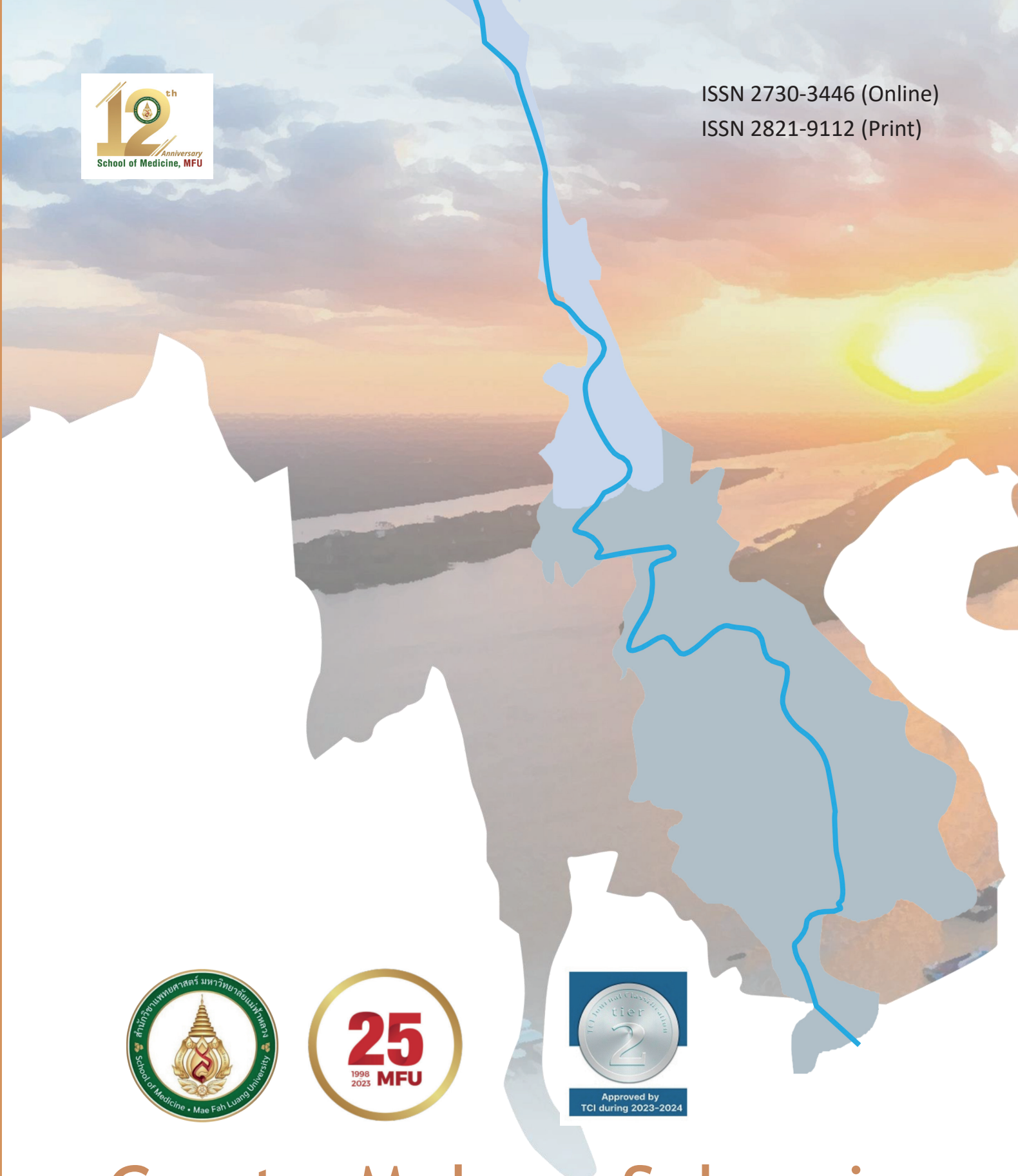

ISSN 2730-3446 (Online)
ISSN 2821-9112 (Print)

Greater Mekong Subregion Medical Journal

GMSMJ

Vol. 4 No. 1 January – April 2024

Journal Name	Greater Mekong Subregion Medical Journal
Abbreviation	GMSMJ
ISSN (Online)	2730-3446
ISSN (Print)	2821-9112
Owner	School of Medicine, Mae Fah Luang University
Aims and Scope	Greater Mekong Subregion Medical Journal is an online and printed, peer reviewed international scientific journal published by Mae Fah Luang University. The journal aims to publish articles in the field of basic and advanced clinical research in medicine and related health sciences, medical education as well as community medicine in Thailand, international and especially in countries of Greater Mekong Subregion. Manuscripts submitted to Greater Mekong Subregion Medical Journal will be accepted on the conditions that the author must not have previously submitted that paper to another journal elsewhere. The journal will not charge for any submission. The reproduction or copy of the articles included the pictures should be under the permission of the publisher.
Language	Full text and Abstract in English
Abstracting and Indexing Information	Thai citation index (TCI) and Google scholar
Frequency	3 issues per year (January-April, May-August and September-December)
Editorial office	School of Medicine, Mae Fah Luang University 365 Moo 12 Nanglae Sub District, Muang District, Chiang Rai 57100, THAILAND Phone: 053-916566 Fax: 053-916570 E-mail: med@mfu.ac.th, apichai.lee@mfu.ac.th Website: http://medicine.mfu.ac.th https://he02.tci-thaijo.org/index.php/gmsmj/issue/view/17968
Support Agency	Mae Fah Luang University

Published by:
Tana Press, Phone +6625304114, Fax +6621088950, Website www.tanapress.co.th

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Publication Ethics

Publication ethics of Greater Mekong Subregion Medical Journal (GMSMJ)

Greater Mekong Subregion Medical Journal presents articles in the field of basic and advanced clinical research in medicine and related health sciences, medical education as well as community medicine in Thailand and international, especially in countries of Greater Mekong Subregion.

The journal publishes 3 issues a year: Issue 1 (January - April), Issue 2 (May - August) and Issue 3 (September -December). All submitted research articles and review articles will be evaluated by a single blinded peer-review process and reviewed by 2 experts who have knowledge, expertise, and experience in the field of medicine and related health sciences prior to publication. The journal encloses the information of authors and reviewers. In case of a difference of evaluation, the article evaluation will be considered and given a final decision.

Greater Mekong Subregion Medical Journal establishes the roles and duties for three different groups in the process of article publication: author (s), editor, and reviewers. The following information is given to the three groups of people so that they will strictly abide by its benefits of those concerns, including readers and others in academia.

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Contents


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Original Article

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Greater Mekong Subregion Medical Journal

Impact of Type 2 Diabetes Mellitus on Severity and Outcomes of the Patients Admitted with COVID-19 Infection: A Case-Control Study

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Received 8 August 2023 • Revised 20 August 2023 • Accepted 22 November 2023 • Published online 1 January 2024

Abstract:

Background: COVID-19 pandemic caused global effects on health care, economics and society for a long period. Significant proportion of COVID-19 infected patients had diabetes mellitus. Meta-analysis showed increase on severity and mortality rate of COVID-19 in diabetes compared with non diabetes. In Thailand, a few clinical research to be conducted in case-control study to determine the effects of diabetes and in hospital glycemic control on outcomes of COVID-19.

Objective: This research aim was to compare the clinical presentations, laboratory findings, x-ray findings and treatment outcomes between patients admitted in the hospital by COVID-19 infection with diabetes and without diabetes and to determine factors contributing to the outcomes of COVID-19 in diabetic subgroup.

Method: A retrospective cohort study in case-control design was carried out. One hundred and eighty five cases of diabetes after 30 year of age was collected as a case. Age and sex matched for each selected case were served as control. Clinical, laboratory, radiological and treatment outcome information were analyzed in comparison between diabetes and non diabetes. Subgroup analysis in diabetic patients was performed to assess factors related to outcomes according to insulin treatment during admission. Chi-square and unpaired t-test were used in statistical analysis to determine the difference between groups.

Results: Clinical manifestations of COVID-19 infection were not different between diabetes and non diabetes. Diabetic group had more pulmonary infiltration, more white blood cell and neutrophil count at admission. On treatment and outcomes, diabetic group need more and longer antiviral treatment, more steroid treatment and oxygen treatment than non diabetic group. Severe pulmonary complication, ARDS, developed more significantly in diabetic group and need transfer for ventilatory support. Subgroup analysis of diabetic patients revealed that insulin treatment group had longer duration of antiviral treatment, higher percentage

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GMSMJ 2024; 4 (1): 1-16

on steroid and high flow oxygen treatment and more ARDS which need transfer for mechanical ventilatory support than non insulin treatment group.

Conclusion: This study confirmed the impact of diabetes mellitus on clinical, laboratory findings, radiological findings and the severity, outcomes and complications of patients admitted with COVID-19 infection in comparison with non diabetes in Thai patients. The level of HbA1c at admission in diabetic patients did not affect the severity, outcomes and complications, but the need of insulin treatment during admission was the important predictor of poor clinical outcome.

Keywords: Case-control study, COVID-19, Diabetes Mellitus

Introduction

The pandemic of Coronavirus disease or COVID-19 caused by infection of the SARS CoV-2 virus was first recognized 4 years ago in Wuhan, The People Republic of China in December 2019. This pandemic has had a great impact on the entire globe since that time. COVID-19 spread into Thailand early in 2020 and also caused disaster in health care, economics and society that still continues. Due to an aging society, a significant percentage of people had concurrent non communicable diseases (NCDs), diabetes mellitus was the one of the most common of these. A large volume of clinical research on COVID-19 and diabetes came from 5 leading countries with the highest number of scientific articles: United States, China, India, United Kingdom and Italy.[1] Furthermore, much meta-analysis showed increased severity, complications, ICU admission and mortality in diabetic patients who had contracted COVID-19 compared with non-diabetes.[2-4] Diabetes mellitus, one of the leading cause of non- communicable diseases (NCDs) was associated with chronic and low grade inflammatory response in the body. COVID-19 infection caused an acute inflammatory response in the body, characterized by a cytokine storm. The collision of acute on chronic inflammatory state cause many consequences, including acute tissue damage, endothelial dysfunction, hypercoagulability and increased insulin resistance resulting in rapid deterioration to infected patients.[5] In Thailand although there was a large amount of basic research and clinical research on COVID-19, only a small amount of clinical research on the impact of diabetes mellitus and other co-morbid diseases on severity and outcomes of COVID-19 infection were published.[6-10]

Our study was one of the few studies in Thailand that designed as a case-control to determine the impact of type 2 diabetes mellitus on hospitalized COVID-19 patients in clinical presentations, laboratory findings, radiological findings, treatment modalities, treatment outcomes and complications. The second goal was to assess the factors that influenced on the outcomes of COVID-19 between subgroups of diabetic patients.

Materials and method

Study design and population

The study was designed as retrospective cohort and performed in single center at Mae Fah Luang University Medical Center, Chiang Rai, Thailand. The patient data from electronic medical record of all COVID-19 admission between April 2021 and September 2022 were retrieved. The hospital policy had glycosylated hemoglobin (HbA1c) to be assessed in all COVID-19 patients over the age of 30 on the day of admission. Therefore we were able to screen all cases with elevated HbA1c results to identify cases of diabetes mellitus. Laboratory

investigations included glycosylated hemoglobin (HbA1c), complete blood count (CBC), liver function test (LFT) and chest x-ray and were done on admission day. The diagnosis of diabetes mellitus was based on HbA1c criteria proposed by American Diabetes Association guideline 2023 using HbA1c of 6.5%.[11] COVID-19 infection was diagnosed by RT-PCR or rapid COVID-19 antigen test by Antigen Test Kid (ATK) of secretion obtained from nasopharyngeal swabs.

Inclusion criteria:

- Male or female
- Age over 30 years
- Diagnosed as COVID-19 infection by RT-PCR or ATK via secretion from nasopharyngeal swab
- Admission HbA1c ≥ 6.5 % and/or history of type 2 DM in case notes
- Admission HbA1c < 6.5 % as a control

Exclusion criteria:

- Incomplete laboratory or radiological data
- Having had treatment by herbal or alternative medicine for COVID-19 infection

After case selection, a control group was selected by age and sex match of each selected case. The process of screening for case selection was shown in Figure 1.

