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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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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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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.

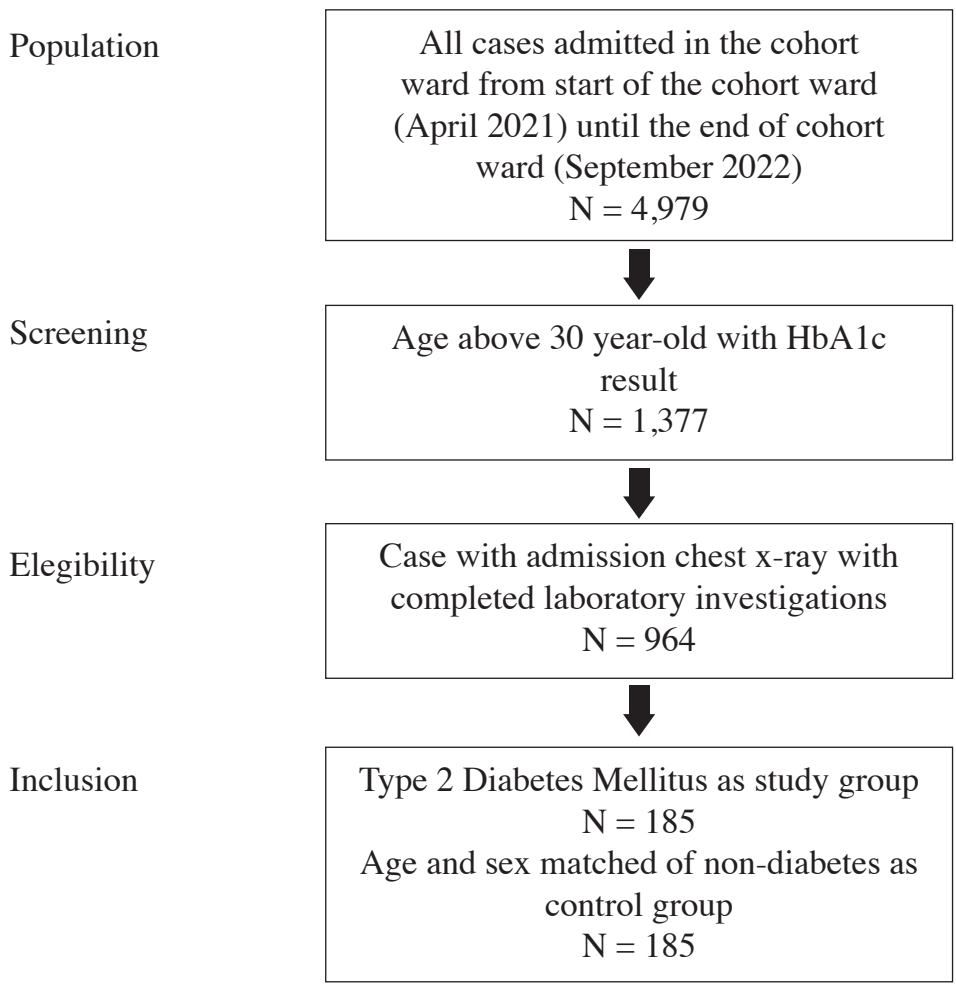


Figure 1 Flow diagram of selection process for case-control

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.

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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

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