Accepted Article

The impact of type 2 diabetes and its management on the prognosis of patients with severe COVID-19

Zihui Xu[1], Zhongjing Wang[2], Shuo Wang[1], Yingchun Ye[1], Deng Luo[1], Li Wan[1], Ailin Yu[1], Lifang Sun[3], Solomon Tesfaye[4]*, Qingtao Meng[5*], Ling Gao[1]*

1.Department of Endocrinology & Metabolism, Renmin Hospital of Wuhan University, Wuhan, China;

2.Department of Endocrinology, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China;

3.Intensive Care Unit, Renmin Hospital of Wuhan University, Wuhan, China.

4. Diabetes Research Unit, Sheffield Teaching Hospitals, Royal Hallamshire Hospital, Sheffield, UK

5. Anesthesiology Department, Renmin Hospital of Wuhan University, Wuhan, China.

Running Title: DM Treatment on the prognosis of severeCOVID-19

Ling Gao, M.D., Ph.D.

Department of Endocrinology & Metabolism, Renmin Hospital of Wuhan University

Jiefang RD #238, Wuhan China 430060

Tel: +86 15927469449

Fax: +86 (27) 88042292

E-mail: ling.gao@whu.edu.cn

*Contribute equally to this paper

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1753-0407.13084

This article is protected by copyright. All rights reserved.

Accepted Article

Abstract

Background: Although T2DM patients with COVID-19 develop a more severe condition compared to those without diabetes, the mechanisms for this are unknown. Moreover, the impact of treatment with anti-hyperglycemic drugs and glucocorticoids is unclear.

Methods: From 1584 COVID-19 patients, 364 severe/critical COVID-19 patients with clinical outcome were enrolled for the final analysis and patients without pre-existing T2DM but elevated glucose levels were excluded. Epidemiological data were obtained and clinical-status evaluation carried out to assess the impact of T2DM and its management on clinical outcomes.

Results: Of 364 enrolled severe COVID-19 inpatients, 114 (31.3%) cases had a history of T2DM. 27(23.7%) cases died in T2DM patients, who had more severe inflammation, coagulation activation, myocardia injury, hepatic injury, and kidney injury, compared with non-DM patients. In severe COVID-19 patients with T2DM, we demonstrate a higher risk of all-cause fatality with glucocorticoid treatment (Adjusted HR, 3.61; 95%CI, 1.14 - 11.46; P = 0.029), and severe hyperglycemia (FPG ≥ 11.1 mmol/L) (Adjusted HR, 11.86; 95%CI, 1.21-116.44; P=0.034).

Conclusions: T2DM status aggravated the clinical condition of COVID-19 patients and increased their critical illness risk. Poor fasting blood glucose (≥ 11.1 mmol/L) and glucocorticoid treatment are associated with poor prognosis for T2DM patients with severe COVID-19.

Highlights

- T2DM with severe SARS-CoV-2 infection had more severe inflammation, coagulation activation, myocardia injury, hepatic injury, and kidney injury. T2DM aggravated the clinical status of COVID-19, increased their critical illness rate and mortality.
- Glucocorticoid treatment and poor fasting blood glucose (≥11.1mmol/L) control were found risk factors of fatality in T2DM patients with severe COVID-19.

Keywords: corona virus disease 2019 (COVID-19), type 2 diabetes, glucocorticoid, anti-hyperglycaemic drugs, clinical status.

This article is protected by copyright. All rights reserved.

Accepted Article

Introduction

The pandemic of COVID-19 has now infected over 9 million people worldwide.[1] It has had a catastrophic impact on human lives, particularly the elderly and those with comorbidities.[2, 3] People with type 2 diabetes (T2DM) appear to have a higher risk for SARS-CoV-2 infection with a prevalence of 5-20%,[2-7] because they are generally older and often have other comorbidities. Previous studies have also shown that diabetes is a risk factor for severe cases of viral infections, including SARS, MERS, and H1N1.[8-11] Moreover, most diabetes patients with COVID-19 end up with a severe form of the disease.[3] In a series of 174 inpatients with COVID-19, 24 of whom had diabetes, there was a rapid progression of the chest infection necessitating a chest CT scan test within 24-48h,[12] a worse prognosis and higher risk/percentage to develop composite endpoints,[3] in the diabetes patients. More importantly, diabetes patients appear to have a higher fatality rate.[3, 13]

Patients with diabetes may be susceptible to more severe SARS-CoV-2 infection due to immune system dysfunction.[14] Viral infections could also induce a diabetes state, or worsen hyperglycemia in people with diabetes, which may adversely influence prognosis.[15-18] Moreover, glucocorticoid use may further aggravate the situation. Anti-hyperglycaemic treatments may be limited because some oral drugs (i.e. metformin) are potentially harmful to COVID-19 patients with hypoxia. In this observational study, we characterized risk factors for severe COVID-19 with and without T2DM, and described the effects of commonly prescribed anti-hyperglycaemic drugs, and glucocorticoid therapy on clinical outcomes in hospitalized T2DM patients with severe COVID-19, which still remain unanswered. [19-22]

Methods

Study design and participants

The diagnosis and clinical classification (mild, moderate, severe, and critical) of COVID-19 patients were carried out by two independent doctors based on the

This article is protected by copyright. All rights reserved.

Guideline of Novel Coronavirus Pneumonia (7th Edition) issued by the Chinese National Health Commission.[23] Real-time reverse transcription polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 was performed based on the recommendation by the National Institute for Viral Disease Control and Prevention (China).[24] All enrolled patients were confirmed COVID-19 cases with RT-PCR and admitted to Renmin Hospital of Wuhan University from January 30, 2020, when the first COVID-19 patient was admitted, to April 26, 2020, when the last COVID-19 patient was discharged. The clinical outcomes (cured or died) and laboratory parameters on admission and endpoint were recorded. This case series study was approved by the institutional ethics board of Renmin Hospital of Wuhan University (NO. WDRY2020-K081). Written, informed consent was waived in light of the urgent need to collect the data for this study.