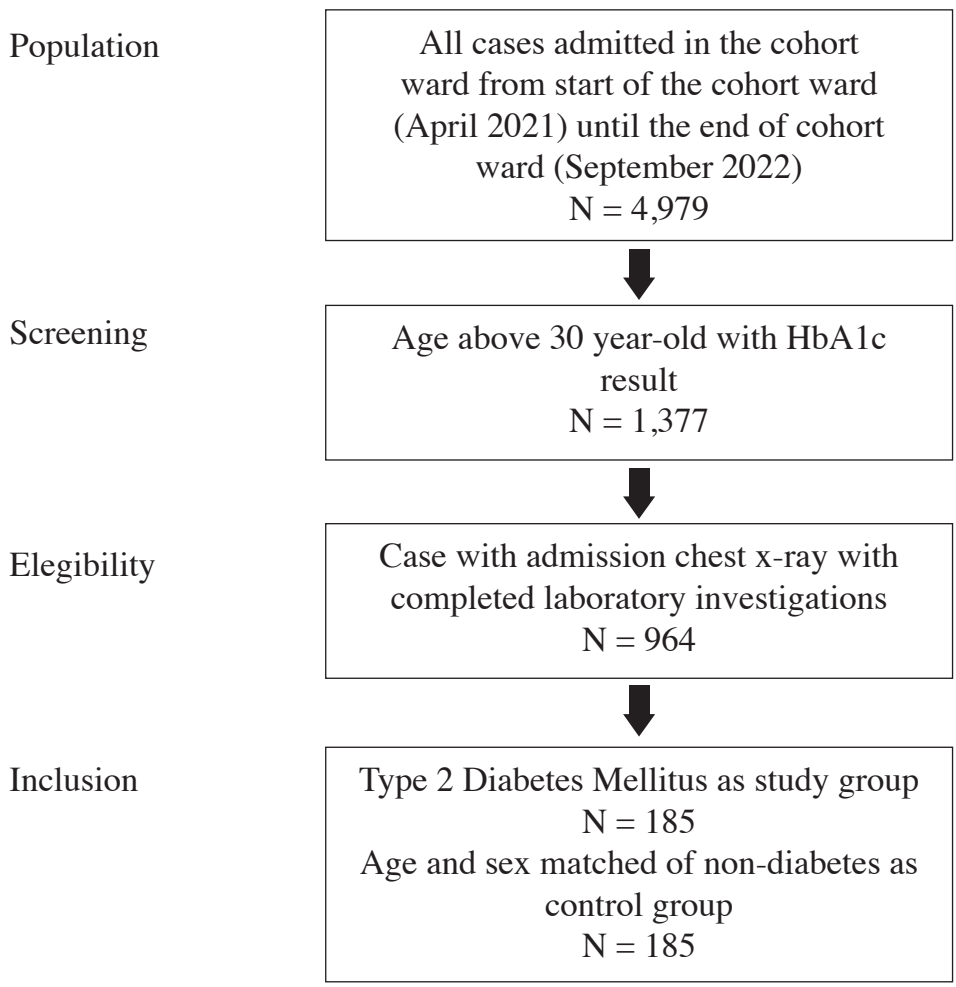

Figure 1 Flow diagram of selection process for case-control

Data collection

Four components of information were gathered from electronic medical record. *Clinical information* consisted of age, sex, presenting symptoms such as fever, cough, secretion, dyspnea, anosmia, myalgia and chest pain. *Laboratory information* consisted of CBC, LFT, HbA1c. *Radiological information* consisted of chest x-ray at PA - upright position and follow up chest x-ray in the following days during hospital admission if available. Chest x-ray was classified by 3 categories. Category 0 showed no evidence of pulmonary infiltration, category 1 was infiltration in one side of the lung, category 2 was infiltration in both lung fields. The chest x-ray was determined by attending physician at the cohort ward and re-assessed by one of the investigator (KC). In some cases, from June 2021 to August 2021, chest x-ray was assessed by computer program using artificial intelligence technology (A.I.) before the films were seen by the attending physicians. The last component of information was *treatment outcome information* which consisted of duration of admission, percentage and duration of antiviral treatment, percentage of bacterial pneumonia co-infection, steroid treatment, oxygen treatment via cannula, need of high flow oxygen treatment, complications especially acute respiratory distress syndrome (ARDS) and referral for mechanical ventilatory support in cases of impending respiratory failure.

Statistical analysis

Demographic data, presenting symptoms, and categories of chest x ray as well as treatment outcomes in categorical variables were analyzed by Chi-square test. Continuous variables consisted of laboratory results such as HbA1c, CBC, LFT, percent of oxygen saturation were compared between groups by unpaired t-test. Clinical treatment outcomes as continuous variables were also compared between groups by unpaired t-test. P-value less than 0.05 was considered as statistical significance. All data analyses were performed using IBM SPSS statistical software version 25.0.

Results

Demographic, clinical characteristics and radiographic findings on admission

For both diabetes and non-diabetes, the mean age was 56. Sixty percent of each group was female. Regarding clinical symptoms during admission, the most common manifestation was cough followed by fever and secretion which were not different between diabetes and non-diabetes groups as well as dyspnea and anosmia. The non-diabetes group had significantly more myalgia and chest pain compared with the diabetic group. Radiographic findings were classified into three groups: no pulmonary infiltration, unilateral infiltration and bilateral infiltration. Comparison between diabetes and non-diabetes revealed significant differences in percentage of every category of chest x-ray. The diabetes group had more pulmonary infiltration at the time of admission compared to non-diabetes group, nevertheless the oxygen saturation in both groups were similar (Table 1).

Table 1 Clinical characteristics, chest x-ray and laboratory findings of age and sex matched of diabetes and non-diabetes COVID-19 infected patients

Characteristics	DM	Non – DM	Statistic	p-value
Total	185 (100.0)	185 (100.0)		
Age (year) Mean (S.D.)	56.0 (11.5)	56.0 (11.5)		
Sex, n (%)				
Male	74 (40.0)	74 (40.0)		
Female	111 (60.0)	111 (60.0)		
Fever, n (%)				
Yes	60 (29.4)	50 (27.0)	1.29[a]	0.255
No	125 (70.6)	135 (73.0)		
Cough, n (%)				
Yes	109 (58.9)	100 (54.0)	0.89[a]	0.345
No	76 (41.1)	85 (46.0)		
Secretion, n (%)				
Yes	57 (30.8)	48 (25.9)	1.08[a]	0.299
No	128 (69.2)	137 (74.1)		
Myalgia, n (%)				
Yes	27 (14.5)	44 (23.8)	5.04[a]	0.025*
No	158 (85.5)	141 (76.2)		
Anosmia, n (%)				
Yes	7 (3.8)	16 (8.6)	3.75[a]	0.053
No	169 (96.2)	178 (91.4)		
Chest pain, n (%)				
Yes	4 (2.2)	14 (7.6)	5.84[a]	0.016*
No	181 (97.8)	171 (92.4)		
Dyspnea, n (%)				
Yes	55 (29.7)	48 (25.9)	0.66[a]	0.417
No	120 (70.3)	137 (74.1)		
Chest x-ray				
Category 0[c]	27 (14.6)	82 (44.3)	41.59[a]	<0.001*
Category 1[d]	66 (35.7)	53 (28.6)		
Category 2[e]	92 (49.7)	50 (27.1)		

Table 1 Clinical characteristics, chest x ray and laboratory findings of age and sex matched of diabetes and non-diabetes COVID-19 infected patients (cont.)

Characteristics	DM	Non – DM	Statistic	p-value
Laboratory	Mean (S.D.)	Mean (S.D.)		
HbA1c (%)	8.2 (2.0)	5.6 (0.4)	-17.07[b]	<0.001*
Hb (g/dl)	13.6 (1.8)	13.3 (1.6)	-1.56[b]	0.119
Hct (%)	39 (4)	39 (4)	-1.26[b]	0.208
WBC (cell/cu.mm.)	6719 (2731)	5903 (2251)	-3.13[b]	0.002*
Neutrophil (cell/cu.mm.)	4715 (2823)	3807 (2127)	-3.49[b]	0.001*
Lymphocyte (cell/cu.mm.)	1513 (640)	1606 (625)	1.42[b]	0.158
Platelet (cell/cu.mm.)	255232 (88909)	243189 (86512)	-1.32[b]	0.188
Albumin (g/dL)	4.1 (0.4)	4.3 (0.3)	3.74[b]	<0.001*
Globulin (g/dL)	3.4 (0.5)	3.4 (0.5)	-0.03[b]	0.976
ALT (U/L)	46 (38)	39 (37)	-1.68[b]	0.095
AST (U/L)	51 (43)	45 (41)	-1.29[b]	0.198
Direct bilirubin (mg/dL)	0.20 (0.11)	0.18 (0.12)	-1.41[b]	0.159
Total bilirubin (mg/dL)	0.43 (0.20)	0.45 (0.24)	0.61[b]	0.543
Alkaline phosphatase (U/L)	87.25 (36.95)	85.18 (38.68)	-0.53[b]	0.599
Oxygen saturation (%)	96.70 (1.96)	97.00 (1.52)	1.63[b]	0.104

[*] statistical significance
[a] categorical variables, Chi square was used to determine statistical difference
[b] continuous variables, Unpaired t-test used to determine statistical difference
[c] no pulmonary infiltration, [d] unilateral pulmonary infiltration
[e] bilateral pulmonary infiltration

Laboratory findings

The average HbA1c in diabetes group was 8.2% and non-diabetes group was 5.6%. The diabetes group tended to have higher white blood cell (6719 vs 5903, p = 0.002) and neutrophil count (4715 vs 3807, p = 0.001) than the non-diabetes group. Liver function test showed that albumin in diabetes group was lower than that in non diabetes group (4.1 vs 4.3, p < 0.001). Other parameters in liver function tests were not different between two groups at the day of admission (Table 1).

Treatment, clinical outcomes and complications

Although a duration of admission between diabetes and non-diabetes group were not different, the percentage requiring antiviral therapy use was higher in diabetes group (92.4% of diabetes group and 69.7% of non-diabetes group had Favipiravir, and 5.9% of diabetes group and none of non-diabetes group had Remdesivir). In addition, a duration of antiviral treatment was longer in the diabetes group (8.0 days vs 5.4 days,

p < 0.001). The incidence of development of bacterial pneumonia diagnosed by sputum examination or clinical pictures was similar between two groups. Because of the increased severity of pulmonary involvement at admission as seen on chest x-ray, the diabetes group required more steroid treatment (51.9% vs 32.4%, p < 0.001). During the stay in hospital, diabetes group developed complication rates of pulmonary infection, adult respiratory distress syndrome (ARDS) that were higher than non diabetes group (12.4% vs 1.6%, p < 0.001) and also required more high flow oxygen therapy (9.2% vs 1.6%, p = 0.001). Consequently the percentage of referral of cases for mechanical ventilatory support was higher in diabetes group (16.8% vs 8.6%, p = 0.019) (Table 2).

Table 2 Treatment, complications and clinical outcomes compared between diabetes and non-diabetes COVID-19 infected patients

Parameters	DM n (%)	Non - DM n (%)	Statistic	p-value
Duration of admission (days)				
Mean (S.D.)	8.6 (3.7)	8.8 (3.0)	0.51	0.607
Duration of anti-viral treatment (days) Mean (S.D.)	8.0 (3.1)	5.4 (4.2)	-6.56	<0.001*
Antiviral treatment: Favipiravir	171 (92.4)	129 (69.7)	31.08	<0.001*
Antiviral treatment: Remdesivir	11 (5.9)	0 (0.0)	3.36	0.001*
Bacterial pneumonia	30 (16.2)	18 (9.7)	3.45	0.063
Steroid treatment	96 (51.9)	60 (32.4)	14.36	<0.001*
Oxygen treatment	55 (29.7)	29 (15.7)	10.41	0.001*
High flow oxygen treatment	17 (9.2)	3 (1.6)	10.36	0.001*
Complication: ARDS	23 (12.4)	3 (1.6)	16.55	<0.001*
Refer for mechanical ventilation	31 (16.8)	16 (8.6)	5.48	0.019*

* statistical significance

By analyzing both groups together (n = 370) and by division into 3 categories due to chest x-ray findings: no pulmonary infiltration (category 0), unilateral infiltration (category 1) and bilateral infiltration (category 2), the group of bilateral infiltration tended to have a greater proportion suffering from cough and dyspnea than the unilateral infiltration group and non-infiltration group. In addition, the level of HbA1c correlated with the severity of pulmonary infiltration as seen on chest x-ray. This finding confirmed that in COVID-19 infected patients with raised sugar levels at admission tended to have more severe inflammatory response to COVID-19 infection. Similarly, increased level of white blood cell and neutrophil count were detected in those patients with bilateral pulmonary infiltration (Table 3).

