**Trial Protocol**

**Registration number** : ClinicalTrials.Gov Identifier: NCT05348759

**Protocol ID:** 302/64 E

**Title**: Follow-up Study of the Pulmonary Function and CT scan finding in Chronic Kidney Disease Patients After COVID-19 **I**nfection

**1 Principle Investigators:**

**Name**  Solos Jaturapisanukul

**Position**  Nephrologist,Instructor

**Department** Medicine ,Faculty of Medicine,Vajira Hospital

**Telephone** 66-2244-3482 Mobile 6686-29165562

**E-mail:** solos@nmu.ac.th

**Job description** Conceptual design, acquisition, analysis, interpretation of data,drafting the manuscript

**Name** Dr. ThanandaTrakarnvanich

**Position**  Associate Professor

**Department** Medicine ,Faculty of Medicine,Vajira Hospital

**Telephone** 0-2244-3482 Mobile 081-443-1628

**E-mail:** thananda@nmu.ac.th

**Job description** supervised the project, interpreted the data, and contributed towards the writing of the manuscript, had full access to the data in the study, and contributed to the study design

**Name** Dr. Nadwipa Yuangtrakul

**Position**  Pulmonologist,Instructor

**Department** Medicine ,Faculty of Medicine,Vajira Hospital

**Telephone** 6682-2443461

**E-mail:** nadwipa@nmu.ac.th

**Job description** Contributed to data collection , conceived and designed the study,analyze the data of pulmonary function tests,drafting the manuscript

**Name** Assistant Professor Dearada Wangcharoenrung

**Position**  Radiologist,Instructor

**Department** Radiology ,Faculty of Medicine,Vajira Hospital

**Telephone** 6689-0269242

**E-mail:** dearada@nmu.ac.th

**Job description** conducted with the participants and collected the data.Interpret the computer scan,drafting the manuscript

**Name** Dr. Krongkan Kanchanarat

**Position**  Radiologist,Instructor

**Department** Radiology ,Faculty of Medicine,Vajira Hospital

**Telephone** 6682-2443000

**E-mail:** krongkan@nmu.ac.th

**Job description** conducted with the participants and collected the data, Interpret the computer scan

**Name** Dr. Kan Radeesri

**Position**  Radiologist,Instructor

**Department** Radiology ,Faculty of Medicine,Vajira Hospital

**Telephone** 6682-2443000

**E-mail:** kan@nmu.ac.th

**Job description** conducted with the participants and collected the data, Interpret the computer scan,drafting the manuscript