Data collection

The Chinese guideline classified the patients into five categories: asymptomatic (positive virology test without symptoms), mild (symptoms), moderate (CT scan test for viral pneumonia), severe (oxygen saturation ≤93% or oxygenation index < 300), critical (require ICU admission or invasive oxygen treatment).[23]

We encountered many difficulties in justifying to request some tests during the outbreak of COVID-19. Oral glucose tolerance test (OGTT) to diagnose T2DM and HbA1c were not routinely requested since they were considered low priorities for COVID-19 patients, making the diagnosis of new onset T2DM screening impossible. We have therefore included patients with known T2DM history for the Diabetes group excluding patients with elevated glucose (Fasting Blood Glucose ≥ 6.1mmol/L or random glucose ≥ 11.1mmol/L) from non-diabetic group to make the analysis more coherent.

Epidemiological, clinical characteristics, laboratory parameters, clinical status and outcomes were obtained from the electronic medical records of Renmin Hospital of Wuhan University. The data were entered and cross-reviewed by at least two independent team members. Information recorded included demographic data, medical history, underlying comorbidities, symptoms, signs, laboratory findings (e.g., random blood glucose on admission, cellular immunity, metabolic enzymes and other

Accepted Article

This article is protected by copyright. All rights reserved.

biochemical parameters), treatment measures (e.g., oxygen therapy, ventilator use), and drugs (e.g., insulin, anti-hyperglycaemic agents and glucocorticoids use). Fasting plasma glucose (FPG) was measured for all patients during hospitalization.

Comorbidities, including diabetes, cerebral diseases, cardiovascular diseases, chronic renal diseases, digestive diseases, pulmonary diseases and surgical history, were defined as documented history in the admission notes. Cerebral diseases refer to cerebral infarction, epilepsy, Alzheimer's disease, and Parkinson's disease. Cardiovascular diseases refer to hypertension, coronary heart disease, arrhythmia, cardiomyopathy and heart failure. Chronic renal diseases refer to chronic renal insufficiency, chronic renal failure, chronic nephritis and nephrotic syndrome. Digestive diseases refer to gastritis, gastric and duodenal ulcer, enteritis, cholecystitis and pancreatitis. Pulmonary diseases refer to asthma, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, tuberculosis, pulmonary embolism, and interstitial pneumonia. Surgical history refers to major abdominal, brain surgery and cardiothoracic surgery including cardiac bypass, lung surgery etc.

Clinical Status Evaluation. Five-category ordinal scale of clinical status was used for ventilation status evaluation which ranged from 1-5 including [25]: 1-not requiring supplemental oxygen; 2-requiring low-flow oxygen therapy; 3-requiring high-flow nasal cannula oxygen therapy (HFNC); 4-requiring noninvasive mechanical ventilation (NIV); 5-requiring extracorporeal membrane oxygenation (ECMO)/invasive mechanical ventilation (IMV). National Early Warning Score 2 (NEWS2) is an aggregated weighted score of 0–20, based on measurements of heart rate, systolic blood pressure, arterial oxygen saturation, respiratory rate, level of consciousness, temperature and supplemental oxygen.[26]

Statistical analysis

Categorical variables were described as frequency and percentages (%), and continuous variables were described with median and interquartile range (IQR) values. Means for continuous variables were compared using independent group *t* tests when the data were normally distributed; otherwise, the Mann-Whitney test was used. Proportions for categorical variables were compared using Fisher's exact test or the χ^2 test. Logistic regression analysis was used to analyze independent risk factors for

Accepted Article

This article is protected by copyright. All rights reserved.

mortality of COVID-19 patients. The risk for composite endpoints and corresponding hazard ratio (HR) were analyzed using Cox proportional hazard model. The cumulative rates of death were plotted by applying Kaplan-Meier method. All statistical analyses were performed using SPSS 22.0 (IBM Software) and Graphpad Prism 8 (Graphpad), and $p < 0.05$ was considered statistically significant.

Results

Study sample

From January 30, 2020 to April 26, 2020, 1584 patients diagnosed with COVID-19 were admitted to Renmin Hospital of Wuhan University, 1093 of whom in the first month, from January 30 to February 29, 2020. After excluding patients with pregnancy (n = 30), and those transferred to other facilities (n = 243), 274 mild/moderate cases and 546 severe/critical cases were included in the study sample. Patients with fasting glucose ≥6.1mmol/L or random glucose ≥11.1mmol/L in those without a previous diagnosis of T2DM (n = 182) were excluded. This left 114 patients with T2DM history and 250 patients without T2DM history (Figure 1).

Presenting characteristics

Of the 364 confirmed severe/critical COVID-19 patients, 305 (83.8%) cases were discharged, and 59 (16.2%) died. 66.5% (242) had one or more coexisting co-morbid medical conditions. The five most common coexisting conditions were: cardiovascular diseases (42.3% (n=154)), DM (31.3% (n=114)), surgical history (12.4% (n=45)), pulmonary disease (10.7% (n=39)), and digestive disease (10.2% (n=37)). The patients aged 60–69 years had the highest percentage (31.0%(n=113)) of COVID-19 compared to other age groups. Fatality rate increased with increasing age (Figure 2A). There was a higher fatality rate [(27(23.7%) vs. 32(12.7%); $P = 0.014$]; and older age [Median (IQR), 66(57-73) vs. 64(52-73); $P = 0.044$] in T2DM patients compared with non-DM patients (Table 1). Days from symptom onset to admission or gender did not differ between T2DM and non-DM patients (Table 1).

In multiple logistic regression analysis for fatality cohorts including age, gender, and co-morbidities (diabetes, cerebral diseases, cardiovascular diseases, chronic renal diseases, digestive disease, pulmonary disease, and surgical history), age (OR, 1.04;

Accepted Article

This article is protected by copyright. All rights reserved.

