
mg/L	milligram per Litre
MOE	Ministry of Higher Education
MOH	Ministry of Health
ng/mL	Nanogram per mililitre
NIV	Non-invasive ventilation

nmol/L	Nanomol per litre
OR	Odd ratio
PaO ₂ /FiO ₂	Partial pressure of oxygen over fraction of inspired oxygen
PCR	Polymerase chain reaction
PPSP	Pusat Pengajian Sains Kesihatan (School of Health Sciences)
RTK-Ag	Antigen rapid test kit
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
UK	United Kingdom
VS	Versus
25(OH)D	25-hydroxyvitamin D
%	Percentage
<	less than
>	more than
=	equals

APPENDICES

Appendix A: Data Collection Sheet (Page 69)

ABSTRAK

Pengenalan: Vitamin D mempunyai sifat imunomodulasi, bukan sahaja dengan mengurangkan pembebasan sitokin pro-radang, tetapi juga mengurangkan replikasi virus influenza dan pemusnahan patogen yang menyerang. Kekurangan vitamin D boleh menjadi faktor risiko yang mudah diubah suai yang berpotensi untuk mempengaruhi hasil COVID-19. Kami berhasrat untuk mencari perkaitan antara kekurangan vitamin D terhadap perkembangan penyakit, kematian dan morbidity dalam COVID-19.

Kaedah: Ini adalah kajian keratan rentas, yang melibatkan seramai 88 pesakit yang telah didiagnosis dengan COVID-19 dan dimasukkan ke ICU. Pesakit dikelaskan kepada kumpulan mencukupi vitamin D plasma ($25(\text{OH})\text{D} \geq 75 \text{ nmol/L}$; $n = 14$), dan kumpulan kekurangan vitamin D ($25(\text{OH})\text{D} < 75 \text{ nmol/L}$; $n = 74$). Hasil utama yang diukur adalah perkaitan kekurangan vitamin D plasma dengan kematian, dengan menggunakan ujian Chi-Square. Hasil sekunder termasuk perkaitan kekurangan vitamin D plasma dengan tahap CRP puncak, keperluan mesin pengudaraan mekanikal invasif, dan tempoh penggunaan mesin pengudaraan mekanikal invasif, dengan ujian Mann-Whitney. Analisis regresi multivariate dilakukan untuk menentukan factor predisposisi untuk tahap vitamin D.

Keputusan: Tidak terdapat perbezaan yang ketara antara vitamin D yang mencukupi berbanding kekurangan vitamin D terhadap kematian: 37.5% lawan 37.84%; $p = 0.880$. Penilaian hasil sekunder mendedahkan perbezaan yang tidak ketara dalam CRP puncak; (median 151.3mg/L, IQR $\pm 132.875\text{mg/L}$ lawan median 144.2mg/L, IQR $\pm 195.1\text{mg/L}$; nilai $p = 0.350$), keperluan mesin pengudaraan mekanikal; 64.29% lawan

52.70%; nilai $p = 0.425$, dan tempoh penggunaan mesin pengudaraan mekanikal; (median 3 hari, IQR $\pm$ 18.25hari lawan median 3.5hari, IQR $\pm$ 15.25hari; nilai $p = 0.675$).

Kesimpulan: Tiada perkaitan yang ketara ditemui antara kekurangan vitamin D dan tahap CRP puncak, keperluan mesin pengudaraan mekanikal invasif, tempoh penggunaan mesin pengudaraan mekanikal invasif, dan kematian.

Kata kunci: Kekurangan vitamin D, tahap vitamin D plasma, COVID-19, SARS-CoV-2, 25(OH)D, ribut sitokin, CRP, mesin pengudaraan mekanikal invasive, kematian.

ABSTRACT

Background: Vitamin D has immunomodulation properties by reducing the release of pro-inflammatory cytokines besides reducing influenza virus replication and destruction of invading pathogens. Vitamin D deficiency could be a readily modifiable risk factor that can potentially affect the outcome of COVID-19. We aim to study the association between vitamin D deficiency with disease progression, mortality and morbidity in COVID-19.