**Name** Assistant Professor Jakravoot Maneerit

**Position**  Dean of Faculty of Medicine

**Department** Faculty of Medicine,Vajira Hospital

**Telephone** 6681-7509110

**E-mail:** jakravoot@nmu.ac.th

**Job description** Administrative, technical, material support and supervision

**Name** Associate Professor AnanManomaipiboon

**Position**  President of the Navamindradhiraj University

**Department** Faculty of Medicine,Vajira Hospital

**Telephone** 6681-8700250

**E-mail:** anan@nmu.ac.th

**Job description** Administrative, technical, material support and supervision

**Name** Ms. Khemika Rojtangkom

**Position**  Research assistant

**Department** Faculty of Nursing, Suan Sunandha Rajabhat University

**Telephone** 662-1601023

**E-mail:** khemika.ro@ssru.ac.th

**Job description** Conducted with the participants and collected the data

**Name** Ms. Chompoonuth Ananthanalapa

**Position**  Research assistant

**Department** Faculty of Nursing, Suan Sunandha Rajabhat University

**Telephone** 662-1601023

**E-mail:** chompoonuth.an@ssru.ac.th

**Job description** Conducted with the participants and collected the data

**Name** Ms. Siwaporn Rungrojthanakit1

**Position**  Research assistant

**Department** Faculty of Medicine, Vajira Hospital

**Telephone** 662-2443000

**E-mail:** siwaporn.ro@nmu.ac.th

**Job description** Conducted with the participants and collected the data

**Name** Ms. Peerawit Thinpangnga

**Position**  Research assistant

**Department** Faculty of Medicine, Vajira Hospital

**Telephone** 662-2443000

**E-mail:** peerawit.t@nmu.ac.th

**Job description** Conducted with the participants and collected the data

**Name** Ms. Joshua Alvior

**Position**  Medical student

**Department** USF Health Morsani College of Medicine,Tampa,Florida,USA

**Telephone** +1-813-468-0954

**E-mail:** peerawit.t@nmu.ac.th

**Job description** Conducted with the participants and collected the data,edited the manuscript

 **2. Responsible person for the participants**

**Name**  Dr. ThanandaTrakarnvanich

**Position**  Associate Professor

**Department** Medicine ,Faculty of Medicine,Vajira Hospital

**Telephone** 0-2244-3482 Mobile 081-443-1628

**E-mail:** thananda@nmu.ac.th

**Protocol Summary**

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| --- | --- |
| **Project name** |  Follow-up Study of the Pulmonary Function and CT scan finding in Chronic Kidney Disease Patients After COVID-19 **I**nfection |
| **Objectives** | **Primary objectives:**- To study the Chest CT and pulmonary function tests in ESRD patients after recovered from COVID-19**Secondary objectives** - To study the factors affecting the pulmonary sequalae after COVID-19 in CKD patients such as oxygen requirement,ventilator need and levels of inflammatory cytokines such as interleukin-6 (IL-6) and C-reactive protein (CRP) |
| **Type of study** | Prospective observational cohort study  |
| **Participants** | Inclusion Criteria:* CKD stage 5 requiring HD or continuous peritoneal dialysis (CAPD ) for more than 3 months
* Age 18-80 years
* Diagnosis of COVID-19 confirmed by real time polymerase chain reaction (RT-PCR) and recovered for more than3 months previously

 Exclusion Criteria:* Patients with history of chronic lung diseases i.e chronic obstructive pulmonary disease (COPD) and restrictive lung disease

Criteria to withdraw from the protocol * Patients who have active disease after enrollment
 |
| **Number of participants** | 100 |
| **Place of study** | - Faculty of Medicine,Vajira Hospital ,Navamindradhiraj University |
| **Outcome measurement** | 1. CT findings :

CT scores reflecting the extent of lobar involvement were obtained using a five-point scale (0: 0%, 1: <5%, 2: 5%-25%, 3: 26%-50%, 4: 51%-75%, 5: >75%; range, 0-5; global score, 0-25).1. Pulmonary function tests

Spirometry will be was performed and mearsure the forced vital capacity (FVC), forced expiratory volume in the first second of exhalation (FEV1), forced mid-expiratory flow (FEF25%-75%), and the FEV1/FVC ratio before and after bronchodilator administration (2 puffs of salbutamol via spacer)  |
| **Follow up** | V1 – At 3 months after COVID-19 recovery  |
| **Statistical analysis** | Continuous variables were reported as mean and standard deviation or median and interquartile range (IQR), as appropriate. The PFT and CT scan results were reported as absolute and relative frequencies and percentages [%] of prevalence with the 95% confidence interval [95% CI]). The associations of various factors, such as ventilator usage, oxygen requirements, laboratory markers (IL-6 and CRP), mode of RRT, and changes in PFT and CT scan results were estimated using chi-squared test or Fisher’s exact test when the data were qualitative, and Kruskal–Wallis or Mann–Whitney U test when the data were quantitative. IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY, USA: IBM Corp) was used for all statistical analyses. Statistical significance was defined as p(two-sided) ≤ .05. |
| **Duration of follow up** | 3 month or more |
| **Duration of study** | 6 month |

