Clinical Profile and Outcomes of COVID-19 Patients with Diabetes Mellitus: A Case Series

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Summary

COVID 19 infection has taken millions of lives to date but knowledge regarding its occurrence is still new and evolving. Among the consistent data gathered over the past few months since it was declared as a pandemic by the WHO is that patients with underlying comorbidities, notably diabetes mellitus, hypertension, and obesity have worse clinical course and outcomes. The time frame when this study was conducted was during the period when the Philippines experienced the so-called "first wave" of the coronavirus in the local setting. This was also the time when any established drug therapy for COVID-19 infection was yet to be supported by any randomized controlled trials.

Of the 12 patients enrolled in the case series, all of them had one or more underlying illnesses; the most common of which were hypertension, Vitamin D deficiency/insufficiency and cancer. Majority of the patients had an HbA1c level between 7.0%-8.0%, while an average HbA1c level of 7.5% was seen in those who expired. A greater proportion of patients (33%) were classified under obese category 1; this was followed by 25% of patients who are overweight. However, 50% of the patients who expired were morbidly obese.

Treatment regimens for both diabetes mellitus and COVID-19 were also taken into consideration. Basal plus rescue dose regimen was the most common therapy comprising 50% of the patients. Only one patient was placed on insulin drip. For COVID-19 regimen, 40% of patients received combination antiviral therapy (ritonavir/lopinavir/oseltamivir) plus hydroxychloroquine. Half of the mortality seen in this study were given the combination of antiviral plus hydroxychloroquine. Thirty-Five percent of patients eventually expired, and these were also the set of patients who were placed on renal replacement therapy, inotropic support and mechanical ventilation during the course of their illness.

Keywords: diabetes mellitus, COVID-19, comorbidities, clinical outcomes

Introduction

Every now and then, we get to live through moments that make history. Such is the pandemic caused by the novel coronavirus known as SARS-CoV-2. Infection caused by this virus (COVID-19) was declared a pandemic by the WHO in January 2020 and has since then caused tremendous damage to both human lives and economies alike. However, our knowledge on this new disease is still evolving.

The most distinctive comorbidities of 32 non-survivors from a group of 52 intensive care unit patients with novel coronavirus disease 2019 (COVID-19) in the study by

Xiaobo Yang and colleagues were cerebrovascular diseases (22%) and diabetes (22%).[1] Although the pathophysiological mechanisms are still not understood, it has been observed that most severe and fatal cases with COVID-19 have occurred in the elderly or in patients with underlying comorbidities, particularly cardiovascular diseases, diabetes mellitus (DM), chronic lung and renal disease, hypertension, and cancer.[2] In the 2014 prevalence estimates published by the International Diabetes Federation, it is estimated that there are 3.2 million cases of Type 2 DM in the Philippines with a 5.9% prevalence rate in adults between the ages of 20 and 79 years.[3]

Background Information and Brief Literature Review. According to various literature, individuals with DM, hypertension, and severe obesity (BMI 40 kg/m^{2}) are more likely to be infected and are at a higher risk for complications and death from COVID-19.[4-10] The median age of patients infected with SARS-CoV-2 is in the range of 47–56 years. Males comprised more than half of the

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Table I: Characteristics of all study subjects (N=12)

Characteristic	N (%)
Gender	
Male	7 (58)
Female	6 (42)
Age	
Mean age in years	50.8
40-59 years old	8 (66)
60-69 years old	1 (8)
70-79 years old	3 (25)
Average BMI	28.23
Normal	2 (17)
Overweight	3 (25)
Obese I	4 (33)
Obese II	3 (25)
Co morbidities present	
Hypertension	6 (50)
Vitamin D Deficiency	4 (33)
Cancer	4 (33)
HASCVD/ CKD/ Pulmonary Conditions/Dyslipidemia	3 (25)
Thyroid Dysfunction	2 (16)
Mean HbA1c	7.05%
Mean HBA1c (Expired)	7.5%
COVID-19 Category	
Mild	4 (33)
Moderate	1 (8)
Severe	2 (16)
Critical	5 (42)
Average Number of hospital days per COVID-19 Category	
Mild	18
Moderate	20
Severe	32
Critical	33
Outcome at Completion of study	
Discharged	8 (66)
Transferred	0
Decreased	4 (33)

cases, with the average incubation period of 5.2 days, and 98% of those who develop symptoms will do so within 11.5 days.[11-13]