Methods: This was a cross-sectional study involving a total of 88 patients who were diagnosed with COVID-19 and were admitted to the ICU. Patients were classified into the plasma vitamin D sufficient group ($25(\text{OH})\text{D} \geq 75 \text{ nmol/L}$) and the vitamin D deficient group ($25(\text{OH})\text{D} < 75 \text{ nmol/L}$). The primary outcome measured was the association of plasma vitamin D deficiency with ICU mortality using the Chi-Square test. Secondary outcomes were the association of plasma vitamin D deficiency with peak C-Reactive Protein (CRP) level, the requirement of invasive mechanical ventilation, and the duration of invasive mechanical ventilation using the Mann-Whitney test.

Results: Vitamin D deficiency was observed in 84.09% of the study population. There was no significant difference between vitamin D sufficient vs vitamin D deficient towards mortality; 37.5% vs 37.84%; $p = 0.880$. The assessment of secondary outcomes revealed insignificant difference in peak CRP (median 151.3 mg/L, IQR $\pm$ 132.875 mg/L vs median 144.2 mg/L, IQR $\pm$ 195.1 mg/L; p -value = 0.350), requirement of mechanical ventilator (64.29% vs. 52.70%; p -value = 0.425), and duration of mechanical ventilation

(median 3 days, IQR $\pm$ 18.25 days vs median 3.5 days, IQR $\pm$ 15.25 days; p -value = 0.675).

Conclusion: No significant associations were found between vitamin D deficiency and peak CRP level, the requirement of an invasive mechanical ventilator, duration of invasive mechanical ventilator, and mortality.

Keywords: *Vitamin D deficiency, plasma vitamin D level, COVID-19, SARS-CoV-2, 25(OH)D, cytokine storm, CRP, invasive mechanical ventilation, mortality.*

CHAPTER 1: INTRODUCTION

Introduction

Novel coronavirus (SARS-CoV-2), the causative agent for Coronavirus disease 2019 (COVID-19) pandemic were first reported in Wuhan, China, in December 2019. The disease has a spectrum of manifestations which can present as mild upper respiratory tract infection symptoms such as fever, sore throat, cough, runny nose, myalgia, and malaise, to a moderate or severe parenchymal lung disease that may lead to acute respiratory failure, septic shock, or even death (1).

Vitamin D is a naturally occurring fat-soluble secosteroid with many properties, including immune modulation, anti-inflammation, antioxidant, and antifibrosis (2). The association between vitamin D deficiency and COVID-19 severity was initially postulated in a narrative review by Rhodes et al.. The study has shown that every 1 degree of latitude increase to the north of 28 degrees is associated with a 4.4% increase in mortality. The association of COVID-19 mortality and latitude suggests that the effect of ultraviolet light exposure plays a role in the activation of vitamin D in the skin, as a possible modifiable risk factor in COVID-19 disease severity and mortality (3).

As of 3rd January 2021, Malaysia recorded 119,077 cumulative cases of COVID-19. EPI update COVID-19 ending on 3rd January 2021 shows 26.6% ICU utilisation rate and 0.4% cumulative deaths (4). A study conducted by Baktash V et al. involving COVID-19 patients in a district general hospital in the UK found that patients with vitamin D deficiency demonstrated higher peak CRP levels, higher incidences of ventilation requirement and high dependency unit (HDU) admissions (5). Similarly, a case-controlled study conducted in Guangxi People's Hospital, China, by K.Ye et al. reported that 80% of severe cases of COVID-19 have vitamin D deficiency, whereas 36% of mild to moderate cases have vitamin D deficiency (6).

We conducted a single-centre, retrospective observational study of patients admitted to the intensive care unit (ICU) with laboratory evidence of COVID-19 infection. Patients were divided into serum vitamin D deficient and sufficient groups. Analysis was conducted on serum C-reactive protein (CRP), which is a marker of inflammation, requirement of invasive mechanical ventilation, duration of ventilation, and mortality.

Literature Review

In early 2020, Ye et al. conducted a case-control study at The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China, to determine the relationship between serum vitamin D levels and the severity of COVID-19 infection. Patients diagnosed with COVID-19 were stratified into mild/moderate or severe/critical disease status based on respiratory rate, oxygen saturation, the ratio of partial pressure of oxygen to fraction of inspired oxygen, and lung imaging study (6).