1. **Rational and Background**

COVID-19 is associated with increased morbidity and mortality in patients with chronic kidney disease (CKD) on dialysis. CKD requires particular emphasis during the pandemic due to concern for increased susceptibility to infection from greater use of health facilities in people undergoing maintenance hemodialysis. COVID-19 due to SARS-CoV-2 involves multiple organs and lung injury is one of the most clinical manifestations. The binding of SARS-CoV-2 to the ACE2 receptors at target cells ,including type II pneumocytes ,and alveolar macrophages in the lung could arise into acute systemic inflammatory responses and cytokine storm.The consequentially leading to lung-resident dentritic cells (rDCs) activation, T lymphocytes production and release antiviral cytokines into the alveolar septa and interstitial compartments resulting in diffuse alveolar epithelium destruction,hyaline membrane formation, alveolar septal fibrous proliferation and pulmonary fibrosis.Although it has been reported that subgroups of COVID-19 survivors developed persistent lung parenchymal injury that persisted at least after 6 months 5-6 ,the data in CKD patients has not been reported yet.In addition, a study of pulmonary function test after COVID-19 is needed to be investigated.Thus,we plan to assess pulmonary sequalae of COVID-19 in hemodialysis (HD) patients and pulmonary function test after recovered of infection at least 3 months.

1. **Objectives:**

 **Primary objectives:**

- To study the Chest CT and pulmonary function tests in ESRD patients after recovered from COVID-19

**Secondary objectives**

 - To study the factors affecting the pulmonary sequalae after COVID-19 in CKD patients such as oxygen requirement,ventilator need and levels of inflammatory cytokines such as interleukin-6 (IL-6) and C-reactive protein (CRP)

### 6. **Study design**

6.1 Type of study

Prospective observational cohort study

**6.2** Inclusion,exclusion and criteria to terminate the study

Inclusion Criteria:

* CKD stage 5 requiring HD or continuous peritoneal dialysis (CAPD ) for more than 3 months
* Age 18-80 years
* Diagnosis of COVID-19 confirmed by real time polymerase chain reaction (RT-PCR) and recovered for more than3 months previously

 Exclusion Criteria:

* Patients with history of chronic lung diseases i.e chronic obstructive pulmonary disease (COPD) and restrictive lung disease

Criteria to withdraw from the protocol

* Patients who have active disease after enrollment

**7. Sample size calculation**

 This study aimed to identify the prevalence of pulmonary abnormalities in both radiographic findings and PFT results after recovery from COVID-19 infection. We used the following equation for estimating an infinite population proportion:

$$n\_{ }=\frac{Z\_{α/2}^{2} p(1-p)}{d^{2}}$$

where, *n* is the sample size

 *Zα/2*is the area under the normal curve

 The significance level for the hypothesis was set to α = 0.05; thus Zα/2 = 1.96

 d is the acceptable error (d = 0.10)

 *p* is the prevalence of lung abnormality, defined as *p* = 0.50, that yielded the maximum sample size; thus,

*n = 1.962 x 0.50 (1 - 0.50)*

*0.102*

*n = 97*

We recruited 100 cases by convenience sampling from a population of end-stage kidney disease (ESKD) patients who had recovered from COVID-19 infection.

**8. Methodology:**

1. After written inform consent is obtained, we then collect demographic data and information regarding disease history, coexisting medical conditions, medication history, treatment during COVID-19 infection, including oxygen requirement, and laboratory data (complete blood count [CBC] and measurement of interleukin-6 [IL-6] and C-reactive protein [CRP] levels).

2. At least 3 months post COVID-19 infection, all patients will be evaluated for ongoing respiratory symptoms and undergo PFT and chest CT scans as followed:

**Computed tomography technique**
High-resolution computed tomography (HRCT) was performed in a single breath-hold on a 128-slice multidetector computed tomography (MDCT) scanner (Ingenuity 128; Philips Healthcare Nederland B.V, Netherlands). HRCT was performed with a 1-mm slice thickness with the patient in the supine position during end-inspiration and prone position during end-inspiration.

**Computed tomography interpretation**
Using a Picture Archiving and Communication System (PACS; EV Insite version 3.11.1.500; PSP Corporation, Japan), three radiologists with 9, 10, and 14 years of experience performed consensus interpretations blinded to the patients’ clinical information. The readers assessed the presence of the following CT patterns; consolidation, ground-glass opacities (focal, multifocal, diffuse), mosaic attenuation patterns (hypoattenuating and hyperattenuating areas), perilobular consolidation (organizing pneumonia-like pattern), reticulations, architectural distortion, honeycombing, traction bronchiectasis, pneumatocele, curvilinear lines, nodules, and pleural thickening or pleural effusion.16 Additional findings were annotated separately. The distribution of the patterns was recorded as the upper lobe, middle lobe/lingual, or lower lobe. CT scores reflecting the extent of lobar involvement were obtained using a five-point scale (0: 0%, 1: <5%, 2: 5%-25%, 3: 26%-50%, 4: 51%-75%, 5: >75%; range, 0-5; global score, 0-25).