Although a significant number will remain asymptomatic and be able to transmit the virus, the estimated proportion of symptomatic individuals requiring hospitalization increases with age.[14] Furthermore, in this older group, the percentage of hospitalized patients requiring care in an intensive care unit (ICU) is 27–71% with an infection fatality rate (IFR) ranging from 2.2 to 9.3%.[14] Angiotensin-converting enzyme 2 (ACE 2) receptor is where the SARS-CoV-2 binds with the cell.[15] In a study done by Rao et al. they found that DM was causally associated with increased lung ACE 2 expression.[16]

Circulating levels of furin, a cellular protease involved in facilitating viral entry by cleaving the S1 and S2 domain of the spike protein, are also found to be elevated in patients with DM.[17] Insulin administration attenuates ACE 2 expression while hypoglycemic agents such as glucagon-like peptide-1 (GLP-1) agonists (such as liraglutide) and thiazolidinediones, antihypertensives

such as ACE inhibitors, and statins upregulate ACE 2.[18-24] Potential mechanisms that may increase the susceptibility to COVID-19 in patients with DM include: 1) higher affinity cellular binding and efficient virus entry, 2) decreased viral clearance, 3) diminished T cell function, 4) increased susceptibility to hyper-inflammation and cytokine storm syndrome, and 5) presence of CVD.[25]

Objectives and Methods

This is a descriptive study using a case series protocol involving all patients 18 years old or above with DM and COVID-19 infection admitted at the intensive care unit or general ward starting March 5, 2020 until June 30,2020 who were referred to the service of Endocrinology. This study aimed to describe the demographic, clinical profile and outcomes of diabetic patients with COVID-19 infection admitted at both the general ward and intensive care unit. Furthermore, specific data such as age, gender, type of exposure, presenting symptom, associated comorbidities, body mass index, biochemical indices (Hemoglobin A1c, serum creatinine) as well as outcome was collected and collaborated. The study population included all adult patients 18 years old or above diagnosed with DM (Type 1 or Type 2) and COVID-19 infection uncontrolled DM (based on either HbA1c or CBG monitoring) and will be given steroids or those with steroid induced dysglycemia, those who require high dose insulin regimen or on insulin drip, those who are solely maintained on oral hypoglycemic agents while admitted. Exclusion Criteria included patients with Gestational Diabetes and with prediabetes. Data gathered are described using mean and standard deviation for quantitative variables and frequencies and proportions for categorical variables.

Ethical Considerations

The study abided by the Principles of the Declaration of Helsinki (2013) and was conducted along the Guidelines of the International Conference on Harmonization-Good Clinical Practice (ICHGCP), E6 (R2) and other ICH-GCP 6 (as amended); National Ethical Guidelines for Health and Health-Related Research (NEG HHRR), 2017.

Results

Twelve patients were included in the study and a summary of their characteristics, clinical course and outcome are summarized in *Table I*.

Gender distribution was 58% male and 42% female. The age group between 40-59 years old included more than half of the patients enrolled in the study. This was followed by the age group between 70-79 and 60-69 years old. The most common presenting symptom was fever reported by 40% of patients; 20% of patients reported difficulty of breathing and abdominal pain; and this was followed by complaints relating to other illness or as an incidental finding prior to surgery, diarrhea and decreased sensorium (*Figure 1*).
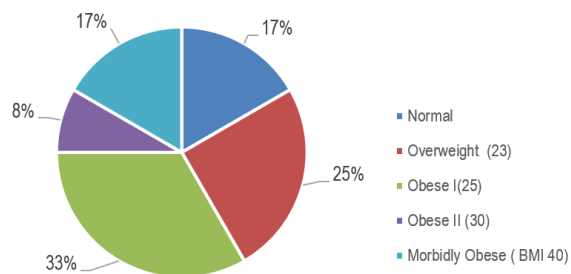
40% of patients were not able to specify any type of exposure while an equal proportion identified exposure
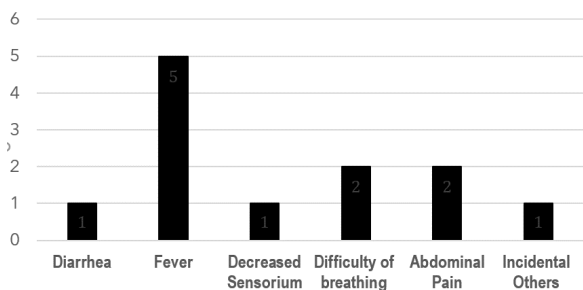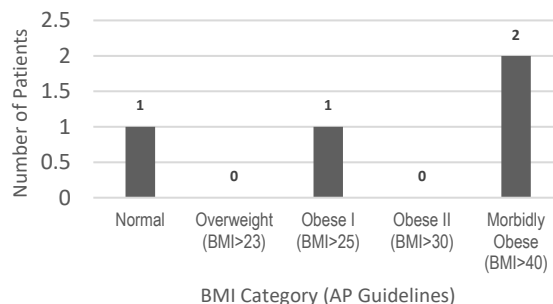
Figure 1. Distribution of Patient Symptoms at Presentation
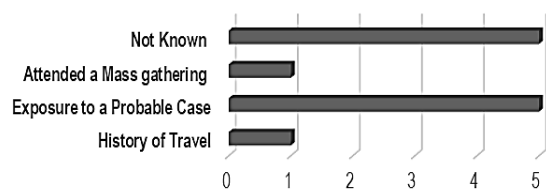
Figure 2. Distribution of Patients According to Type of Exposure