Serum vitamin D level was defined as deficiency ($25(\text{OH})\text{D} < 50 \text{ nmol/L}$), vitamin D insufficiency ($50 \text{ nmol/L} \leq 25(\text{OH})\text{D} < 75 \text{ nmol/L}$), vitamin D sufficiency ($25(\text{OH})\text{D} \geq 75 \text{ nmol/L}$) according to the Endocrine Society clinical practice guideline. The study found that serum vitamin D levels were significantly lower in severe/critical COVID-19 (38.2 nmol/L) than in mild/moderate cases (56.6 nmol/L), with 80% of severe/critical patients having vitamin D deficiency, and only 36% of mild/moderate cases having vitamin D deficiency (OR: 7.11; 95% CI:1.63–37.16). This study shows a strong correlation between vitamin D deficiency and severity, despite the statistical strength of 0.764, slightly lower than most epidemiologic studies with a power of 0.8 (6).

A retrospective, cross-sectional study by Maghbooli et al. was conducted at Sina Hospital, Tehran, to investigate the association between serum vitamin D level and its effect on adverse clinical outcomes and parameters of immune function and mortality in COVID-19. In their study involving 235 patients, vitamin D sufficiency was defined as serum $25(\text{OH})\text{D} \geq 30 \text{ ng/mL}$. It was found that vitamin D-sufficient patients in their study were associated with a lower risk of unconsciousness, hypoxia (arterial blood oxygen saturation $< 90\%$), lower serum CRP level and lymphocyte percentage in the blood. However, there was no significant difference in the rate of

ICU admissions, ARDS, the requirement of intubation, multiorgan damage, and acute kidney injury.

The study's major limitations were that not all COVID-19 patients in Sina Hospital had their serum vitamin D measured, and not all patients had laboratory tests to confirm their COVID-19 status.

Study Objectives

General Objectives

To study the association between vitamin D deficiency and the disease progression and outcome of COVID-19 in the Intensive Care Unit (ICU) at Penang General Hospital.

Specific Objectives

To study the association between vitamin D level with:

1. Disease progression in terms of ventilator requirement and peak CRP level.
2. Morbidity in terms of days of invasive mechanical ventilation.
3. ICU Mortality.

Null Hypothesis

There was no difference observed between the vitamin D-sufficient and vitamin-D deficient groups in:

1. Disease progression in terms of ventilator requirement and peak CRP level.
2. Morbidity in terms of days of invasive mechanical ventilation.
3. ICU Mortality.

Alternative Hypothesis

There was significant difference observed between the vitamin D-sufficient and vitamin-D deficient groups in:

1. Disease progression in terms of ventilator requirement and peak CRP level.
2. Morbidity in terms of days of invasive mechanical ventilation.
3. ICU Mortality.

CHAPTER 2: STUDY PROTOCOL

Research Methods and Methodology

Research Design

Cross-sectional, retrospective, observational study.

Study Period

Six months (January 2021 to June 2021)

Study Population

COVID-19 patients who were positive for SARS-CoV-2 on qualitative polymerase chain reaction assays (PCR) or antigen rapid test kit (RTK-Ag), admitted to the intensive care unit of Penang General Hospital who do not have any contraindications as mentioned in the exclusion criteria.

Study Area

Intensive Care Unit, Penang General Hospital, Georgetown, Penang.

Subject Criteria

Inclusion Criteria

- Positive PCR/ rapid PCR/ RTK-Ag/ gene expert
- Patients aged 18 years and above
- Admitted to ICU of Penang General Hospital
- Baseline plasma 25(OH)D level assay done on admission into ICU

Exclusion Criteria

- Patient age below 18 years
- Pregnancy
- Diagnosed with advanced (stage 3 to 4) cancer
- Chronic steroid therapy
- Severely immunocompromised (AIDS, CD4<200)
- Pre-existing autoimmune diseases
- Massive brain infarct or intracranial bleed
- Pre-existing liver failure

Sample Size Estimation

Sample size was estimated for association of serum vitamin D level and mortality for this study. We planned a study of a continuous response variable from independent control and experimental subjects with 0.25 control(s) per experimental subject. In a previous study, the response within each subject group was normally distributed with a standard deviation of 77.8 (7). If the true difference in the experimental and control means is 55, we will need to study 80 experimental subjects and 20 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. The Type I error probability associated with this test

of this null hypothesis is 0.05. A 10% dropout rate was taken into account. Therefore a total of 88 samples were collected.