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Collected demographic data and information regarding disease history, and laboratory data

Perform CT chest and lung function test

Analyze factors that affect primary outcomes

CKD stage5 on dialysis recovered from COVID-19 for more than 3 months เดือนขึ้นไป

**9. Safety considerations**

The participants will have minimal effects from the measurements performed in this study.The anticipated side effects from radiation or pulmonary function testss will be closely monitored.

**10. Declare Conflict of Interest**

None

**11.Case record forms**

 As attached

### **12. Data management and statistical analysis**

Continuous variables were reported as mean and standard deviation or median and interquartile range (IQR), as appropriate. The PFT and CT scan results were reported as absolute and relative frequencies and percentages [%] of prevalence with the 95% confidence interval [95% CI]). The associations of various factors, such as ventilator usage, oxygen requirements, laboratory markers (IL-6 and CRP), mode of RRT, and changes in PFT and CT scan results were estimated using chi-squared test or Fisher’s exact test when the data were qualitative, and Kruskal–Wallis or Mann–Whitney U test when the data were quantitative. IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY, USA: IBM Corp) was used for all statistical analyses. Statistical significance was defined as p(two-sided) ≤ .05.

### **13. Quality assurance**

The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines, and all study methods were carried out in accordance with relevant guidelines and regulations. All patients participating in the study signed an informed consent before enrollment.

**14. Expected outcomes of the study**

This trial contribute to new knowledge, including the consequences of the most affected organ (lung) after COVID-19, which has rarely been reported previously. In addition, the factors that associated with poor pulmonary outcome will also be considered.

**15. Dissemination of results and publication policy**

The data supporting the findings of this study are available from the corresponding author.

**16. Duration of the project**

|  |  |
| --- | --- |
| **Activities** | **Duration of study 2021-2022** |
| Dec2021 | Jan 2022 | Feb 2022 | March2022 | April 2022 | May 2022 | June2022 | July2022 | Aug2022 |
| Review literature |  |  |  |  |  |  |  |  |  |
| Write protocol |  |  |  |  |  |  |  |  |  |
| Propose proposal |  |  |  |  |  |  |  |  |  |
| Start study |  |  |  |  |  |  |  |  |  |
| Analysis and conclusion |  |  |  |  |  |  |  |  |  |
| Present  |  |  |  |  |  |  |  |  |  |
| Write paper |  |  |  |  |  |  |  |  |  |

**17. Problems anticipated**

 The number of patients needed to be recruited may not be adequate.We then may have to include more samples from other centers.The technician to perform the PFT may not be enough .This may be managed by hiring the outsource staffs.

**18. Project management**

TT: supervised the project, interpreted the data, and contributed towards the writing of the manuscript, had full access to the data in the study, and contributed to the study design.

**Acquisition, analysis, and interpretation of data:** SJ, NY, DW, KK, KR, SR, PT, CA, JA, and TT

**Drafting the manuscript:** TT, SJ, NY, and DW

**Critical revision of the manuscript for important intellectual content:** all authors

**Administrative, technical, and material support**: TT, NW, AM, JM, and DW

**Supervision:** TT, AM, and JM

**19.Ethics**

 This trial was prospective registered at ClinicalTrials.Gov Identifier: NCT05348759

on 26/04/2022 and was approved by the institutional review board of the Faculty of Medicine,Vajira Hospital,Navamindradhiraj University,Bangkok,Thailand (COA 302/64)

**19.Informed consent forms**

The participants will be contacted and received information from the research coordinator.The right and decision to participate the study depend on the patients without enforcement . The participants will get the information they need to make an informed decision.

**20.Budget**

 This work was supported by a grant from Navamindradhiraj University Grant (no: 018/2566)

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