95% CI, 1.02 - 1.07; $P < 0.001$), T2DM (OR, 1.81; 95% CI, 1.06 - 3.07; $P = 0.029$), and surgical history (OR, 2.37; 95% CI, 1.20 - 4.71; $P = 0.014$) were found to be risk factors for fatality of severe/critical inpatients with COVID-19.

Laboratory parameters in COVID-19 patients with and without diabetes

There were several differences in laboratory findings between T2DM and non-DM patients, including lower levels of serum albumin and estimated glomerular filtration rate (eGFR), as well as higher levels of white blood cells (WBC), C-reactive protein (CRP), IL-6, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), NT-proBNP, creatine kinase isoenzyme-MB (CK-MB), myoglobin, cardiac troponin I (cTnI), and D-dimer in T2DM ($P < 0.05$ or $P < 0.001$). The levels of lymphocyte (LYM), alanine aminotransferase (ALT), creatinine (Cr), creatine kinase (CK), lactic acid (LA), and cellular immune (CD3+, CD4+, CD8+, CD19+, and CD16+56 + cell counts, and CD4+/CD8+) did not differ between T2DM and non-DM (Table 1). Taken together, our results suggest that T2DM patients with COVID-19 had more severe inflammation, coagulation activation, myocardia injury, hepatic injury, and kidney injury.

The impact of T2DM status on the prognosis of COVID-19 patients

On admission, NEWS2 score of T2DM patients was higher than non-DM patients (Median (IQR), 5(4-8) vs. 5(3-6); $P = 0.018$) (Figure 2C). It indicated that T2DM patients were more severely ill than non-DM patients on admission. During hospitalization, their ventilation therapy was defined as five-category ordinal scale of clinical status, the score in T2DM was higher than non-DM (Median (IQR): 3(2-3) vs. 2(2-3); $P < 0.001$) (Figure 2D). More T2DM patients required IMV/ECMO therapy than non-DM patients (15(13.2%) vs. 8(3.2%); $P < 0.001$). After adjusting for age, gender, comorbidities, and NEWS2 on admission, the survival rate of T2DM (Adjusted HR, 1.77; 95%CI, 1.02 - 3.05; $P = 0.041$) was lower than non-DM patients with COVID-19 (Figure 2B).

Glucocorticoid therapy and the prognosis of COVID-19 patients with T2DM

In this study, 74(64.9%) of T2DM patients and 134(53.6%) of non-DM patients had glucocorticoid (GC) therapy (dose from 20mg/day to 160 mg/day, duration range of 1-28 days). Admission NEWS2 scores didn't differ significantly between GC and no GC

Accepted Article

This article is protected by copyright. All rights reserved.

treatment in both T2DM and non-DM patients (*P* > 0.05; Figure 3D). After adjusting for age, gender, comorbidities, and NEWS2 on admission, the results significantly demonstrated a lower overall survival rate in the patients treated with GC compared with no GC treatment (Adjusted HR, 3.61; 95%CI, 1.14 - 11.46; *P* = 0.029) (Figure 3A). This contrasted with non-DM patients in whom GC treatment was not risk factor for fatality (Adjusted HR, 1.41; 95%CI, 0.67 - 2.96; *P* = 0.362) (Figure 3B). The fatality for DM patients treated with GC was 31.1%, which was about 3 times than that with no GC treatment in both T2DM (10.0%, *P*=0.012) and non-DM patients (10.3%, *P*<0.001), and about twice than that with GC treatment in non-DM patients (14.9%, *P*=0.007) (Figure 3C). During hospitalization, more patients treated with GC required invasive ventilation than patients without GC treatment both in T2DM and non-DM patients (*P* < 0.001; Figure 3E). The level of IL-6, a marker of inflammation, increased significantly after GC treatment in T2DM patients (*P* = 0.049), but not in non-DM patients (*P* = 0.36) (Figure 3F).

Anti-hyperglycaemic drugs use and prognosis of diabetes patients with COVID-19

Among the 114 T2DM patients, 83.3% (n=95) with treated with one or more anti-hyperglycaemic drugs including: basal insulin (24.6%(n=28)), premixed insulin(14.0%(n=16)), Aspart/Lispro/Human insulin (42.1%(n=48)), acarbose (46.5%(n=53)), metformin (26.3%(n=30)), sulfonylureas (14.9%(n=17)), dipeptidyl peptidase-4 inhibitors (DDP4i) (6.1%(n=7)), and sodium-glucose co-transporter-2 inhibitors (SGLT2i) (0.9%(n=1)). All these drugs were prescribed the conventional dosages according to their instructions. 16.7% (n=19) of T2DM patients didn't use any anti-hyperglycaemic drugs and were on diet treatment alone. The fatality rates of patients treated with basal insulin (14.3%, *P* = 0.045), premix insulin (6.3%, *P* = 0.022), metformin (6.7%, *P* = 0.008), acarbose (7.5%, *P* = 0.002), sulfonylureas (5.9%, *P* = 0.02), insulin (including basal insulin, premixed insulin, and Aspart/Lispro/Human insulin) and oral anti-hyperglycemic drugs (OAHs, including acarbose, metformin, sulfonylureas, DDP4i, and SGLT2i, 7.3%, *P* = 0.003), and OAHs alone (7.4%, *P* = 0.009) were lower than that of diet alone treated T2DM patients (42.1%)(Table 2). NEWS2 scores on admission didn't differ among these patients (*P* > 0.05). Patients

Accepted Article

This article is protected by copyright. All rights reserved.

treated with DDP4i or OAHs alone had lower ventilation score than that with diet treatment alone ($P < 0.05$). Premix insulin, acarbose, metformin, DDP4i, insulin and OAHs, and OAHs alone improved fasting blood glucose metabolism ($P < 0.05$ or $P < 0.001$) (Table 2).