Figure 3. Patients Categorized According to Body Mass Index based on Asia Pacific Cut Off Values

Figure 4. Distribution of Patients According to BMI Category Using Asia Pacific Guidelines

to a probable case as an antecedent risk. *Figure 2* provides a summary of the type of exposure of patients included in the study. Majority of the patients have an HbA1c level between 7.0%-8.0% with an average value of 7.05%. Meanwhile, the average Hba1c of 7.5% was seen in those who expired. Patients were also stratified based on their body mass index as defined by the Asia-Pacific Guidelines. A greater proportion of patients (33%) were classified under obese category I, this was followed by 25% of patients who are overweight. Only 17% of patients had normal body mass index. (*Figure 3*). We also took into consideration the body mass index of patients who died and have found that out of the 4 patients who expired 50% were morbidly obese (*Figure 4*)

All patients had one or more underlying illnesses, the most common of which was hypertension. This is followed by Vitamin D deficiency/insufficiency and cancer. A detailed description of the comorbidities is described in *Figure 5*.

Majority (58%) of the admissions were admitted at the general wards while 42% of the cases were managed in the intensive care unit. Treatment regimen for both DM and COVID 19 were also investigated. Basal plus rescue dose regimen was the most common therapy done in 50% of the patients (*Figure 6*). Only one patient was placed on insulin drip for hyperglycemic hyperosmolar state. For COVID-19 regimen, 40% of patients received the combination of ritonavir/lopinavir/oseltamivir plus hydroxychloroquine (*Figure 7*). Another 40% received no additional treatment while one patient each received hydroxychloroquine alone and remdesivir alone. Half of the mortality seen in the study were given the combination of antiviral plus hydroxychloroquine (*Figure 8*). 33% of patients eventually expired, and these were also the set of patients who were placed on renal replacement therapy, inotropic support and mechanical ventilation during the course of their illness. (*Figure 9*). Only three of the four mortalities were managed in the critical care unit as the course of the remaining mortality was so rapid that intensive care transfer and any other additional interventions could not be done

Average number of hospital days were 18, 20, 32 and 33 days for mild, moderate, severe and critical cases, respectively. Patients who had prolonged hospitalization (>30days) were either being treated for another infection or awaiting a negative repeat swab prior to planned discharge.

Discussion

This retrospective case series of diabetic patients affected by COVID-19 infection are more commonly males who are between the ages of 40-50 years old with multiple other co-morbidities. Male preponderance was also seen in a case series done by Hafidh et al. in Dubai.[26] Notable is the frequency of co-morbidities such as hypertension, vitamin D insufficiency and coexisting
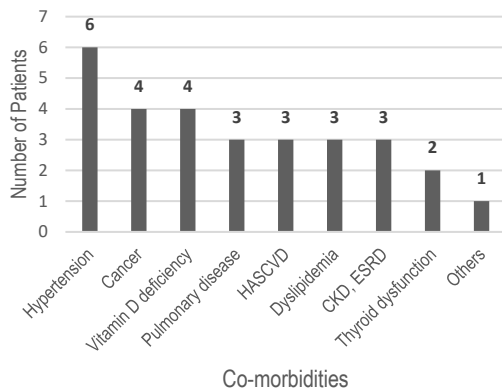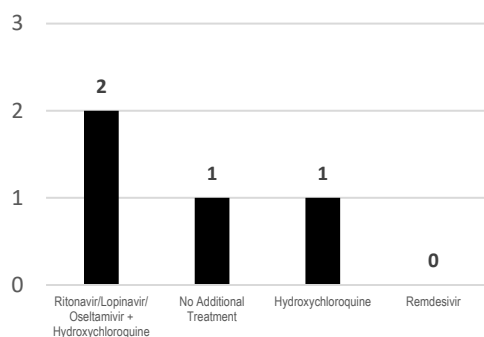
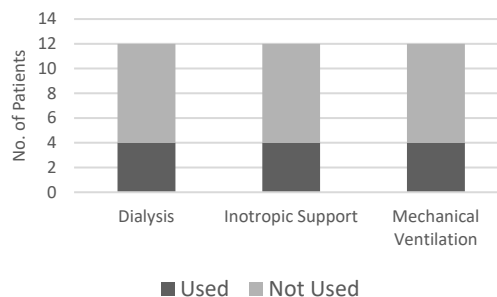Figure 5. Distribution of Patients According to Co-morbidities
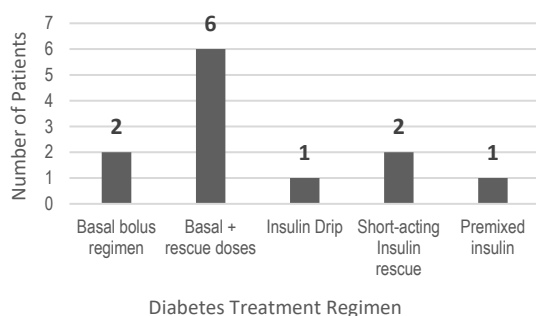
Figure 6. Distribution of Patients According to Diabetes Treatment Regimen
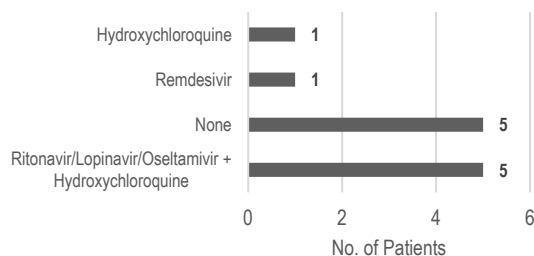
Figure 7. Distribution of Patients According to COVID-19 Anti-viral Treatment