Subgroup analysis in diabetic patients

According to their HbA1c level, diabetic patients were divided into 3 groups: (1) HbA1c <8%, (2) HbA1c 8-10% and (3) HbA1c >10%. There were no significant difference in presenting symptoms, chest x-ray findings, laboratory investigations, treatment, clinical outcome and complications. However, by division of diabetic patients into two groups, an insulin treatment group and non-insulin treatment group, insulin treatment group showed a notable increase in age, HbA1c and white blood cell count and a decrease in lymphocyte count and albumin level. Table 4 summarized the clinical and laboratory features between diabetes group with insulin treatment and non-insulin treatment. In addition, the data analysis showed that insulin treatment group had longer duration of antiviral treatment (8.8 days vs 7.2 days, p = 0.001), more percentage of bacterial pneumonia (22.6% vs 10.8%, p = 0.031), more steroid treatment (64.3% vs 41.6%, p = 0.002) and oxygen treatment including high flow oxygen (14.2% vs 4.9%, p = 0.029) than non insulin treatment group. Nevertheless, the refer rate for mechanical ventilatory support between the two groups were indifferent (14.3% vs 18.8%, p = 0.412) (Table 5).

Table 3 Demographic, clinical characteristics and laboratory findings of 370 case of COVID-19 classified by chest x-ray, irrespective of diabetic status

Characteristics	Chest x-ray category 0 n (%)	Chest x-ray category 1 n (%)	Chest x-ray category 2 n (%)	Statistic	p-value
Sex					
Male	39 (35.8)	47 (39.5)	62 (43.7)	1.61	0.446
Female	70 (64.2)	72 (60.5)	80 (56.3)		
Fever					
Yes	28 (25.7)	36 (30.3)	46 (32.4)	1.35	0.509
No	81 (74.3)	83 (69.7)	96 (67.6)		
Cough					
Yes	45 (41.3)	78 (65.5)	86 (60.6)	15.18	0.001*
No	64 (58.7)	41 (34.5)	56 (39.4)		
Secretion					
Yes	24 (22.0)	32 (26.9)	49 (34.5)	4.92	0.085
No	85 (88.0)	87 (73.1)	93 (65.5)		
Myalgia					
Yes	19 (17.4)	22 (18.5)	30 (21.1)	0.59	0.741
No	90 (82.6)	97 (81.5)	112 (78.9)		

Table 3 Demographic, clinical characteristics and laboratory findings of 370 case of COVID-19 classified by chest x-ray, irrespective of diabetic status (cont.)

Characteristics	Chest x-ray category 0 n (%)	Chest x-ray category 1 n (%)	Chest x-ray category 2 n (%)	Statistic	p-value
Anosmia					
Male	4 (3.7)	9 (7.6)	10 (7.0)	1.75	0.417
Female	105 (96.3)	110 (92.4)	132 (93.0)		
Chest pain					
Yes	7 (6.4)	5 (4.2)	6 (4.2)	0.81	0.667
No	102 (93.6)	114 (95.8)	136 (95.8)		
Dyspnea					
Yes	11 (10.0)	41 (34.5)	51 (35.9)	24.29	<0.001*
No	98 (90.0)	78 (65.5)	91 (64.1)		
Laboratory investigation	**Mean (S.D.)**	**Mean (S.D.)**	**Mean (S.D.)**		
HbA1c	6.1 (1.3)	7.0 (2.0)	7.4 (2.1)	15.83	<0.001*
Hb (g/dL)	13.4 (1.5)	13.2 (1.9)	13.8 (1.7)	3.21	0.041*
Hct (%)	39 (3)	38 (5)	40 (4)	4.32	0.014*
WBC (cell/cu.mm.)	5808 (1946)	6230 (2308)	6765 (3003)	4.58	0.011*
Neutrophil (cell/cu.mm.)	3648 (1804)	4157 (2332)	4819 (3031)	6.94	0.001*
Lymphocyte (cell/cu.mm.)	1658 (585)	1584 (638)	1464 (655)	3.05	0.048*
Platelet (cell/cu.mm.)	245844 (82653)	250294 (89227)	250887 (90937)	0.12	0.892
Albumin (g/dL)	4.3 (0.2)	4.2 (0.4)	4.0 (0.4)	18.42	<0.001*
Globulin (g/dL)	3.3 (0.4)	3.4 (0.5)	3.4 (0.5)	1.09	0.338
ALT (U/L)	38 (33)	44 (41)	45 (38)	1.16	0.316
AST (U/L)	43 (39)	45 (31)	54 (50)	2.45	0.088
Direct bilirubin (mg/dL)	0.17 (0.09)	0.21 (0.13)	0.19 (0.11)	3.15	0.044*
Total bilirubin (mg/dL)	0.45 (0.23)	0.45 (0.23)	0.42 (0.20)	0.62	0.537
Alkaline phosphatase (U/L)	89 (42)	84 (33)	85 (36)	0.56	0.574
Oxygen saturation (%)	97 (1)	97 (1)	96 (2)	11.65	<0.001*

Table 4 Demographic, clinical characteristics, laboratory and chest x-ray findings of DM patients with COVID-19, comparison between insulin treatment and non-insulin treatmen

Characteristics	DM with insulin treatment (n = 84)	DM with non-insulin treatment (n = 101)	Statistic	p-value
Age, mean (S.D.)	59.6 (11.1)	53.0 (10.8)	4.013	<0.001*
Sex, n (%)				
Male	29 (34.5)	44 (43.6)	1.57	0.210
Female	55 (65.5)	57 (56.4)		
Fever, n (%)				
Yes	31 (36.9)	29 (28.7)	1.40	0.236
No	53 (63.1)	72 (71.2)		
Cough, n (%)				
Yes	47 (55.9)	62 (61.3)	0.56	0.454
No	37 (44.1)	39 (38.7)		
Secretion, n (%)				
Yes	26 (30.9)	30 (29.7)	0.03	0.854
No	58 (69.1)	71 (70.3)		
Myalgia, n (%)				
Yes	7 (8.3)	20 (19.8)	4.84	0.028*
No	77 (91.7)	81 (80.2)		
Anosmia, n (%)				
Yes	5 (5.9)	10 (9.9)	0.96	0.327
No	79 (94.1)	91 (90.1)		
Chest pain, n (%)				
Yes	2 (2.3)	2 (1.9)	0.04	0.852
No	82 (97.7)	99 (98.1)		
Dyspnea, n (%)				
Yes	30 (35.7)	25 (24.8)	2.64	0.104
No	54 (64.3)	76 (75.2)		
Chest X-ray, n (%)				
Category 0	11 (13.0)	16 (15.8)	0.71	0.700
Category 1	33 (39.2)	34 (33.6)		
Category 2	40 (47.6)	51 (50.4)		

Table 4 Demographic, clinical characteristics, laboratory and chest x-ray findings of DM patients with COVID-19, comparison between insulin treatment and non-insulin treatment (cont.)

Characteristics	DM with insulin treatment (n = 84)	DM with non-insulin treatment (n = 101)	Statistic	p-value
Laboratory	Mean (S.D.)	Mean (S.D.)		
HbA1c	8.9 (2.2)	7.6 (1.7)	4.504	<0.001*
Hb (g/dl)	13.3 (2.0)	13.8 (1.6)	-1.965	0.051
Hct (%)	39 (5)	40 (4)	-2.019	0.045*
WBC (cell/cu.mm.)	6882 (2929)	6572 (2556)	0.767	0.004*
Neutrophil (cell/cu.mm.)	5045 (3007)	4447 (2645)	1.439	0.152
Lymphocyte (cell/cu.mm.)	1381 (680)	1610 (571)	-2.484	0.014*
Platelet (cell/cu.mm.)	256226 (88327)	252782 (88805)	0.263	0.793
Albumin (g/dL)	4.0 (0.5)	4.2 (0.4)	-3.787	<0.001*
Globulin (g/dL)	3.4 (0.5)	3.3 (0.4)	1.571	0.118
ALT (U/L)	41 (36)	50 (38)	-1.640	0.103
AST (U/L)	50 (42)	52 (43)	-0.257	0.802
Direct bilirubin (mg/dL)	0.21 (0.09)	0.20 (0.11)	0.327	0.744
Total bilirubin (mg/dL)	0.41 (0.18)	0.46 (0.23)	-1.440	0.152
Alkaline phosphatase (U/L)	86 (42)	87 (32)	-0.187	0.852
Oxygen saturation (%)	96 (2)	96 (1)	-0.16	0.870

* statistical significance

Discussion

The research design of this study was retrospective cohort study to include all case of diabetes mellitus admitted in the isolated cohort ward in single medical center. The diagnosis of diabetes was confirmed by HbA1c at admission. More than 90% of adult diabetes cases in Thailand are type 2 diabetes mellitus.[12] None of the patients included in the study developed diabetic ketoacidosis during admission. All of the patients after 30 years of age. Therefore, the researchers were confident that no type 1 diabetes mellitus were included in the study. We analyzed the data on both known diabetes and newly diagnosed diabetes in comparison with non-diabetes. In many clinical studies during the early period of COVID-19 pandemic, patients with diabetes tended to be of an older age compared with non-diabetes and age was recognized as the important factor that contributed to the severity of COVID-19 infection and poor outcome of treatment.[13,14] Consequently, in this study, by using case-control study with age and sex match between

diabetes cases and non-diabetic cases, we eliminated the effect of age on treatment outcome. By following our hospital policy in the outbreak of COVID-19 infection, all patients with COVID-19 infection admitted to the hospital, age above 30 had their HbA1c measured to identify undiagnosed diabetes. We then identified 1377 cases with raised HbA1c at admission, but only 964 cases had completed laboratory records (CBC, LFT and chest x-ray). By using the cut-off point of HbA1c 6.5% to diagnose diabetes, 185 cases of diabetes with completed medical history, laboratory and chest x-ray were identified.