The average fasting plasma glucose (FPG) was analyzed, and divided into three groups including: euglycemia (3.9-6.0 mmol/L), moderate hyperglycaemia (6.1-11.0 mmol/L), and severe hyperglycaemia (≥11.1 mmol/L). No hypoglycemia readings (<3.9 mmol/L) were recorded. By applying mixed-effect Cox model adjusting for age, gender, comorbidities, NEWS2 on admission, GC treatment, and anti-hyperglycaemia treatment, compared with euglycemia, severe hyperglycaemia (Adjusted HR_1, 11.86; 95%CI, 1.21-116.44; P=0.034) showed higher risk of all-cause fatality in T2DM patients; however, moderate hyperglycaemia (Adjusted HR_2, 4.51; 95%CI, 0.40-51.30; P=0.225) showed no difference (Figure 4).

Discussion

Diabetes has been suggested that confers worse prognosis on COVID-19.[3,13] However, the impact of T2DM and its management, especially fast glucose control on the prognosis of patients with COVID-19 have not been fully evaluated. Until now, no specific treatment has been validated for its effectiveness, and no antiviral agent has been found to provide benefit in reducing mortality of COVID-19 patients, except for oxygen therapy or early hospitalization.[25] In this observational study, we described that SARS-CoV-2 infection in T2DM was associated with more severe inflammation, coagulation activation, myocardia injury, hepatic injury, and kidney injury. T2DM aggravated the clinical status of COVID-19, increased their critical illness rate and mortality. GC treatment and fasting blood glucose ≥11.1 mmol/L were found risk factors of fatality in these patients.

The prevalence of diabetes or the comorbidities of diabetes in COVID-19 is from 5-20%.[2-7] During the early outbreak, hospitalized patients consisted of severe cases older patients amongst whom diabetes patients were well represented. However, later on, more mild cases were hospitalized due to expansion of medical services for

Accepted Article

This article is protected by copyright. All rights reserved.

COVID-19 patients, and the proportion of diabetes patients started to reflect that of the general population. The most recent survey showed that the overall prevalence of diabetes in China is 12.8% with only half (6%) having a history of diabetes (self-reported diabetes).[27] The overall prevalence of diabetes in those aged ≥40 years was 15.6%.[5] Our data shows that the prevalence history of diabetes in patients with severe COVID-19 is 31.3%, strongly suggesting that diabetes is a risk factor for more severe COVID-19.

Our study also shows that a history of T2DM is a risk factor for the progression and prognosis of COVID-19,[12] with a higher risk of severe pneumonia and higher chest CT scores. It also showed that T2DM patients had more severe organ impairments and worse inflammation. Moreover, diabetes patients have worse glycaemic control which requires more anti-hyperglycaemic treatment following COVID-19 or hospitalization. Wu et al.[28] reported that diabetes was a risk factor of developing ARDS in COVID-19. All of these indicate that diabetes status is a major risk factor for worse clinical outcomes/fatality in COVID-19 patients. Indeed, based on our analysis of patients' clinical status, the survival curve showed that the prognosis for T2DM patients was worse. NEWS2 analysis on admission demonstrated that patients with a history of T2DM were generally sicker on admission and older which might be the explanation for the lower survival rate. The time of symptom onset to admission showed no difference between T2DM vs. non-DM patients. However, it has been reported that the SARS-CoV-2 infection was more likely to affect older men with diabetes.[6] As is widely reported, age is a strong indicator for COVID-19 prognosis. Further logistic regression analysis showed that T2DM is an independent risk factor for severe status and fatality of COVID-19 patients. Our data also shows that SARS-CoV-2 infection affects men and women equally, and also indicates that gender may not be a risk factor for a poor outcome, in keeping with recent reports from China.[4,13]

Huang et al.[2] reported that SARS-CoV-2 infection in Wuhan caused multiple organ dysfunction and death in severe COVID-19 patients. In our study, laboratory parameters associated with multiple organ function were tested on admission. The results showed abnormal or worse albumin, eGFR, WBC, CRP, IL-6, AST, LDH, NT-proBNP, CK-MB, myoglobin, cTnI, and D-dimer in COVID-19 patients with T2DM.

Accepted Article

This article is protected by copyright. All rights reserved.

These data indicate that SARS-CoV-2 infection in T2DM is associated with more severe inflammation, coagulation activation, myocardia injury, hepatic injury, and kidney injury. Therefore, diabetes patients are more likely to develop multiple organ failures and die as a result.[4] ACE2, the SARS-CoV-2 receptor, is present in endothelial and smooth muscle cells in multiple organs,[29] suggesting that SARS-CoV-2 infection may induce multiple organ injury, possibly via ACE2. It is well recognized that viral infections can worsen blood glucose control. It has also been found that ACE2 protein shows strong immunostaining in islets, suggesting that SARS-CoV-2 may contribute to the development of diabetes or exacerbation of hyperglycaemia by damaging pancreatic islets via ACE2.[30] Moreover, high levels of inflammatory cytokines such as IL-6 and TNF-a in diabetes patients and animal models suggests that diabetes may significantly promote the production of TLR4-induced IL-6 increase.[12,31] IL-6-dominated cytokine storms have been identified as one of the leading causes of death from pneumonia caused by SARS-CoV-2 infection.[32, 33]

During the current pandemic of COVID-19, systemic GC was used for their potent anti-inflammatory properties.[34] The use of GC requires a knowledge of the related side effects (e.g. avascular necrosis, psychosis, diabetes), their adequate prevention and a prompt treatment if necessary. A randomized, controlled clinical trial in a preprint posted to medRxiv has found that dexamethasone with mechanic ventilation was shown to reduce deaths from severe COVID-19. [35] However, whether GC should be used for the treatment of lung injury related to SARS-CoV-2 infection is still debatable.[36] In the past, steroid administration did not clearly improve the mortality rate of patients affected by SARS-CoV and MERS-CoV.[36] Our study found that a higher risk of all-cause fatality with GC treatment in severe COVID-19 patients with T2DM. Although GC was more likely to be used in critical cases, our data indicated that GC treatment may be potentially harmful to T2DM patients with critical COVID-19 if not properly used. Firstly, the fatality in DM patients treated with GC was about twice than that in non-DM patients with GC treatment. Secondly, GC treatment was associated with an increased IL-6 levels in T2DM, but not in non-DM patients. It suggested that we need to further define the indications for GC treatment and use it on the right patients.