The data were recorded using Microsoft Excel and analysed using IBM SPSS Statistics for Windows Version 26.0. The numerical data (age, days of mechanical ventilation, peak CRP level, serum vitamin D level) was presented as median with inter-quartile range (IQR). The Mann-Whitney test was used to analyse continuous data. Categorical data (gender, race, ventilated or not ventilated, vitamin D sufficient or deficient) was presented as the frequency with percentage and analysed with the Chi-square test. Multivariate logistic regression analysis was employed to adjust for the confounding effect. P-values <0.005 is deemed significant.

Sampling Method

Convenience sampling was applied by tracing the list of COVID-19 patients admitted into the ICU during the study period from the ICU census.

Subject Recruitment

The list of patients obtained from the ICU census was screened for the availability of plasma 25(OH)D level assay from the hospital's centralised electronic laboratory reporting system. Medical records of the shortlisted patients were traced from the record office and were assessed for eligibility for recruitment into this study based on the inclusion criteria. The patients who fit into the exclusion criteria were excluded from the study.

Research Tools

Clinical data were extracted from the medical records and stored in a predefined electronic data extraction sheet created for this study. The extracted data were cross-validated and included baseline demographic information, clinical characteristics, and laboratory data during the stay in the intensive care unit.

Operational Definitions

COVID-19 Patients

Patients tested SARS-CoV-2 positive with PCR/rapid PCR/RTK/gene expert.

Plasma Vitamin D level

We adopted the JCEM recommendation in our study, in which patients with total plasma 25(OH)D $\geq 75\text{nmol/L}$ ($\geq 30\text{ng/mL}$) were classified into the vitamin-D sufficient group, whereas patients with total plasma 25(OH)D $< 75\text{nmol/L}$ ($< 30\text{ng/mL}$) were classified into the vitamin D deficient group.

Serum CRP level

The consensus reference interval for C-Reactive Protein for adults used in this study was $< 5\text{mg/L}$. We recorded the serum CRP level in mg/L .

Invasive Mechanical Ventilation

Ventilated patients are those who require endotracheal intubation and the use of a ventilator to control and maintain their respiration. This term excludes the patients who were put on high-flow nasal cannula (HFNC) or non-invasive ventilation via a mask (NIV). The duration of invasive mechanical ventilation was recorded as the number of days.

Data Collection Method

All data were extracted from the medical record by an investigator and recorded on predefined electronic data extraction sheet.

The recorded information includes:

- Demographic information: Registration number, age, gender, race, age, the date of COVID-19 tests, date of admission to ICU, date of discharge from hospital, date of death, presence of co-morbid (hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, and obesity), and vaccination status.
- Supplemental oxygen therapy: High flow nasal cannula, non-invasive ventilation, date of intubation/extubation, PaO₂/FiO₂ ratio.
- Blood investigations: Plasma vitamin D (25(OH)D) level, CRP level, full blood count, renal profile with electrolytes, liver function test, and other marker of inflammations.
- Outcome and cause of death.

Proposed Data Analysis

The data were recorded using Microsoft Excel and analysed using IBM SPSS Statistics for Windows Version 26.0. The numerical data (age, days of mechanical ventilation, peak CRP level, serum vitamin D level) was presented as median with inter-quartile range (IQR). The Mann-Whitney test was used to analyse continuous data. Categorical data (gender, race, ventilated or not ventilated, vitamin D sufficient or deficient) was presented as the frequency with percentage and analysed with the Chi-square test. Univariate logistic regression analysis was employed to adjust for the confounding effect. $P = <0.005$ is deemed significant.