Figure 8. Distribution of Patient Mortality According to COVID-19 Treatment Given

Figure 9. Distribution of Patients According to Additional Management

malignancies. Hypertension was also the most common comorbidity present during admission in patients included by the study of Hafidh comprising 32% of patients as compared to 50% of the patients seen in this study population. Hypertensive patients were previously managed with a regimen that included a calcium channel blocker and an angiotensin receptor blocker. Also worth mentioning is that there was a large proportion of patients who are overweight and obese that were included in the study. This result is also consistent with the mean BMI finding in the study of Hafidh which is 28.2.[26]

The patients' average blood sugar control in the previous three months prior to admission was between 7%-8%, depicting good to fair glycemic control. There is an almost equal proportion of patients with mild to moderate vs severe to critical infection. Only a minority of patients died from the infection. Of those patients who expired from COVID-19 infections, all of them had one or more co morbidities and were in the overweight to obese category. The COVID-19 management used during the time of data collection were all compassionate drug with no published efficacy studies for COVID-19 management.

Conclusion

The pathogen known as the novel coronavirus causes respiratory and gastrointestinal symptoms, ranging from mild to severe manifestations. The most common age group affected were those in the 40-59 years of age. Majority of patients, including those who eventually expired from the infection, were with one or more co-morbidities, the most striking of which are hypertension, obesity and vitamin D deficiency. Glycemic control of the enrolled subjects was described as good to fair glycemic control. This is also seen among those patients who eventually succumbed to the illness. Majority of the infection were classified as mild to moderate not necessitating intensive care admission and only a third of patients died of the infection, among whom majority were morbidly obese.

Strengths and Limitations

This study presented local data on COVID-19 infection specifically seen among patients with DM. Being a case

series, it draws its advantage in the ease to make new observations and formulate hypotheses that can be used as basis for future studies. The limitations of this study are as follows: First, this retrospective study was conducted on a historical group of patients with all recorded events having already transpired. Thus, information on relevant risk factors with potentially profound impact on the progression of COVID-19 may not be included in the database. Second, the nature of the study is simply descriptive and with a very limited sample size. Therefore, the findings observed in the present study justifies further validation through a future study with a larger sample size and statistical analysis to further strengthen the results.

Conflict of Interest

The authors of this study declare that neither their spouse or their children participate in any financial arrangement with the Sponsor/CRO/Collaborator/Supplier relevant to the clinical trial or research study, whereby the value of the compensation could be influenced by the outcome of the study.

During the time the study was being conducted and the one year following completion of the study, neither the authors, their spouses, dependent children nor the institution have received any significant payments of other sorts from the Sponsor/CRO/Collaborator/Supplier relevant to the clinical trial or research study which is exclusive of the costs of conducting the clinical study.

The authors, their spouses or dependent children, do not hold any proprietary interest in the product. Proprietary interest would include, but not limited to, a patent, trademark, copyright or licensing agreement.

The authors, their spouses or dependent children, do not hold any significant interest in the Sponsor/CRO/Collaborator/Supplier relevant to the clinical trial or research study such as any ownership interest stock options or other financial interest.

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