Accepted Article

This article is protected by copyright. All rights reserved.

The anti-hyperglycaemic treatment approach for T2DM patients with COVID-19 is uncertain because some oral drugs have not been recommended.[19-22] It seems that insulin may be the safest choice during this uncertainty. We analyzed the influences of anti-hyperglycemic drugs on the prognosis of COVID-19 with T2DM. There were three types of insulin with Aspart/Lispro/Human insulin the most widely used, and four types of oral anti-hyperglycemic drugs with acarbose the most commonly used. Of these anti-hyperglycemic drugs, basal insulin, premix insulin, metformin, acarbose, sulfonylureas, insulin and OAHs, and OAHs alone showed lower fatality than diet treatment alone, despite their similar NEWS2 or clinical status on admission/at baseline. It seems to be consistent with their effects on improving fasting blood glucose metabolism. A recent study reported that a "good blood glucose control (3.9-10moml/L)" was associated with less fatality.[37] Our study indicated similarly but more precisely, we recommended to aim fast blood glucose at (3.9-11.0 mmol/L) for better survival.

We have excluded patients with elevated glucose (FPG ≥ 6.1mmol/L or random glucose ≥ 11.1mmol/L) from non-diabetic group in our analysis. However, they showed same results as pre-existing diabetes patients for those with GC treatment or FPG ≥11.1 mmol/L (Supplementary Table). Moreover, elevated glucose was found in 182 patients (59 without GC treatment), indicating there is undiagnosed diabetes in these patients.

In summary, a history of T2DM aggravated the clinical status of COVID-19 patients, increased their critical illness and mortality rates. SARS-CoV-2 infection in diabetes led to more severe inflammation, coagulation activation, myocardia injury, hepatic injury, and kidney injury. GC treatment and fasting plasma glucose ≥11.1 mmol/L were found to be risk factors for fatality in diabetes patients with COVID-19. There are some limitations of this study that took place within the context of an emergency outbreak including: lack of a control group- either as a matched control to compare patient groups or randomized control for the assessment of treatments. Besides, our study is based on small numbers of diabetic patients. However, our study provided evidence for informing clinical decisions.

Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article

Article information

Duality of Interest. No conflicts of interest relevant to this article have been reported. The opinions and conclusions of this paper are solely the responsibility of the authors and do not necessarily represent the official positions of the Centers for Disease Control and Prevention.

Acknowledgements. The authors thank all study participants.

Funding Information. Ling Gao was supported from Natural Science Funding of China (No. 81571376), and China Young Scientific Talent Research Fund for diabetes 2017; Zihui Xu was supported from 2018-2020 Wuhan Young and Middle-aged Medical Talent Award Plan.

This article is protected by copyright. All rights reserved.

Accepted Article

References

1. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report-157. Accessed June 25, 2020. https://www.who.int/docs/default-source/ coronaviruse/ situation -reports/ 20200625-covid-19-sitrep-157.pdf.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; **395**: 497-506.
3. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; **382**:1708-1720.
4. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020; **323**:1061-1069.
5. Wang L, Gao P, Zhang M, et al. Prevalence and Ethnic Pattern of Diabetes and Prediabetes in China in 2013. JAMA. 2017; **317**: 2515-2523.
6. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; **395**: 507-513.
7. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020; **20**: 425-434.
8. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA. 2003; **289**: 2801-2809.
9. Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med. 2006; **23**: 623-628.
10. Allard R, Leclerc P, Tremblay C, Tannenbaum TN. Diabetes and the severity of pandemic influenza A (H1N1) infection. Diabetes Care. 2010; **33**: 1491-1493.

This article is protected by copyright. All rights reserved.

Accepted Article

11. van den Brand JM, Smits SL, Haagmans BL. Pathogenesis of Middle East respiratory syndrome coronavirus. J Pathol. 2015; **235**: 175-184.

12. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020; e3319. Doi: 10.1002/dmrr.3319.[Epub ahead of print].

13. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020; Doi: 10.1111/all.14238. [Epub ahead of print].

14. Schmid S, Molteni A, Fuchtenbusch M, et al. Reduced IL-4 associated antibody responses to vaccine in early pre-diabetes. Diabetologia. 2002; **45**: 677-685.

15. Zhou J, Tan J. Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China. Metabolism. 2020; **107**: 154216. Doi: 10.1016/j.metabol.2020.154216. [Epub ahead of print].

16. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020; **367**: 1260-1263.

17. Xuan X, Gao F, Ma X, et al. Activation of ACE2/angiotensin (1-7) attenuates pancreatic beta cell dedifferentiation in a high-fat-diet mouse model. Metabolism. 2018; **81**: 83-96.

18. Takeda M, Yamamoto K, Takemura Y, et al. Loss of ACE2 exaggerates high-calorie diet-induced insulin resistance by reduction of GLUT4 in mice. Diabetes. 2013; **62**: 223-233.

19. Drucker DJ. Coronavirus Infections and Type 2 Diabetes-Shared Pathways with Therapeutic Implications. Endocr Rev. 2020; 41.pii: bnaa011.

20. Zhang P, Zhu L, Cai J, et al. Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19. Circ Res. 2020; **126**:1671-1681.

21. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress. Diabetes Res Clin Pract. 2020; **162**: 108142.

22. Li J, Wang X, Chen J, et al. Association of Renin-Angiotensin System Inhibitors With Severity or Risk of Death in Patients With Hypertension Hospitalized for Coronavirus Disease 2019 (COVID-19) Infection in Wuhan, China. JAMA Cardiol. 2020; Doi: 10.1001/jamacardio.2020.1624. [Epub ahead of print].