GANTT Chart

Table 1: Projected Chronological Progress of Retrospective Observational Study

	Feb 21	Dec 21 – Jan 22	May – July 22	July – Aug 22	Aug 22	Sept 22	Oct 22	Nov 22
Proposal presentation								
Proposal submission								
Data collection								
Data analysis								
Project write-up								
Presentation of the preliminary report								
Presentation of the final report								
Submission to PPSP								

Study Flow Chart

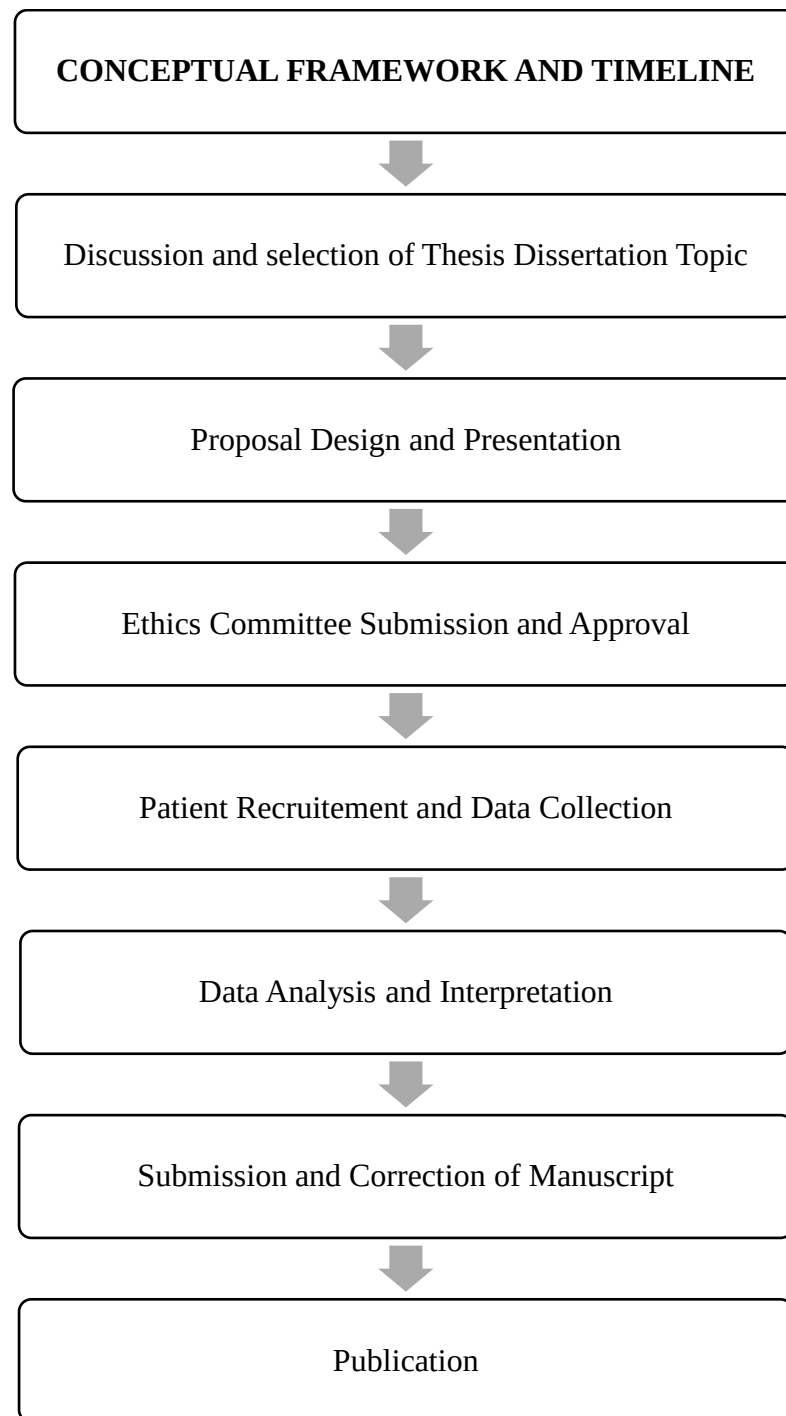


Figure 1: Study Flowchart

Ethical Consideration

Vulnerability

This study was commenced after a full review and authorisation from the ethics review panel of the Jawatankuasa Etika Penyelidikan Manusia USM (JEPeM) and the Medical Research and Ethics Committee of the Ministry of Health, Malaysia (MREC).