Table 5 Treatment, complications and clinical outcomes in diabetic patients comparison between insulin treatment and non-insulin treatment

Parameters	DM with insulin treatment (n = 84)	DM with non-insulin treatment (n = 101)	Statistic	p-value
Duration of admission (days) Mean (S.D.)	8.8 (4.1)	8.4 (3.3)	0.746	0.456
Duration of anti-viral treatment (days) Mean (S.D.)	8.8 (2.3)	7.2 (3.5)	3.551	<0.001*
Antiviral treatment Favipiravir: n (%)	80 (95.2)	91 (90.1)	1.731	0.188
Antiviral treatment Remdesivir: n (%)	9 (10.7)	2 (1.9)	6.256	0.012*
Bacterial pneumonia n (%)	19 (22.6)	11 (10.8)	4.643	0.031*
Steroid treatment n (%)	54 (64.3)	42 (41.6)	9.467	0.002*
Oxygen treatment n (%)	39 (46.2)	16 (15.8)	20.537	<0.001*
High flow oxygen treatment	12 (14.2)	5 (4.9)	4.789	0.029*
Complication: ARDS n (%)	12 (14.3)	11 (10.9)	0.485	0.486
Refer for mechanical ventilation n (%)	12 (14.3)	19 (18.8)	0.674	0.412

When comparing clinical manifestations at admission between diabetes and non-diabetes group, many clinical studies did not show significant differences in certain clinical manifestations.[14,15] However our study, as well as study from another hospital in Thailand,[9] we found that patients in the non-diabetes group had more muscle ache than the diabetes group. The laboratory investigations revealed consistent findings, shown in many studies that the diabetes group had greater white blood cell and neutrophil count and less lymphocyte count and this indicated that diabetes patients had more pronounced inflammatory responses. Albumin level was lower in diabetes group compared with non-diabetes group, whilst other parameters of liver function tests showed little difference. Diabetes patients had a greater percentage of bilateral pulmonary infiltration, as a result of their greater inflammatory response, as shown in previous clinical studies, with elevated cardiac

troponin, d-dimer, C-reactive protein and procalcitonin.[14]

As part of the mechanism of infection of SARS-CoV-2 virus, the viral particles use ACE-2 molecules on the surface of pulmonary epithelial cells for cell entry.[16,17] After infection of lung epithelial cells, production and release of a significant amounts of inflammatory mediators such as IL-1, IL-12, TNF-α trigger the state of "cytokines storm" leading to high grade inflammation and severe pulmonary tissue damage. This rapid and severe pulmonary infection can lead to acute respiratory distress syndrome (ARDS) which can then affect the liver, kidney, cardiovascular and nervous systems leading to multiple organ failure and death.[18] Diabetes patients basically have an ongoing low grade inflammatory state, with endothelial dysfunction and hypercoagulability state when compared with non-diabetes patients. Therefore, the cytokines storm, induced by SARS-CoV-2 virus infection, leads to significant tissue damage when compared with non-diabetes COVID-19 infected patients.[5]

Regarding treatment outcomes, most of our cases in the diabetes group need antiviral treatment. During that time favipiravir and remdesivir were the only available antiviral treatments in our cohort ward. The duration of antiviral treatment was significantly longer in diabetes group. By mechanisms of cytokine storm induced severe tissue damage as mentioned above, the higher proportion of our diabetes group need systemic steroid treatment as same as study from Fox et al.[20] and Charoenngam et al.[21] Subgroup analysis revealed that the level of glycemic control in diabetes group (classified into 3 groups by using HbA1c less than 8%, 8-10% and more than 10%) did not correlate with severity of COVID-19 infection. This finding was compatible with study from Nakhonpathom Hospital, Thailand which studied 595 diabetes patients admitted with COVID-19.[10] Also further subgroup analysis of the diabetes patients, showed no difference in presenting symptoms, laboratory investigations, treatment outcomes and complications between each subgroup of diabetes with different HbA1c levels.

The need of insulin treatment for glucose control during admission for COVID-19 infection was an important predictor of poor treatment outcome. The patients who required insulin treatment had longer duration of antiviral treatment, a higher percentage of bacterial pneumonia co-infection, a greater need for steroid treatment, a greater requirement for high flow oxygen treatment and increased incidence of the development of ARDS when compared to the non-insulin treatment diabetes patients. Study from Peru stressed on modality of insulin treatment during admission that patients who got fixed-dose insulin had less mortality rate than patients who got sliding scale insulin alone.[22]

Limitation

By retrieval of the clinical and laboratory data on electronic medical records, there were significant amounts of missing data especially patient's weight and height and full patient history related to comorbid diseases. The other source of clinical data came from the referral letters in cases referred from outlying district hospital to our medical center and history of underlying diseases was not included. We therefore could not include body mass index (BMI) of the patients and comorbid diseases in the data analysis. Another possible confounder that could have contributed to the severity and outcome analysis of the study was the variations in the strains of SARS-CoV-2 virus. Because the duration of data collection was rather long, over an 18 months period, the different strains of SARS-CoV-2 virus encountered played a role and different strains of virus affected the severity and outcome of infection. The diagnosis of

COVID-19 infections in our study were confirmed by RT-PCR, but in some cases the diagnosis were only relied on ATK alone. The differing virus strains were not able to be identified during the hospital admission.

Finally, the local area health policy of COVID-19 management decided that Mae Fah Luang Medical Center Hospital would be responsible for the care of only mild to moderate cases of COVID-19. If the patients need intensive respiratory support, especially endotracheal intubation and mechanical ventilation they were referred to the other tertiary hospital within the same provincial area. Consequently we did not intubate the patients in our institution and the data on mortality of these cases was not available for analysis.

Conclusion

This research confirmed the impact of diabetes mellitus on clinical, laboratory, radiological findings and especially on the severity, outcomes and complications of COVID-19 infection when compared to non-diabetes Thai patients. Whilst the level of initial glycemic control (HbA1c) in diabetic patients did not affect the severity, outcomes and complications, the need of insulin treatment for glucose control during admission was the major predictor of poor outcome.

Compliance with ethical standards

This study was reviewed and approved by The Mae Fah Luang University Ethic Committee on Human Research, under the title: A comparative study in clinical characteristics and outcomes of adult inpatients COVID-19 between diabetes and non-diabetes: A single center retrospective analysis. Certificate of approval was COA: 111/2022. Date of approval was July 11, 2022.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercials and non-profit sectors.

Conflict of Interest

The authors do not have conflict of interest to be declared.

Data sharing statement

Clinical and laboratory data in this study are available on request from the corresponding author.

Author's contribution

Conceptulization: KC

Methodology: KC, PS

Data collection and management: KC, WC

Statistical analysis: PS, KC

Manuscript writing: KC, WC, PS

Manuscript review: SM

Acknowledgement

The authors would like to thank to Roger Timothy Callaghan MB.,Ch.B, a family physician and lecturer of School of Medicine, Mae Fah Luang University for his valuable recommendation on grammar and writing following a careful reading of the manuscript.

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Transforming COPD Care in Tertiary Settings: The Role of Telerehabilitation

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Received 14 September 2023 • Revised 16 October 2023 • Accepted 1 November 2023 • Published online 1 January 2024

Abstract:

Telerehabilitation holds promise as an innovative and underrecognized approach for managing chronic obstructive pulmonary disease (COPD) patients within tertiary care settings. This paper aims to shed light on the potential of telerehabilitation as a management strategy for COPD patients who often face challenges accessing traditional rehabilitation methods. Through a comprehensive review of recent academic literature, this study explores the benefits, challenges, and future prospects of implementing telerehabilitation within tertiary care contexts. Telerehabilitation, characterized by remote exercise interventions, monitoring, education, and patient support, has demonstrated positive outcomes in terms of exercise capacity enhancement, symptom alleviation, and improved quality of life for COPD patients. Despite these potential advantages, the implementation of telerehabilitation faces challenges such as patient engagement, technological proficiency, and data security concerns. Real-world case studies highlight successful instances of telerehabilitation deployment in tertiary care, underscoring its practical viability. In light of the ongoing transformation of healthcare delivery, telerehabilitation emerges as an essential tool to address the underrecognized management needs of COPD patients in tertiary care settings. This paper advocates for further research, collaboration between healthcare providers and policy makers, and the integration of telerehabilitation into comprehensive COPD management strategies. By recognizing telerehabilitation's potential and overcoming implementation barriers, the healthcare community can ensure equitable access to rehabilitation services, thereby improving patient outcomes in the tertiary care setting.

Keywords: Telerehabilitation, Chronic obstructive pulmonary disease, COPD, Tertiary care, Remote rehabilitation, Patient management

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GMSMJ 2024; 4 (1): 17-28

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent and debilitating respiratory condition characterized by progressive airflow limitation and impaired lung function.[1] Traditional rehabilitation approaches have often focused on in-person interventions, such as pulmonary rehabilitation programs conducted within healthcare facilities.[2] However, the emergence of telerehabilitation as an innovative management strategy holds significant promise, particularly for patients with severe COPD who face challenges in accessing traditional rehabilitation centers.[3-4] Telerehabilitation, a form of remote healthcare delivery, involves the use of digital communication technologies to enable the provision of rehabilitation services to patients within the comfort of their homes.[5] In the context of COPD management, telerehabilitation presents an underrecognized and potentially transformative approach, offering solutions to the limitations of conventional care and rehabilitation methods.

While conventional pulmonary rehabilitation has shown benefits in terms of improving exercise tolerance, functional capacity, and quality of life in COPD patients[6-7], the reach and accessibility of such programs remain limited, particularly for patients residing in remote or underserved areas.[8] Telerehabilitation, however, has the potential to bridge this gap by providing COPD patients with a viable alternative that can be tailored to their individual needs and circumstances.[9] Moreover, the growing body of evidence suggests that telerehabilitation can offer benefits similar to traditional rehabilitation, including improvements in exercise capacity, functional dyspnea, and quality of life.[10] The exploration of underrecognized approaches like telerehabilitation is therefore essential to expand the scope of COPD management options and enhance patient outcomes.[3,11]

The primary objective of this paper is to shed light on the concept of telerehabilitation as an underrecognized management approach for COPD patients in tertiary care settings. By delving into the existing literature, this paper aims to provide a comprehensive overview of the efficacy, feasibility, and potential benefits of telerehabilitation interventions for COPD patients.[12-13] Furthermore, the paper will critically assess the challenges, limitations, and considerations associated with the implementation of telerehabilitation in the context of COPD management.[14-15] By synthesizing evidence from a diverse range of studies, this paper seeks to offer insights into the role of telerehabilitation in overcoming barriers to access, improving patient engagement, and enhancing the overall quality of care for individuals with COPD.

The Significance of Telerehabilitation in COPD Management

Traditional rehabilitation methods for patients with COPD have encountered numerous challenges and limitations.[10-11,16] These challenges include barriers to accessing healthcare facilities, geographical limitations, and difficulties in sustaining long-term engagement.[17-19] As the burden of COPD continues to rise, there is a pressing need to explore innovative approaches that can address these limitations and expand management options.[14,20-21] The emergence of telerehabilitation as a novel approach in tertiary care has garnered attention as a potential solution to the shortcomings of traditional methods.[5,22-23] Telerehabilitation leverages advanced telehealth technology to bridge the gap between patients and healthcare providers, offering a remote means of delivering exercise therapy, monitoring, education, and support.[10,15,24] This approach

holds promise in providing COPD patients with accessible and personalized inter ventions without the constraints of physical proximity.[6,25-26]

One of the key advantages of telerehabilitation is its potential to improve exercise capacity, functional dyspnea, and overall quality of life.[10,21,23] This is particularly significant for patients with COPD who face limitations in physical activity due to their condition.[7,27-28] Telerehabilitation offers a way to engage patients in exercises tailored to their needs, gradually increasing their capacity while minimizing the risk of exacerbations.[9,26,29] The underrecognition of telerehabilitation in tertiary care settings has hindered its widespread adoption.[3,8,30] However, evidence from systematic reviews and clinical trials highlights the potential benefits of telerehabilitation for COPD patients.[21,31-32] Telerehabilitation has demonstrated its effectiveness in improving exercise tolerance, patient-reported outcomes, and quality of life.[6,11,26] It also presents a cost-effective alternative to traditional outpatient rehabilitation.[11,29,33]

The inclusion of telerehabilitation as part of COPD management requires careful consideration of several factors. Ensuring patient engagement, addressing technological literacy challenges, and safeguarding data security are crucial for successful implementation.[14,34-35] Moreover, the development of user-centered platforms tailored to the preferences and needs of patients can enhance compliance and empower individuals to actively participate in their own rehabilitation.[14,36-37] While the benefits of telerehabilitation for COPD patients are evident, further research is needed to define essential elements and features of this approach.[22,25,30] Long-term maintenance and patient outcomes also warrant more investigation.[3,22,32] Future studies should focus on refining telemedicine strategies, overcoming barriers related to digital literacy, and establishing standardized protocols for evaluating telerehabilitation interventions.[5,38-39]

The challenges and limitations of traditional rehabilitation methods for COPD patients have underscored the need for innovative approaches in tertiary care. Telerehabilitation has emerged as a promising solution, offering the potential to expand management options, improve exercise capacity, and enhance quality of life. While hurdles to its widespread adoption remain, the evidence supports its efficacy and cost-effectiveness. As the field of telerehabilitation continues to evolve, efforts should be directed toward refining strategies, addressing barriers, and empowering patients with chronic respiratory diseases to achieve improved outcomes.