23. National Health Commission of the People's Republic of China. Diagnosis and treatment protocols of pneumonia caused by a novel coronavirus (trial version 7). 2020; http://www.nhc.gov.cn/xcs/zhengcwj/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml .

24. National Institute for Viral Disease Control and Prevention (China) . Specific primers and probes for detection 2019 novel coronavirus. 2020; http://ivdc.chinacdc.cn/kyjz/202001/t20200121_211337.html.

25. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020; **382**:1787-1799.

This article is protected by copyright. All rights reserved.

26. Williams B. The National Early Warning Score 2 (NEWS2) in patients with hypercapnic respiratory failure. Clin Med. 2019; **19**: 94-95.

27. Li Y, Teng D, Shi X, et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association: national cross sectional study. BMJ. 2020; **369**: m997.

28. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020; Doi: 10.1001/jamainternmed.2020.0994. [Epub ahead of print].

29. Hamming I, Timens W, Bulthuis ML, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004; **203**: 631-637.

30. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020; **579**: 265-269.

31. Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes Metab Res Rev. 2020; e33213321.Doi: 10.1002/dmrr.3321. [Epub ahead of print].

32. Ascierto PA, Fox B, Urba W, et al. Insights from immuno-oncology: the Society for Immunotherapy of Cancer Statement on access to IL-6-targeting therapies for COVID-19. J Immunother Cancer. 2020; **8**.pii: e000878. doi: 10.1136/jitc-2020-000878.

33. Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents. 2020; **34**.pii: 1. doi: 10.23812/CONTI-E. [Epub ahead of print]

34. Shang L, Zhao J, Hu Y, et al. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet. 2020; **395**: 683-684.

35. Horby P, Lim WS, Emberson J, et al. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. Preprint at medRxiv. 2020. https://doi.org/10.1101/2020.06.22.20137273.

36. WHO (2020) Clinical management of severe acute respiratory infection when COVID-19 is suspected. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. Accessed 21 May 2020.

37. Zhu L, She ZG, Cheng X, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab. 2020; **31**: 1068-1077.

Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article

Tables and Figures

Characteristics	DM (n=114)	non-DM (n=250)	Total (n=364)	P
Age, years	66(57-73)	64(52-73)	65(55-73)	0.044
Gender - Men	62 (54.4%)	144 (57.6%)	206 (56.6%)	0.571
Days onset to Ad	10(7-14)	10(7-14)	10(7-14)	0.568

This article is protected by copyright. All rights reserved.

Died cases	27(23.7%)	32(12.7%)	59(16.2%)	0.014
Laboratory Parameters/Ad				
WBC(×10^9/L)	6.77(5.30-8.61)	5.27(3.99-7.28)	5.64(4.26-7.86)	<0.001
LYM(×109/L)	0.87(0.55-1.27)	1.0(0.75-1.41)	0.97(0.71-1.38)	0.134
CRP(mg/L)	56.6(17.2-111.9)	28.6(6.6-70.5)	37.8(9.4-81.3)	<0.001
IL-6(pg/mL)	17.34(6.59-38.39)	6.56(3.34-23.13)	8.99(4.28-28.81)	0.009
ALT(U/L)	24.5(17.8-57.0)	23.0(16.0-36.0)	24.0(16.0-40.0)	0.873
AST(U/L)	28.5(20.0-47.3)	28.0(20.0-40.0)	28.0(20.0-41.0)	0.032
ALB(g/L)	34.5(31.8-37.4)	36.0(32.8-39.3)	35.5(32.4-38.6)	0.012
Cr(μmol/L)	65.0(52.0-74.8)	64.0(51.0-76.5)	64.0(51.0-76.0)	0.729
eGFR(mL/min·1.73m2)	94.4(74.0-101.8)	94.2(85.1-106.0)	94.3(83.1-104.6)	0.007
LDH(U/L)	326(238-449)	281(216-360)	295(222-377)	<0.001
NT-proBNP(pg/mL)	289.8(133.1-986.0)	122.4(46.3-429.4)	171.2(56.1-544.8)	0.014
CK(U/L)	55(36-119)	63(40-111)	61(38-113)	0.835
CK-MB(ng/mL)	1.31(0.85-2.62)	1.05(0.66-1.59)	1.14(0.70-1.90)	<0.001
Myoglobin(μg/L)	60.59(34.13-122.80)	45.59(29.38-82.35)	49.99(31.46-92.01)	0.008
cTnI(ng/mL)	0.008(0.005-0.029)	0.005(0.005-0.018)	0.005(0.005-0.022)	<0.001
D-dimer(mg/L)	1.31(0.62-5.79)	0.89(0.42-3.31)	1.03(0.49-3.91)	0.02
LA(mmol/L)	2.1(1.7-2.9)	2.0(1.6-2.8)	2.1(1.6-2.9)	0.488
CD3(/μl)	505(284-850)	604(399-847)	561(364-846)	0.131
CD4(/μl)	321(167-491)	380(239-531)	357(217-514)	0.215
CD8(/μl)	136(75-289)	209(129-327)	194(110-305)	0.147
CD4/CD8	1.94(1.34-3.16)	1.77(1.23-2.69)	1.83(1.24-2.78)	0.109
CD19(/μl)	136(80-192)	127(76-196)	129(77-193)	0.5
CD16+56(/μl)	111(55-191)	116(75-188)	112(70-190)	0.755

Table 1: Demographic, laboratory indices and clinical course and outcomes of diabetes (DM) vs. non-diabetes (non-DM) patients with COVID-19.

Accepted Article

This article is protected by copyright. All rights reserved.