This was a retrospective observational study, whereby patients enrolled in this study were not subjected to any form of risk to their health and well-being. The study did not affect the patient's management and medication. It did not affect the doctor's judgement in the decision-making, regardless of their plasma vitamin D level.

There will be no change of management or medication, or educational sessions to be conducted in the future after the study results are obtained. We hoped that this study would establish the role of vitamin D in the disease process and severity to allow healthcare personnel to provide evidence-based advice to encourage vitamin D supplementation in the Malaysian population as a reasonable primary prevention measure.

Declaration of conflict of interest

All investigators conducting this study are practising as anaesthesiology medical officers and specialists under the Ministry of Higher Education (MOE) and Ministry of Health (MOH) and are not affiliated with any third party that may influence the outcome of this study. Neither the patient nor the principal investigators will receive any form of reimbursement or incentives.

Privacy and Confidentiality

All information obtained in this study will be kept and handled in a confidential manner in accordance with applicable laws and/or regulations. When publishing or presenting the study results, the identity of the participant will not be revealed without the participant's expressed consent. Individuals involved in this study, qualified monitors and auditors, and governmental or regulatory authorities may inspect the study data where appropriate and necessary.

The study data will be stored in the principal investigator's laptop, which requires a password to access the file. The study data will be stored for a minimum of 3 years after the study's completion. After the period of storage, all paper files or CDs will be shredded, and any electronic files on memory drives, PCs, laptops and files saved will be permanently deleted.

All the researchers will adhere to the principles of the Declaration of Helsinki and the Malaysian Good Clinical Practice Guidelines.

Ethical Approval



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



Tel: 03-3362 8888/8205

Ref : 22-00650-XT6 (2)

Date : 15-April-2022

DR UNG XIU MING
HOSPITAL PULAU PINANG

Dear Sir/ Mdm,

ETHICS INITIAL APPROVAL: NMRR ID-22-00650-XT6 (IIR)
VITAMIN D DEFICIENCY IN COVID-19 PATIENT: AN ASSOCIATION TOWARDS DISEASE PROGRESSION, MORBIDITY AND MORTALITY

This letter is made in reference to the above matter.

- The Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) has provided ethical approval for this study. Please take note that all records and data are to be kept strictly **CONFIDENTIAL** and can only be used for the purpose of this study. All precautions are to be taken to maintain data confidentiality. Permission from the District Health Officer / Hospital Administrator / Hospital Director and all relevant heads of departments / units where the study will be carried out must be obtained prior to the study. You are required to follow and comply with their decision and all other relevant regulations.

- The investigators and study sites involved in this study are:

HOSPITAL PULAU PINANG
Ung Xiu Ming (Principal Investigator)
Chin Ji Zhang
Mohamad Hasyizan Hassan
Huda Zainal Abidin
Lim Chew Har

- The following study documents have been received and reviewed with reference to the above study:

Documents received and reviewed with reference to the above study:

- Study Protocol Version 5, dated 15-March-2022
- Clinical Report Form / Data Collection Form Version 1, dated 12-November-2021
- Investigator's documents: Declaration of Conflict of Interest (COI), IA-HOD-IA, and CV:
 - Ung Xiu Ming (Principal Investigator)
 - Chin Ji Zhang
 - Mohamad Hasyizan Hassan
 - Huda Zainal Abidin
 - Lim Chew Har

- Please note that ethical approval is valid until **14-April-2023**. The following are to be reported upon receiving ethical approval. Required forms can be obtained from the National Medical Research Registry (NMRR) website:

- Continuing Review Form** has to be submitted to MREC within 2 months (60 days) prior to the expiry of ethical approval.

22-00650-XT6 (2)

- ii. **Study Final Report** upon study completion to the MREC.
- iii. Ethical approval is required in the case of **amendments/changes** to the **study documents/ study sites/ study team**. MREC reserves the right to withdraw ethical approval if changes to study documents are not completely declared.

6. This study involves the following methods:

- i. **Retrospective**
- ii. **Secondary Data**

7. Please take note that the reference number for this letter must be stated in all correspondence related to this study to facilitate the process.