Telerehabilitation in Tertiary Care: Concept and Implementation

Telerehabilitation is an innovative approach to healthcare delivery that has garnered significant attention in recent years. It represents a paradigm shift from traditional rehabilitation methods by leveraging technology to remotely provide rehabilitation services to patients, particularly those with COPD within tertiary care settings. This article explores the fundamental aspects of telerehabilitation in tertiary care, shedding light on its distinctive components, technological prerequisites, and potential implications for COPD management.

1. Defining Telerehabilitation and its Distinction from Traditional Rehabilitation

Telerehabilitation, often referred to as tele-rehabilitation or TR, is a novel healthcare model that employs telecommunication and digital technologies to provide rehabilitation services to patients at a distance. Unlike traditional rehabilitation, where

patients physically attend rehabilitation centers, telerehabilitation enables patients to engage in exercise interventions, monitoring, education, and support from the comfort of their own homes.[3] This flexibility not only enhances patient convenience but also addresses challenges associated with transportation barriers and accessibility to healthcare facilities.

2. Key Components of Telerehabilitation in COPD Management

Telerehabilitation programs designed for COPD patients encompass several essential components that collectively contribute to comprehensive care and improved patient outcomes. Exercise interventions form a cornerstone of these programs, focusing on enhancing exercise capacity and physical functioning.[10] Monitoring tools, often integrated with wearable devices, enable remote tracking of patients' vital signs, oxygen saturation, and activity levels.[15] These measures ensure personalized care and early detection of any deterioration. Furthermore, education plays a pivotal role in empowering patients with knowledge about COPD management, proper inhaler techniques, and lifestyle modifications.[32] Patient support, facilitated through virtual interactions with healthcare professionals, fosters engagement, adherence, and motivation.[23] The combination of these elements creates a holistic approach to COPD management, addressing both physical and educational aspects.

3. Technological Infrastructure and Implementation in Tertiary Care

The successful implementation of telerehabilitation within tertiary care settings hinges upon a robust technological infrastructure. High-speed internet connectivity, secure platforms for data transmission, and user-friendly interfaces are foundational to enabling seamless virtual interactions.[13] Importantly, telehealth platforms should adhere to privacy regulations and ensure the confidentiality of patient information.[35] The use of videoconferencing, wearable devices, and mobile applications facilitates real-time interactions between patients and healthcare providers, enabling exercise supervision and personalized feedback.[36] Moreover, tele-rehabilitation platforms integrate data analytics to monitor patients' progress over time, aiding clinicians in tailoring interventions and assessing efficacy.[19]

Telerehabilitation presents a revolutionary approach to COPD management within tertiary care settings, offering patients the opportunity to engage in rehabilitation from their homes. The integration of exercise interventions, monitoring, education, and support through digital platforms holds promise for improving functional capacity, quality of life, and self-efficacy in COPD patients. As technology continues to advance, ensuring the scalability, accessibility, and security of telerehabilitation programs is paramount. Nevertheless, further research is warranted to ascertain the long-term sustainability and efficacy of this approach, as well as to define standardized protocols that optimize patient outcomes.

Benefits of Telerehabilitation for COPD Patients

Telerehabilitation has emerged as a promising and innovative approach to address the complex management needs of patients with COPD within tertiary care settings. This underrecognized method holds significant potential in improving the lives of COPD patients by overcoming barriers to access, enhancing exercise capacity, elevating quality of life, and effectively managing symptoms. Drawing from the evidence and insights gleaned from existing studies.

1. Exercise Capacity Enhancement

The utilization of telerehabilitation has demonstrated a substantial positive impact on the exercise capacity of COPD

patients. Studies consistently show that remote exercise interventions through telerehabilitation lead to significant improvements in functional exercise capacity.[21-22] Regular and tailored exercise programs, conducted remotely under professional supervision, empower patients to engage in progressive exercises that ultimately enhance their physical endurance and functional capacity.[9,39] This improvement in exercise capacity contributes not only to the enhancement of daily activities but also to overall well-being.

2. Quality of Life Augmentation

COPD often imposes a considerable burden on patients' quality of life, affecting their physical, emotional, and social aspects. Telerehabilitation interventions have proven to be effective in ameliorating various domains of quality of life.[6,25] By integrating educational components, psychological support, and exercise routines, telerehabilitation enhances patients' self-efficacy, mental health, and overall perception of their well-being.[7,11] This comprehensive approach underscores the potential for holistic quality of life improvement, fostering patient empowerment and fostering a positive outlook on their condition.

3. Symptom Management and Patient Engagement

Effective symptom management remains a critical goal in COPD management. Telerehabilitation offers a patient-centric solution that equips individuals with the tools to better manage their symptoms and exacerbations.[15,19] By providing continuous monitoring and personalized intervention adjustments, telerehabilitation empowers patients to proactively address symptoms, thereby reducing hospital admissions and improving overall health outcomes.[5,40] Moreover, the remote nature of telerehabilitation fosters patient engagement, encouraging active participation and adherence to treatment plans.[32,41] This patient engagement not only supports ongoing management but also instills a sense of responsibility and control over their health.

4. Addressing Access Barriers in Tertiary Care

The implementation of telerehabilitation strategically addresses the challenges of access that many COPD patients face within tertiary care settings. Geographical constraints, transportation limitations, and lack of local resources often hinder patients' ability to access traditional rehabilitation services.[24,26] Telerehabilitation circumvents these barriers by enabling patients to engage in rehabilitation programs from the comfort of their homes, thus eliminating the need for physical travel.[12,42] This approach ensures that patients residing in remote or underserved areas can still benefit from specialized care and support.

The benefits of telerehabilitation for COPD patients are substantiated by a wealth of research evidence. From enhancing exercise capacity and augmenting quality of life to effectively managing symptoms and overcoming access barriers, telerehabilitation emerges as a pivotal underrecognized management strategy in tertiary care settings. The amalgamation of personalized exercise regimens, educational components, and ongoing support within a remote framework empowers patients to actively participate in their own care journey. As the healthcare landscape evolves, the integration of telerehabilitation into COPD management holds the promise of revolutionizing patient outcomes and providing a new standard of care that is patient-centered, accessible, and impactful.

Challenges and Considerations

Telerehabilitation has emerged as a promising approach to address the rehabilitation needs of COPD patients in tertiary care settings. This innovative method offers the potential to overcome geographical

barriers and provide tailored rehabilitation programs.[14,21] However, as with any transformative healthcare approach, several challenges and considerations must be carefully addressed to ensure its effective implementation.[6,20]

1. Patient Engagement and Adherence

A significant challenge in telerehabilitation is maintaining consistent patient engagement and adherence to the program.[14-15] COPD patients often require ongoing motivation and support to adhere to their rehabilitation routines.[19,36] In remote settings, without direct supervision, patients may experience decreased motivation to participate, leading to reduced adherence rates.[20,38] It is crucial to develop strategies that foster patient commitment and active involvement, such as personalized goal setting, regular check-ins, and motivational support.[7,37]

2. Technological Literacy and Accessibility

Another concern lies in the varying levels of technological literacy among COPD patients.[31,43] Not all individuals may possess the skills to effectively navigate and utilize the telerehabilitation platforms.[5,24] Moreover, the availability of appropriate devices and reliable internet connections can be limiting factors for some patients.[4,29] Addressing these challenges requires user-friendly interfaces, clear instructions, and support for patients who require assistance.[8,32]

3. Data Security and Privacy

Data security is a paramount concern in the implementation of telerehabilitation, especially when dealing with sensitive patient health information.[3,44] Ensuring the confidentiality and protection of patient data is crucial to building trust in the system.[40,41] Robust security measures, including encrypted communication channels and compliance with data protection regulations, are imperative to safeguard patient information.[12,30]

4. Tailoring Programs to Individual Needs

COPD patients exhibit diverse needs and levels of severity.[10,18] Tailoring telerehabilitation programs to individual patients' conditions is essential for achieving optimal outcomes.[13,25] This customization requires a comprehensive assessment of each patient's capabilities, limitations, and goals.[34,39] Healthcare providers must carefully design interventions that address the unique challenges faced by each patient to ensure that the program remains effective and relevant.[26-27]

5. Healthcare Professional Training and Support

The successful implementation of telerehabilitation requires well-trained healthcare professionals who can guide patients through the program.[9,35] Healthcare providers need to be proficient in using the technology and in providing remote support to patients.[28,32] Adequate training and continuous professional development programs are necessary to equip clinicians with the necessary skills to effectively engage patients in a virtual environment.[45-46]

While telerehabilitation holds great potential for addressing the rehabilitation needs of COPD patients in tertiary care settings, it is not without its challenges. Patient engagement and adherence, technological literacy, data security, individualized program tailoring, and healthcare professional training are critical aspects that demand careful consideration. Addressing these challenges will be pivotal in ensuring the successful implementation and sustainability of telerehabilitation as an underrecognized management approach for COPD in tertiary care settings. By devising thoughtful strategies to overcome these hurdles, healthcare providers and policymakers can unlock the full potential of telerehabilitation to improve the lives of COPD patients while transforming the landscape of pulmonary rehabilitation.

Transforming Tertiary Care with Innovative Management

Telerehabilitation, an emerging paradigm in healthcare, has demonstrated remarkable potential in revolutionizing the management of COPD within tertiary care settings. This paper examines the underrecognized role of telerehabilitation as an innovative management strategy for COPD patients and presents compelling case studies and success stories that underscore its effectiveness in delivering comprehensive care.

1. Real-World Examples of Telerehabilitation Programs

In recent years, several telerehabilitation programs tailored to COPD patients have been implemented in tertiary care settings, yielding promising outcomes. One such example is the "C☺PD-Life" program, a 26-week interdisciplinary telerehabilitation intervention that transcends traditional barriers and fosters coordination between hospital and municipality healthcare services. Through this program, COPD patients have reported improved illness mastery, enhanced physical and social activity, and personalized support for their unique challenges.[26] This exemplifies how telerehabilitation can transcend geographical constraints and provide patients with a tailored, patient-centered approach.

2. Patient Experiences and Testimonials

Patient experiences within telerehabilitation programs have been overwhelmingly positive, highlighting its tangible impact on COPD management. Testimonials reveal that patients not only appreciate the convenience and ease of using telerehabilitation platforms but also report improvements in exercise capacity, quality of life, and symptom management. Patients participating in telerehabilitation programs have expressed a newfound sense of empowerment and engagement in their own healthcare journey.[7] The patient-centric nature of telerehabilitation fosters a deeper connection between patients and healthcare providers, ultimately promoting a more holistic approach to COPD management.

3. Positive Outcomes and Improvements

Telerehabilitation's success is reflected in measurable improvements observed across various dimensions. Studies have reported enhanced exercise capacity, functional dyspnea, quality of life, and mental health among COPD patients participating in telerehabilitation.[6,10-11] Additionally, the potential to reduce hospital readmissions and maintain clinical improvements over time further underscores its significance.[47] Notably, telerehabilitation's benefits extend beyond the physical realm, positively influencing patients' mental well-being and overall quality of life.[11]

Telerehabilitation's transformative potential in COPD management within tertiary care settings cannot be understated. The convergence of patient-centeredness, interdisciplinary collaboration, and advanced technology marks a pivotal shift towards providing comprehensive care for COPD patients. Through compelling case studies and success stories, this paper has shed light on the tangible impact of telerehabilitation in empowering patients, improving outcomes, and enhancing the overall quality of COPD management. As we navigate the dynamic landscape of healthcare, telerehabilitation emerges as a beacon of innovation, redefining the boundaries of tertiary care and placing patients at the heart of their healthcare journey.

Future Directions and Recommendations

An Underrecognized Management in Tertiary Care has shed light on the transformative potential of telerehabilitation in revolutionizing the care landscape for individuals battling COPD. As we navigate

the evolving healthcare landscape, it is essential to outline the future directions and recommendations that can shape the integration and optimization of telerehabilitation within tertiary care settings. This concluding article delves into the promises, recommendations, and areas for further exploration in this groundbreaking field.