Data was shown with median (interquartile range, IQR) and No. of patients (%). P <0.05 for DM vs. non-DM was considered statistically significant. Abbreviations: DM, diabetes; WBC, white blood cells; LYM, lymphocyte; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; Cr, creatinine; eGFR, estimated glomerular filtration rate; CK, creatine kinase; LDH, lactate dehydrogenase; CK-MB, creatine kinase isoenzyme-MB; cTnI, cardiac troponin I; BNP, B-type natriuretic peptide; LA, lactic acid. Ad: admission

Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article

Anti-hyperglycaemic drugs	Died cases	n	NEWS2 on admission	Ventilation score	FPG		
					admission	endpoint	**P
Insulin alone	14(51.9%)	27	6.0(4.0-8.0)	3.0(2.0-5.0)	9.22(6.49-15.42)	9.20(5.74-12.89)	0.822
OAHs alone	2(7.4%)*	27	5.0(4.0-7.0)	2.0(2.0-3.0) *	9.17(6.59-10.39)	6.23(5.51-8.35)	0.015
Insulin + OAHs	3(7.3%)*	41	5.0(3.0-7.0)	2.0(2.0-3.0)	11.05(7.39-16.77)	6.83(5.80-9.16)	<0.001
Insulin							
Basal	4(14.3%)*	28	5.0(4.0-7.8)	3.0(2.0-3.0)	12.45(8.79-19.99)	7.41(5.80-10.14)	0.145
Premix	1(6.3%)*	16	5.0(4.3-8.0)	2.5(2.0-3.0)	12.70(8.57-18.26)	6.47(5.39-9.60)	0.002
Aspart/Lispro/Human	16(33.3%)	48	5.0(4.0-8.0)	3.0(2.0-4.0)	11.20(7.14-15.97)	8.28(5.80-10.95)	0.144
OAHs							
Metformin	2(6.7%)*	30	4.0(3.0-6.0)	2.0(2.0-3.0)	9.86(6.82-13.86)	6.36(5.87-8.36)	0.021
Acarbose	4(7.5%)*	53	5.0(4.0-8.0)	2.0(2.0-3.0)	10.15(7.17-14.79)	6.83(5.56-9.16)	<0.001
Sulfonylureas	1(5.9%)*	17	4.0(2.5-7.0)	2.0(2.0-3.0)	7.59(5.33-9.95)	5.80(4.91-8.51)	0.134
DDP4i	0(0)	7	6.0(5.0-8.0)	2.0(2.0-2.0) *	10.28(7.13-11.93)	6.10(4.92-9.20)	0.028

This article is protected by copyright. All rights reserved.

SGLT2i	0(0)	1	9.0	3.0	17.22	6.3	/
Diet treatment alone	8(42.1%)	19	6.0(4.0-8.0)	3.0(2.0-4.0)	9.53(6.84-15.21)	6.07(5.84-9.60)	0.595

Table 2: Anti-hyperglycaemic drugs use and prognosis of type 2 diabetes patients with COVID-19.

Data was shown as numbers (percentages, %), and median (interquartile range, IQR). *P<0.05 vs. diet treatment alone; **P, FPG on admission vs. FPG at endpoint. Abbreviations: OAHs, oral anti-hyperglycaemic drugs; NEWS2, National Early Warning Score 2; FPG, fasting plasma glucose; DDP4i, dipeptidyl peptidase-4 inhibitors; SGLT2i, Sodium-glucose co-transporter-2 inhibitors.

Accepted Article

This article is protected by copyright. All rights reserved.

Characteristics	Excluded cases (n=182)
Age, years	65(56-74)
Gender - Men	100 (54.9%)
Days from onset to admission	10(7-14)
Died cases	52(28.6%)
FPG (mmol/L)	**n (mortality)**
6.1 ~ <7.0	77(20.8%)
7.0 ~ <11.1	92(32.6%)
≥11.1	13(46.2%)
GC treatment	123(35.0%)
No GC treatment	59(15.3%)

Supplementary Table: Demographic, fasting plasma glucose (FPG) and GC treatment on the prognosis of excluded patients with COVID-19.

Accepted Article

This article is protected by copyright. All rights reserved.

Fig. 1: Flow diagram showing enrollment of COVID-19 inpatients and the recruitment of severe/critical cases with and without a history of type 2 diabetes.

Fig. 2: The effects of type 2 diabetes and age on the prognosis of patients with COVID-19

A)The effects of type 2 diabetes (DM) vs. non-diabetes (non-DM) on the mortality of COVID-19 patients with severe/critical infection in the different age groups; B) The overall survival rate of DM vs. non-DM; C) The NEWS2 on admission of DM vs. non-DM and D) The ventilation therapy score of DM vs. non-DM. $p<0.05$ is considered as significant and its value is as indicated in the graph.

Fig. 3 The effects of glucocorticoid (GC) therapy on the prognosis of type 2 diabetes (DM) and non-diabetes (non-DM) patients with severe/critical COVID-19.

A)The overall survival rate of GC therapy in DM patients; B) The overall survival rate of GC therapy on non-DM patients; C) The fatality of GC treatment (+) vs. no GC treatment (-) in DM (+) and non-DM (-) patients; D) The NEWS2 of GC treatment (+) vs. no GC treatment (-) in DM (+) and non-DM (-) patients; E) Ventilation therapy scores of GC treatment (+) vs. no GC treatment (-) in DM (+) and non-DM (-) patients; F) The effects of GC on IL-6. $p<0.05$ is considered as significant and its value is as indicated in the graph.

Fig. 4 The overall survival rates of average fasting plasma glucose (FPG)

$p<0.05$ is considered as significant and its value is as indicated in the graph.

Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article

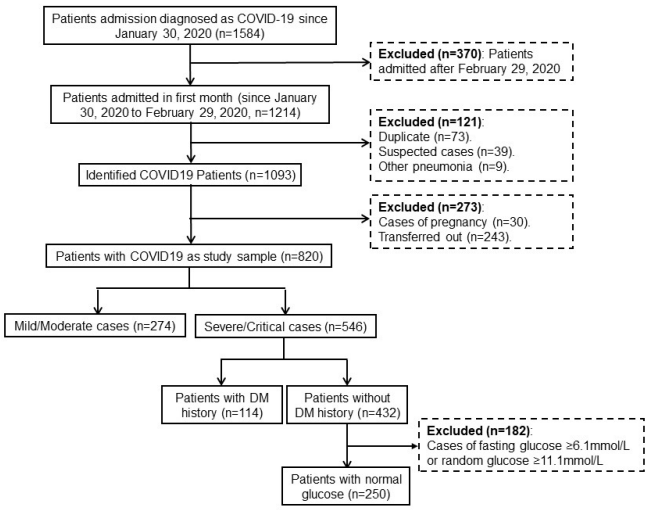

Fig. 1: Flow diagram showing enrollment of COVID-19 inpatients and the recruitment of severe/critical cases with and without a history of type 2 diabetes.

338x190mm (96 x 96 DPI)

This article is protected by copyright. All rights reserved.

Accepted Article

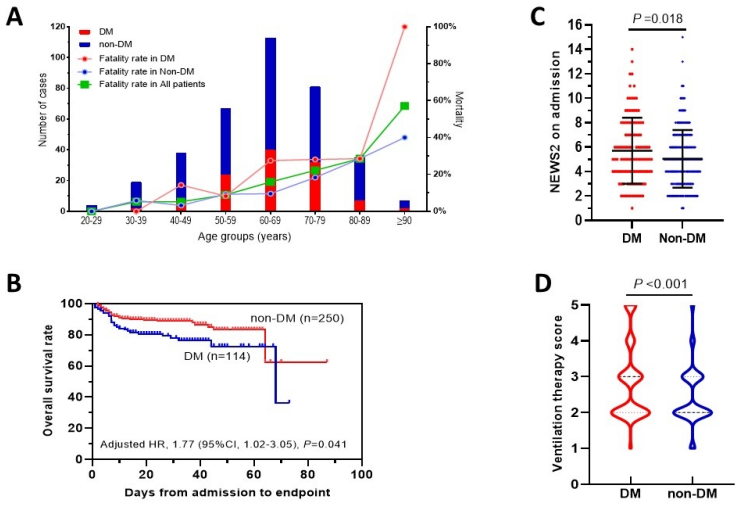

Fig. 2: The effects of type 2 diabetes and age on the prognosis of patients with COVID-19
A)The effects of type 2 diabetes (DM) vs. non-diabetes (non-DM) on the mortality of COVID-19 patients with severe/critical infection in the different age groups; B) The overall survival rate of DM vs. non-DM; C) The NEWS2 on admission of DM vs. non-DM and D) The ventilation therapy score of DM vs. non-DM. $p<0.05$ is considered as significant and its value is as indicated in the graph.

338x190mm (96 x 96 DPI)

This article is protected by copyright. All rights reserved.

Accepted Article

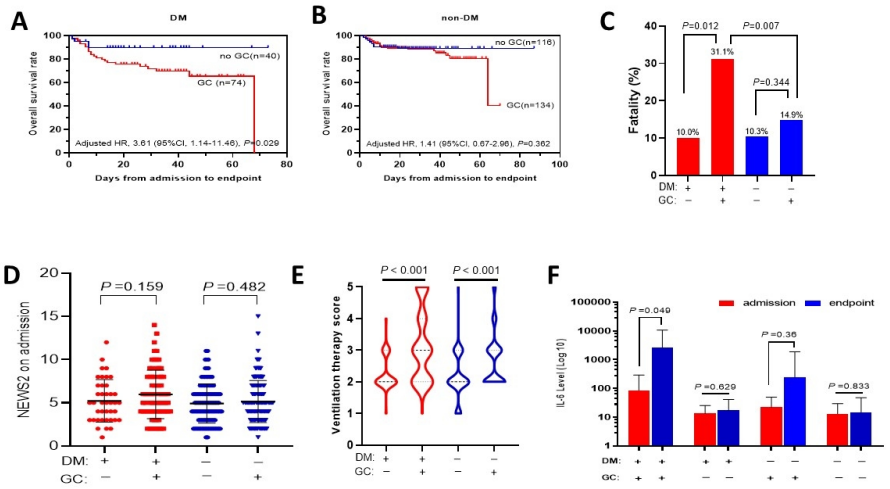

Fig. 3 The effects of glucocorticoid (GC) therapy on the prognosis of type 2 diabetes (DM) and non-diabetes (non-DM) patients with severe/critical COVID-19.
A)The overall survival rate of GC therapy in DM patients; B) The overall survival rate of GC therapy on non-DM patients; C) The fatality of GC treatment (+) vs. no GC treatment (-) in DM (+) and non-DM (-) patients; D) The NEWS2 of GC treatment (+) vs. no GC treatment (-) in DM (+) and non-DM (-) patients; E) Ventilation therapy scores of GC treatment (+) vs. no GC treatment (-) in DM (+) and non-DM (-) patients; F) The effects of GC on IL-6. $p<0.05$ is considered as significant and its value is as indicated in the graph.

338x190mm (96 x 96 DPI)

This article is protected by copyright. All rights reserved.

Accepted Article

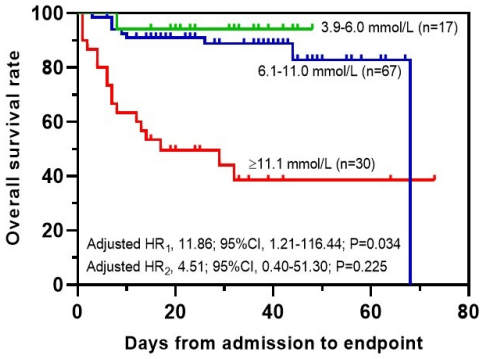

Fig. 4 The overall survival rates of average fasting plasma glucose (FPG)
$p<0.05$ is considered as significant and its value is as indicated in the graph.

338x190mm (96 x 96 DPI)

This article is protected by copyright. All rights reserved.