Comments (if any): NIL

Project Sites:

HOSPITAL PULAU PINANG

Decision by Medical Research & Ethics Committee:

- (☒) Approved
- (☐) Disapproved

Date of Approval: 15-April-2022

DR HJH SALINA ABDUL AZIZ
Chairperson
Medical Research & Ethics Committee
Ministry of Health Malaysia
MMC No: 27117

NA/Approval2022/Mrecshare

11th April 2022

Dr. Ung Xiu Ming
Department of Anesthesiology
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

JEPeM Code : USM/JEPeM/22010006

Protocol Title: Vitamin D Deficiency: An Association Towards Disease Progression, Morbidity and Mortality in COVID-19 Patients – A Retrospective Study.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/22010006**, which should be used for all communications to JEPeM-USM in relation to this study. This ethical approval is valid from **11th April 2022** until **10th April 2023**.

Study Site: Intensive Care Unit, Hospital Pulau Pinang.

The following researchers are also involved in this study:

1. Dr. Mohamad Hasyizan Hassan
2. Dr. Chin Ji Zhang
3. Dato' Dr. Lim Chew Har
4. Dr. Huda Zainal Abidin

The following documents have been approved for use in the study.

1. Research Proposal

In addition to the abovementioned documents, the following technical documents were included in the review on which this approval was based:

1. Case Report Form (CRF)

The list of JEPeM-USM members present during the full board meeting reviewing your protocol is attached.

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

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

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

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

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

Thank you.

"WAWASAN KEMAKMURAN BERSAMA 2030"

"BERKHIDMAT UNTUK NEGARA"

Sincerely,

DR. NOOR AMAN A. HAMID
Deputy Chairperson
Jawatankuasa Etika Penyelidikan (Manusia), JEPeM
Universiti Sains Malaysia

Date of meeting : 28th February 2022
Venue : Through WEBEX Application
Time : 9.00 a.m – 2.00 p.m
Meeting No : 535

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Members of Committee of the Jawatankuasa Etika Penyelidikan (Manusia), JEPeM Universiti Sains Malaysia who reviewed the protocol/documents are as follows:

Member (Title and Name)	Occupation (Designation)	Male/ Female (M/F)	Tick (✓) present during review process
Deputy Chairperson: Dr. Noor Aman A. Hamid	Deputy Chairperson of Jawatankuasa Etika Penyelidikan (Manusia), JEPeM USM	M	✓ (Deputy Chairperson)
Member Secretary: Assoc. Prof. Dr. Wong Kah Keng	Member Secretary of Jawatankuasa Etika Penyelidikan (Manusia), JEPeM USM	M	✓
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Secretariat: Miss Siti Fatimah Ariffin	Research Officer	F	✓
Members :			
1. Assoc. Prof. Dr. Adibah Ibrahim	Lecturer, School of Medical Sciences	F	✓
2. Dr. Juhaida Daud	Representative for Director of Hospital USM	F	✓
3. Prof. Dr. Lee Yeong Yeh	Lecturer, School of Medical Sciences	M	✓
4. Dr. Michael Wong Pak Kai	Lecturer, School of Medical Sciences	M	✓
5. Assoc. Prof. Dr. Mohd Hashairi Fauzi	Lecturer, School of Medical Sciences	M	✓
6. Mrs. Norleha Mohd Noor	Executive Secretary, Office of Director of Hospital USM	F	✓
7. Assoc. Prof. Dr. Saedah Ali	Lecturer, School of Medical Sciences	F	✓
8. Dr. Surianti Sukeri	Lecturer, School of Medical Sciences	F	✓
9. Mrs. Zawiah Abu Bakar	Community Representatives	F	✓

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

DR. NOOR AMAN A. HAMID
Deputy Chairperson
Jawatankuasa Etika Penyelidikan (Manusia), JEPeM
Universiti Sains Malaysia

CHAPTER 3: MANUSCRIPT

Title Page

Title

Vitamin D Deficiency in COVID-19 Patient: An Association towards Disease Progression, Morbidity and Mortality

Running Head

To study the association between vitamin D deficiency and peak CRP level, the requirement of invasive mechanical ventilation, duration of ventilation, and mortality in COVID-19 patients.

Authors

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No conflict of interest between the authors and other research parties is to be declared.