1. Expanding Telerehabilitation in Tertiary Care and Integrated Care Models

The future of COPD management within tertiary care hinges on embracing telerehabilitation as an integral component. It is imperative to recognize the capacity of telerehabilitation to transcend physical limitations, thereby providing equitable access to specialized care.[7,25,43] As we extend our horizons, envisaging the expansion of telerehabilitation, healthcare systems must embrace its potential to bridge geographical gaps and overcome barriers to conventional rehabilitation.[5,11] Telerehabilitation can form a critical thread within integrated care models, establishing seamless connectivity between primary care providers, specialists, and patients.[15, 28]

2. Recommendations for Stakeholders

For healthcare providers, adopting telerehabilitation necessitates a shift in mindset towards patient-centric care.[24,29] Effective implementation demands the integration of technology with clinical expertise.[39] In this light, training programs must equip healthcare professionals with the skills to navigate the digital realm while maintaining a robust patient-provider relationship.[29,35] Policy makers hold the pivotal responsibility of fostering an environment conducive to the widespread adoption of telerehabilitation.[18,23] Policies should ensure reimbursement mechanisms for virtual care services, paving the way for sustainable implementation.[18,25] Moreover, researchers must continue to generate evidence that underscores the clinical effectiveness, cost-efficiency, and patient satisfaction associated with telerehabilitation.[4,25,39]

3. Future Research and Improvements in Telerehabilitation Approaches

While the strides taken in the realm of telerehabilitation are commendable, there remain avenues for further exploration and refinement.[9,29] Research endeavors should delve deeper into the customization of nterventions, tailoring telerehabilitation to individual patient needs.[4,44] The development of advanced telehealth technologies should be pursued, enhancing the interactive capabilities of telerehabilitation platforms.[10, 21] Additionally, the incorporation of patient-generated data and wearable technology can empower individuals to actively participate in their rehabilitation journey.[35] This also beckons research into predictive algorithms that can anticipate exacerbations and optimize interventions.[9,28]

The evolution of COPD management through telerehabilitation within tertiary care settings holds profound implications for healthcare. As we embark on this transformative journey, the path ahead involves expanding telerehabilitation, weaving it into integrated care models, and empowering stakeholders with the necessary tools and knowledge to drive its success. The future beckons us to continue our pursuit of excellence, driving forward research, and innovation to unlock the full potential of telerehabilitation for the benefit of COPD patients within tertiary care.

Conclusion

In this comprehensive exploration of telerehabilitation for COPD patients within tertiary care settings, several critical insights have emerged. The synthesis of evidence from a range of studies underscores the significance of recognizing telerehabilitation as a valuable and underrecognized management approach for COPD patients, specifically in tertiary care contexts.

Summarizing the key points, it is evident that telerehabilitation offers a transformative paradigm in COPD management. The diverse array of articles examined in this study collectively demonstrate the potential benefits of telerehabilitation, from improving exercise capacity and quality of life, enhancing patient engagement and adherence, to its equivalence with traditional pulmonary rehabilitation. Importantly, these findings emphasize its applicability not only in standard COPD scenarios but also in the context of post-COVID-19 recovery. It is clear from the literature that while conventional re habilitation methods have proven efficacy, the implementation of telerehabilitation provides a novel avenue to address barriers such as limited access and geographical constraints. This aligns with the overarching aim of tertiary care – to deliver advanced and comprehensive solutions tailored to individual patient needs. The convergence of telehealth technology and rehabilitation strategies showcases the potential to enhance patient-centered care, bridging the gap between healthcare professionals and individuals with COPD. In the light of the global health challenges and advancements in telemedicine, recognizing the underrecognized role of telerehabilitation in tertiary care becomes crucial. As healthcare systems adapt to the evolving landscape, integrating telerehabilitation in COPD management may help alleviate the strain on healthcare resources. By harnessing the power of technology, healthcare providers can empower patients, facilitate self-management, and ensure continuity of care.

In conclusion, this review underscores the pivotal role of telerehabilitation as an underrecognized yet transformative management approach for COPD patients within tertiary care. Acknowledging and embracing this innovative strategy could herald a paradigm shift in how we approach COPD management, ultimately leading to enhanced patient outcomes and improved quality of life. The journey towards comprehensive and patient-centered COPD care continues, and telerehabilitation stands poised to be a cornerstone in this endeavor.

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Novel Rice Gel for Ultrasound Applications: Physical and Chemical Properties

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Received 23 March 2023 • Revised 11 April 2023 • Accepted 16 November 2023 • Published online 1 January 2024

Abstract:

Background: Ultrasound gel is a medical device that belongs to the category of consumables, which included in charge of radiological diagnosis and treatment such as X-ray, CT scan, ultrasonography, MRI, radionuclide scan and various radiotherapy, etc. This material is a pharmaceutical product, which produced in a gel state and obtained from synthesized for medical or veterinary. For example, physical examination acts a coupling agent between the body and the medical device. This gel is a product that must be imported from abroad at the level of billions of baht every year.

Objective: This research fabricated medical ultrasound gel within the country. The main raw material was being Thai rice to solve the problem of importing ultrasound gel from abroad.

Materials and Method: Novel rice gels containing different compositions of rice starch (RS) powder and additives. The formulations of gels were composed of RS powder, liquid glycerol, and additives by solution method. Five solutions with different concentration of RS powder (0.5 g, 1 g, 1.5 g, 2 g and 2.5 g) were prepared by solution method. These solutions were dried in electric oven at 65^{O}C for 4 hours. The physical and chemical properties of rice gel characterized by turbidity, viscosity, smell, irritation, pH and moisture content of these gels have monitored.

Results: Results showed that 2 g of RS powder is optimized formulation which had turbidity, high viscosity, pleasant smell, non-irritating and easy to clean. The pH value of this gel was 6.92 ± 0.01, and the moisture content was 0.21 ± 0.07 %, which similar to commercial standard of ultrasound gel (UG).

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GMSMJ 2024; 4 (1): 23-35

Conclusion: These results concluded that the application of RS in gel ultrasound was safe and effective for replacement commercial gel ultrasound. This gel should be studied on image quality in ultrasound examination for next step.

Keywords: Ultrasound, Gelatinization, Rice starch, irritation, Ultrasound gel, Water soluble

Introduction

Ultrasound is the mechanical waves those frequencies above 20,000 Hz and beyond the audible range of sound. In ultrasound therapies through the 1930s were used to therapeutic applications such as cancer treatments, pregnant and physical therapy for various diseases. Diagnostic applications of ultrasound began in the late 1940s through cooperation between physicians and engineers experience with SONAR.[1] Ultrasound waves have frequencies between 1 to 20 MHz. The physical and chemical properties of the UG were the significant factor relate to image quality. In biological tissues, ultrasonic energy was spread mainly form of longitudinal waves while it moves in media.[2] UG shall be good acoustic contact between the transducer and the skin.[3] UG used be general include water, various oils, creams and gels. Commercial standard UG are a water soluble, hypoallergenic, non-toxicity, sterile, pH = 6.5 ± 0.75, density = 0.983 g/cm^3, translucent screen with high viscosity, etc.[4] In present, the disadvantages of UG are dissolving of rubber or plastic parts of the transducer[3], expensive[5], irritation[6] and use in large quantity for each examination. Thus, this research has idea for used hydrogels that mainly liquid in composition and display densities similar to aqueous. The network of gel can be composed of a variety of polymers. Polysaccharides are natural polymers which hydrophilic, biodegradable, biocompatible and gelling agent.[7]

Starch is one of a food energy resource in the world. In addition, it is used by the food industry in a broad range of products because of its gelling, thickening and food system stabilizing capacity. Gelling property modified by chemical modifications such as cross-linking and substitution can increase the resistance to shear, acid and high temperatures, reduce retrogradation and improve freeze thaw stability and heat treatment. Besides physical modifications, mixing different additives and plasticizer is another way to obtain new starch properties because of its low cost, nontoxic and innovative.[8] In 2017, Thailand was the number one of rice exporter in the world, followed by India and Vietnam. Thailand produced 480 million tons of unmilled rice in countries, and exports 9.7 million tons of rice.[9] However, rice is contributed only 23% of the total exports value. Therefore, more researches on rice aiming at improving its value are urgently needed. Rice starch (RS) is extensively used in pharmaceutical and biomedical applications. It is produced by Erawan Pharmaceutical Research and Laboratory Co., Ltd., Thailand.[10] This research aimed to study physical and chemical properties of commercial standard ultrasound media and RS gel for basic knowledge to development image quality in ultrasound examination.

Materials and Methods

Sample preparation

6 ml of Glycerol solution (Sigma-Aldrich, 99.5%, United State Pharmacopeia (USP), Thailand) was blended in 5 ml distilled water and added to 1 g of sucrose (Sigma-Aldrich, 99.5% USP, Thailand) to solution and then heated to 80°C. The mixture

stirred for 15 min. Then, 0.02 g of sodium hydroxide (Fluka, 98%, analytical grade, German) dissolved in 20 ml of distilled water, and heated to 85°C (the optimal gelatinization of RS occurs at 85-90°C). Then the RS powder added 0.5, 1, 1.5, 2 and 2.5 g and added 0.32 g of carboxyl methylcellulose (Sigma-Aldrich, 99.5% USP, Thailand). The obtained mixture was stirred for 20 min until homogeneous. Once both solutions prepared, the mixture was blended in homogeneously paste at room temperature for 30 min in a beaker on a hotplate and stirrer until the RS gel produced. Then, neutralization of the RS gel with pH = 7. The RS gel mixed 0.02 g of methyl paraben (Sigma-Aldrich, reagent grade, 95%, Thailand), and then the gel was stirred for 10 min until mixed well. The prepared RS gels took in dried oven 65°C for 4 hour.

Characterization

pH values

The determination of pH values of the samples were carried out using a waterproof pH spear tester (Oakton pH Spear Water proof Pocket Tester EW-35634-40-Pro, Singapore). Measured ranges were from -1 to 15, with a resolution of 0.01, and accuracy was ±0.01. Measurement of temperatures ranged from 0 to 50 °C. Before measurements, the probe was rinsed with de-ionized water before insertion into the body of the samples. After the measurement, it was rinsed with deionized water and immersed in a buffer solution. All samples were measured five times, and data was collected for average values.

Moisture content

The determination of the moisture content was done by using a moisture analyzer (PMB 53, ADAM, Singapore). The samples were prepared by weighing approximately 1 to 2 g, with a resolution of 0.01% and sensitivity of 0.1 mg, and placed on a pan at 0-50˚C for 4 min. Each sample was tested five times, and data was collected to determine the average values.

Viscosity analysis

Viscosity properties of the samples were studied, using a suspension viscometer (DV-III+, Brookfield), needle No. 29, temperature 31-35°C, and speed +20 rpm up to 9 points. Viscosity model was measured by the following equation: $\sigma = \sigma_0 + \eta_B \dot{\gamma}$ where σ is shear stress, σ_0 is the yield stress, η_B is the plastic viscosity of the samples, and $\dot{\gamma}$ is shear rate. All measurements were repeated five times and the mean value was taken.

Appearance evaluation

To observed the appearance of rice gel by the five senses of volunteers. For examples, turbidity, smell, and skin irradiation. Skin irritation test by 1. Evaluate according to the pH value of rice gel. 2. Applying the gel on the skin of 30 volunteers who were not real patients and leaving it for 15 minutes, then observe the changes in the skin, whether there is a rash, itching or not.

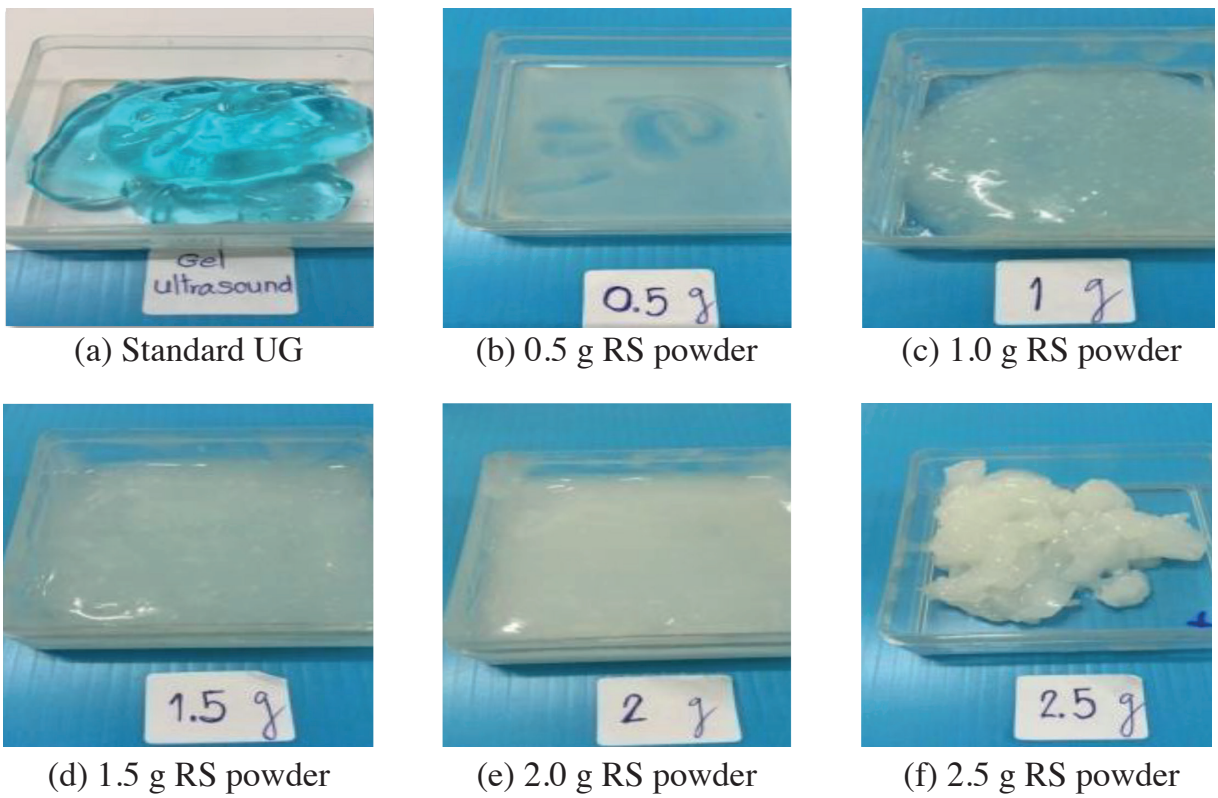
Statistical analysis

All quantitative data were analyzed with origin 8.0 (OriginLab Corporation, USA) and presented as the mean ± standard deviation. Statistical comparisons were carried out using analysis of variance (ANOVA, Origin 8.0). A value of $p < 0.05$ was considered to be statistically significant.

Results and Discussion

Figure 1 shows the various compositions of ultrasonic media that form by starch-based matrix and hot air oven with gelatinized temperature 85-90°C as gelling agent and the other additives for increased viscosity, plasticizer, stability and preservative agent. All formulations with different addition of RS powder ranging 0.5 g to 2.5 g showed physical and chemical properties and

standard UG (Table 1). These results demonstrate that all formulations had turbid more than standard UG except an addition 0.5 g of RS powder in composition due to small content of RS powder (Figure 1b). However, the addition 0.5 g RS powder show viscosity lower than standard UM. Thus, no appropriate use as gel ultrasound. Moreover, the additions of 1 and 1.5 g of RS powder showed that the viscosity lower than standard UG too (Figure 1c and Figure 1d). On the other hand, an addition of 2 g of RS powder (Figure 1e) had the viscosity equivalent standard UG that should be appropriate as ultrasound gel. This due to the viscosity of rice gel was non newtonian gel. While 2.5 g RS powder in composition showed the viscosity higher than standard UG, due to gel became hard jelly (Figure 1f). Thus, no appropriated used as gel ultrasound.



(a) Standard UG (b) 0.5 g RS powder (c) 1.0 g RS powder

(d) 1.5 g RS powder (e) 2.0 g RS powder (f) 2.5 g RS powder

Figure 1 Appearance of comercial standard UG (a), and rice gel at various contents (b) to (f)

All formulations had a pleasant smell, non-irritating when used for skin application, and were easy to clean. They are starch-based gels containing similar compositions that follow their use in ultrasonic applications.

Table 1 Physical and chemical properties of UG derived from standard UG and RS gel

Type	Turbidity	Viscosity (mPa.s)	Smell	irritation	pH	Moisture content (%)
Standard UG	transparent	1966 ± 96	pleasant smell	non irritating	7.14 ± 0.02	0.59 ± 0.04
0.5 g RS	quite transparent	789 ± 2	pleasant smell	non irritating	6.97 ± 0.13	0.34 ± 0.16
1.0 g RS	turbid	354 ± 2	pleasant smell	non irritating	7.03 ± 0.03	0.45 ± 0.04
1.5 g RS	turbid	1479 ± 51	pleasant smell	non irritating	6.90 ± 0.01	0.37 ± 0.11
2.0 g RS	turbid	1898 ± 15	pleasant smell	non irritating	6.92 ± 0.01	0.21 ± 0.07
2.5 g RS	turbid	2865 ± 8	pleasant smell	non irritating	6.95 ± 0.11	0.46 ± 0.17

Data showed pH values were ranged from 6.90 to 7.14, which occur in all formulations, and moisture content showed that all formulations below 0.6%, which was water activity of food that pathogenic or spoilage microorganisms cannot grow.[11] This phenomenon explained by influence of RS powder in compositions occurred from gelatinization of RS powder by base and thermal treatment. RS powder should adequately modified by destroying by its granule. When heated in the presence of water, RS undergoes an irreversible structure. RS powder had swelling pattern, which occurred internal bonding of each granules. Gelatinization optimizes results in the formation of a viscous paste with disorder of between molecular hydrogen bonds. This bonding derived from crystal and amorphous of rice starch, which had low solubility and swelling properties. These were due to both of amylose and amylopectin of RS that amylose made strength of RS structure.[12,13] Thus, transparency and viscosity of rice gel must be through gelatinizing process and mixed other additives. In this research, carboxyl methylcellulose used as emulsifier for stability increased thickener for starch gel[14], and sucrose used as additive for binder[15], water used as plasticizer. The addition of the other plasticizer was a glycerol for increasing water solubility because of glycerin would blend and bond with molecule of RS. Glycerol molecule occurred physical cross linked with neighbor site chain of RS molecules as weak interaction form molecular was structure flexible.[16] Methylparaben was preservative that inhibited the growth of bacteria.

Conclusion

Novel rice gels for ultrasound were modified by base and thermal treatment methods with different compositions of RS powder. The influence of the addition RS powder had an important effect on turbidity, viscosity, smell, irritation, and cleaning. For the addition of RS powder the concentrations from 0.5 to 2.5 g in formulation. The optimized formulation was 2 g of RS powder added in composition which was about 74 wt% of constituent. This concentration showed

appropriate formulation as turbid, high viscosity, pleasant smell, non-irritating, easy to clean, water-soluble and low cost. This research should be further studied on image quality in ultrasound examination.

Acknowledgement

This work was supported by fund Innovative Biomaterials and Medical Device Research Group, Mae Fah Luang University. We sincerely would like to thank for the warm willingness support from Assistance Prof. Sakdiphon Thiansem, Department of Industrial Chemistry, Faculty of Science, Chiang Mai University.

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สำนักวิชาแพทยศาสตร์ มหาวิทยาลัยแม่ฟ้าหลวง
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Case Report

GMSMJ

Greater Mekong Subregion Medical Journal

Cannabinoid Hyperemesis Syndrome

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Received 12 October 2023 • Revised 11 November 2023 • Accepted 11 December 2023 • Published online 1 January 2024

Abstract:

Cannabinoid Hyperemesis Syndrome (CHS) is a condition characterized by cyclic episodes of nausea and vomiting, abdominal pain, and relief of symptoms by taking of hot shower, this syndrome being associated with chronic cannabis use. CHS occurs in approximately one-third of individuals presenting with cannabis use disorder. The pathophysiology of CHS is not fully understood, but it is believed to involve the endocannabinoid system (ECS). This report describes an 18-year-old female, with a history of marijuana consumption spanning nearly two years, who presented with intense nausea and vomiting. The patient made a complete recovery following cannabis abstinence and supportive treatment. Two months follow-up revealed a full resolution of the symptoms.

Keywords: Cannabinoid hyperemesis syndrome, Cyclic vomiting syndrome, Tetrahydrocannabinol

Introduction

Cannabis, a psychoactive drug derived from the Cannabis plant, is globally one of the most widely used recreational drugs.[1] The rise in cannabis use has contributed to an increased incidence of Cannabinoid Hyperemesis Syndrome (CHS). CHS is characterized by cyclic episodes of nausea, vomiting, abdominal pain, and relief of symptoms by taking of hot shower.[2] It is associated with chronic and excessive cannabis use.[3] The overall prevalence of CHS in the Western countries is 0.1% and is more common in young adults. The prevalence of CHS reaches 32% in patients with cannabis use disorder (CUD).[4] This syndrome is difficult to manage due to the limited efficacy of conventional antiemetics.[5] Abstinence from cannabis is the most effective treatment.[6] In this article, we describe a case of CHS in an 18-year-old female who presented with severe nausea and vomiting.

Case Presentation

A previously healthy 18-year-old Thai female presented with a three-day history of intense nausea and vomiting. The frequency of vomiting was recorded as being approximately 10 episodes per day.

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GMSMJ 2024; 4 (1): 37-41

She also reported feeling of lightheadedness. However, she did not manifest other clinical features such as abdominal pain, fever, vertigo, dysphagia, constipation, or diarrhea. She had experienced two similar episodes of lightheadedness during the past 4 months, which led to several visits to an outpatient and emergency department. Her ability to eat and drink was significantly affected. As a result, she had experienced an 11 kilogram weight loss in the preceding month. Symptomatic relief was sought by the patient, using warm bath, taken approximately four times daily.

Initially, the patient denied any history of illicit substance use. However, after several vomiting episodes, she admitted to the consumption of marijuana, quantified at 10-20 sessions daily over a nearly 2-year period. It was pertinent to note that within three months of initiating cannabis use, the patient began experiencing nausea without concomitant emesis. Despite discontinuing cannabis use for three weeks prior to hospital admission, the patient's symptoms persisted.

On hospital admission, the patient had blood pressure of 142/90 mmHg (mean arterial pressure of 107 mmHg), but other vital signs were normal. The physical examination was unremarkable. A laboratory urine screening test for tetrahydrocannabinol (THC) was positive. Blood tests, including complete blood count, glucose, basic metabolic panels, electrolytes, calcium, magnesium, phosphorus, blood urea nitrogen, and creatinine were within the normal range. Radiology and EKG examination also appeared normal.

Hospitalization was required in this patient due to severe recurrent episodes of vomiting and the history of failure of treatment as an outpatient. The diagnosis of CHS was made. The patient received symptomatic treatment, which consisted of hydration, antiemetic, and antipsychotics. Ten days after admission, the patient was discharged from hospital with psychoeducation to continue cannabis abstinence. She confirmed full resolution of vomiting and no further related symptoms at her two months follow-up appointment.

Discussion

Cannabinoid Hyperemesis Syndrome (CHS) is a condition characterized by intermittent periods of symptoms remission. There are 3 main phases of CHS: prodromal, hyperemetic, and recovery.[5-7] The prodromal phase can last for months or years with patients developing early morning nausea, vomiting, and abdominal discomfort. Patients may increase cannabis use for self medication. The hyperemetic phase usually lasts for a few days but may extend up to 10 days.[6] This phase is marked by intense vomiting, abdominal pain, and sympathetic overactivity, which often brings patients to the emergency department. Weight loss is common. Compulsive hot bathing behavior is reported to alleviate the symptoms. The recovery phase can last from days to months. Finally a resolution of symptoms is noted and the patients return to their baseline condition.[4,7]

The diagnosis of CHS depends on clinical characteristics and exclusion of other possible causes. Different criteria of diagnosis have been previously proposed. The currently accepted criteria are Rome IV criteria (Table 1).[8] Although this criteria is widely used, many studies have shown limitations in using the Rome IV criteria, as it provides limited information regarding the definition of chronic cannabis use and the duration of abstinence.[2,8] To enhance the diagnostic precision of CHS, The Cyclic Vomiting Syndrome (CVS) Guidelines Committee has proposed a revised set of criteria (Table 2).[8] However, our patient fits both diagnostic criteria.

Table 1 Rome IV criteria for Cannabinoid Hyperemesis Syndrome[9,10]

Must include all of the following: 1. Stereotypical episodic vomiting resembling cyclic vomiting syndrome (CVS) in terms of onset, duration, and frequency. 2. Presentation after prolonged excessive cannabis use. 3. Relief of vomiting episodes by sustained cessation of cannabis use.
Supportive remarks: • May be associated with pathologic bathing behavior (prolonged hot baths or showers).
Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Table 2 CVS Guidelines Committee for Cannabinoid Hyperemesis Syndrome[8]

Clinical features	Stereotypical episodic vomiting resembling CVS in terms of onset, and frequency ≥3 episodes a year.
Cannabis-use patterns	Duration of use >1 year preceding onset of symptoms. Frequency of use > 4 times a week on average.
Cannabis cessation	[a]Resolution of symptoms should follow a period of cessation from cannabis for a minimum of 6 months or at least equal to a duration that spans three typical cycles in an individual patient.

Note: [a]Patients unwilling or unable to abstain from heavy cannabis use pose a diagnostic challenge and may be considered as having CHS.

Treatment of chemotherapy induced nausea and vomiting was one of the first recognized medical uses of cannabis.[3] Nonetheless, using cannabis at a high dose can cause paradoxical hyperemesis. Several explanations for the pathophysiology of CHS have been suggested. There are two primary G protein-coupled CB receptors (CB1 and CB2) in the endocannabinoid system (ECS). CB1 receptors are located in the central nervous system (CNS) and gastrointestinal (GI) tract, where they influence appetite, gastric secretion, motility, cognition, and addiction. CB2 receptors are in lymphoid tissues and regulate the immune system.[2,3,11] The mainstream theory is that this syndrome is caused by ECS dysregulation. Chronic exposure to high-dose tetrahydrocannabinol (THC), the main psychoactive agent of cannabis and a partial agonist of CB1 receptors, overstimulates CB1 receptors, thereby causing desensitization and/or downregulation of the CB1 receptors. Changes in the ECS, which can trigger nausea and vomiting, affect various systems as follows: a reduction in endogenous cannabinoid via upregulation of degrading enzymes; disruption of the hypothalamic pituitary adrenal (HPA) axis and stress response; elevation of norepinephrine release and overactivation of sympathetic nervous system; upregulation of transient receptor potential vanilloid 1 (TRPV1); producing hypothermia; inhibition of GI mobility; and increasing gastric emptying time.[3,11]

The most effective treatment for CHS is cannabis cessation.[12,13] However, acute management is mainly supportive. Most patients come to the emergency department during the hyperemesis phase. Any life-threatening conditions and complications

of CHS need to be evaluated, such as hypovolemia, impaired consciousness, acute kidney injury and hypokalemia. If the patients are proven to have these conditions, hospital admission is necessary. Another benefit of hospitalization is that it acts as a mandatory cannabis cessation environment.[12,14] Intravenous hydration is usually required as part of the initial management.[5,12] Various antiemetic drugs are given to alleviate symptoms. Many studies have reported that common antiemetic drugs such as ondansetron (serotonin antagonist) and diphenhydramine (antihistamine) have low efficacy.[5,14-16] Capsaicin shows inconsistent results, both in its effectiveness and also a lack of standard dosage regimens.[6,17] Lorazepam (benzodiazepine) and haloperidol (antipsychotic, dopamine antagonist) are indicated as helpful medications.[4,5,11]

Conclusion

Although there are many studies about the cannabinoid hyperemesis syndrome, the exact pathophysiology has not been established, and the gold standard for diagnosis is still being developed. Prompt recognition is crucial to avoid unnecessary procedures, provide appropriate treatment, and prevent complications. Many supportive treatments have been found to have only limited efficacy. Therefore, psychoeducation and explanation regarding the plan of treatment, the doctor-patient relationship, and cannabis cessation advice are the keys to successful management.

Conflict of interest

The authors have no relevant conflict of interest to disclose.

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Short Communication GMSMJ Greater Mekong Subregion Medical Journal

Periorbital Dermatitis from EGFR Tyrosine Kinase Inhibitor

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Received 1 December 2023 • Revised 10 December 2023 • Accepted 20 December 2023 • Published on line 1 January 2024

Abstract:

A 56-year-old woman with EGFR mutation metastatic adenocarcinoma presented with bilateral eyelid inflammation, itching and persistent tearing for 2 months. She had been taking erlotinib 150 mg/day 10 months for lung cancer. She also had pruritic facial rash on both eyebrow area. She was initially diagnosed periorbital dermatitis induced by erlotinib and the drug was discontinued with supportive treatment. After one month, she had complete resolution of eye and skin problem. This was uncommon but quite newly recognized adverse events of erlotinib. The differential diagnosis includes allergic conjunctivitis and infection. Physicians in charge should ask for history of regular medicine and having thorough physical examination of other systems in order to make early diagnosis and management.

Keywords: Tyrosine kinase inhibitor, Non-small cell lung cancer, Periorbital dermatitis

Introduction

Targeted therapy has increasing role in treatment of many types of malignancy. EGFR (Epidermal growth factor receptor) tyrosine kinase inhibitor (TKI) is one of most common use drug for advanced NSCLC (non-small cell lung cancer) patients who have EGFR mutation. It is easier to take by oral and has no serious bone marrow suppression in contrary to intravenous chemotherapy. The common adverse effects are skin and gastrointestinal effects such as dermatitis, skin rash and diarrhea. Because of periorbital dermatitis is less common than skin rash but the patients can present with symptoms similar to conjunctivitis and may be misdiagnosed with allergy or infection and received delayed appropriate treatment.

Case Presentation

A 56-year-old non-smoking woman underlying type 2 DM for 10 years, hypertension and dyslipidemia living in Chiang Rai was diagnosed NSCLC (adenocarcinoma) staging cT3N0M0. She initially received neoadjuvant chemotherapy (carboplatin and paclitaxel) 4 cycles and underwent RUL lobectomy with wedge resection RLL in March 2022, staging pT3N0M0. She was doing well after surgery. CT scan chest during follow-up in December 2022 showed multiple various size nodules scattering at both lungs with right lung predominance, size up to 1.5 cm (Figure 1). She was subsequently diagnosed recurrence metastatic lung cancer and had received EGFR-TKI, erlotinib 150 mg/day because of positive

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GMSMJ 2024; 4 (1): 43-45

EGFR mutation (exon19 deletion) since January 2023. She came in Chemotherapy Clinic of MFU Medical center hospital because of changing UC status in September 2023. At that time, she was doing well with no chest symptoms except having mild skin itching. She later developed bilateral eyelid dermatitis with ectropion, eye irritation, epiphora and sticky tear for 2 months. She had no vision impairment. There was also erythematous rash on eyebrow (Figure 2). With history of erlotinib treatment, she was initially diagnosed erlotinib induced periorbital dermatitis. So, erlotinib was discontinued for 1 month and received cetirizine 1×1 and prednisolone (5 mg) 1×3 for 5 days. Follow up 1 month later, she had complete resolution of periorbital dermatitis with no symptom of eye irritation and also facial rash (Figure 3). She was subsequently planned for switching from erlotinib to gefitinib 250 mg 1×1.

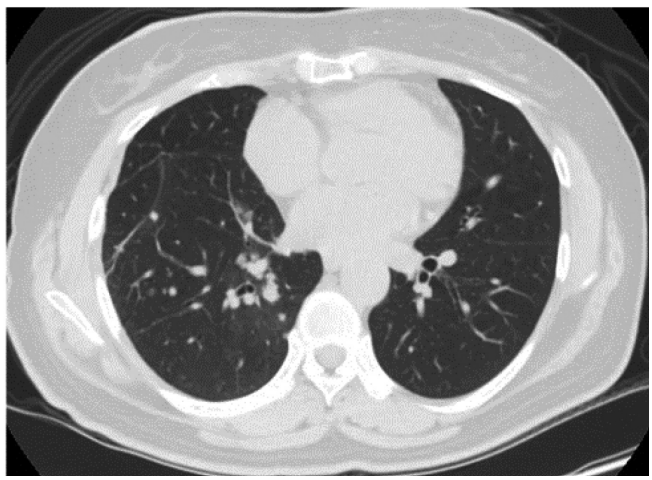

Figure 1 CT scan of chest show multiple various size nodules scattering at both lungs with right lung predominance, size up to 1.5 cm, possibly lung metastases

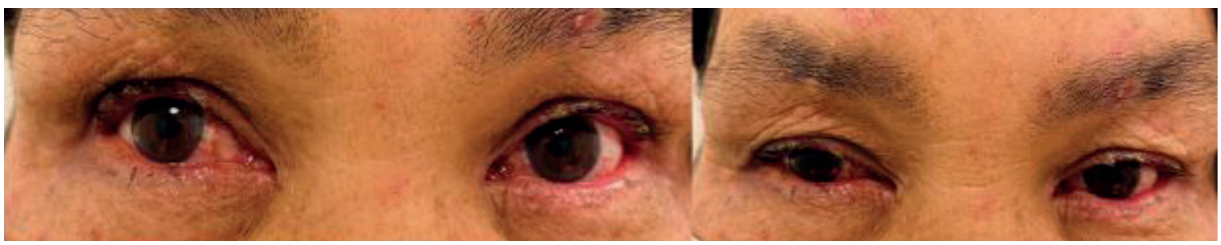

Figure 2 showed periorbital dermatitis with injected conjunctiva, ectropion and epiphora. There was also erythematous rash on eyebrow

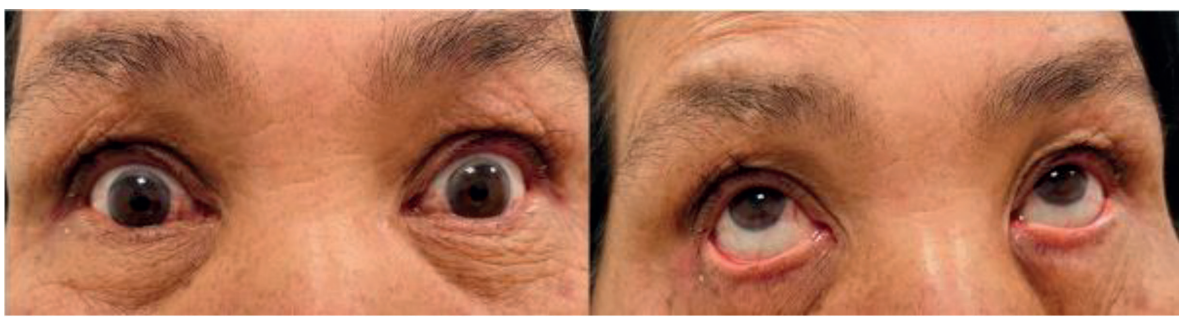

Figure 3 showed resolution of periorbital inflammation and skin rash on eyebrow after discontinuation of erlotinib for one month

Discussion

EGFR-TKIs have increasing role and now are the standard of care in advanced NSCLC with EGFR mutation.[1] Skin and GI tract are common adverse side effects of EGFR-TKIs because EGFR plays an important role in maintaining normal epithelial cells. Thus, EGFR-TKIs may interrupt keratinocyte growth, migration, and chemokine expression, leading to inflammation and skin toxicity.[2] Periorbital rash resulting in bilateral lower eyelid ectropion associated with epiphora is a recently recognized side effect of erlotinib that was completely reversible with discontinuation of the drug. The rash and ectropion should be treated palliatively, and surgical intervention should be avoided unless the patient cannot be removed from treatment.[3] Although ocular complications with erlotinib are usually encountered early in treatment, it should be kept in mind that erlotinib-related ocular complications may also arise with long-term use, and may occur up to 3 years after treatment.[4] Physicians in charge should ask the patients about the underlying disease and current medication. Early recognition of cutaneous and ocular adverse events of targeted therapies should be kept in mind for patients who taking EGFR-TKIs.[5]

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