Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Glucose Tolerance and the Risk Factors for Transmission in Japanese SARS-CoV-2/WA-1/2020 Epicenter: A Retrospective Study

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Purpose: The severe pathogenic ancient-type COVID-19, SARS-CoV-2/WA-1/2020 was the predominant gene variant in early 2020 in Japan, however, its transmissibility was uncertain. The period before the public commenced using any personal protective equipment (PPE) was evaluating to describe the transmissibility of the SARS-CoV-2/WA-1/2020. We analyzed the secondary attack rate (SAR) among close contacts and the risk factor for SAR.

Methods: This retrospective cohort study included a total of 539 patients who were anticipated for the SARS-CoV-2/WA-1/2020 infection at Toho University Medical Center Omori Hospital from February to May 2020. We selected 54 patients with 1) exclude other pathogens infection, 2) include "Three Cs" condition: crowded places between distance< 6 feet, closed spaces indoor and close contact settings involving contact >15min with a person tested positive for SARS-CoV-2/WA-1/2020 without PPE. We evaluated alternative infection risks: the body mass index (BMI) and diabetes (DM) status (non-DM, pre-DM, and DM) as demographic determinants of transmissibility and infectivity of SARS-CoV2/WA-1/2020 cases during the incubation period.

Results: The calculated SAR was 79.3%. BMI was significantly associated with the PCR positivity rate, which was significant in the univariate (CI 95%, 1.02–1.51; P = 0.03) and multivariate (CI 95%, 1.02–1.60; P = 0.03) analyses. Comparing the different BMI groups, the highest BMI group (25.5−35.8 kg/m^2) had an elevated risk of SAR compared to the lowest BMI group (14.0–22.8 kg/m^2), with an odds ratio of 1.41 (95% CI, 1.02–1.59; P = 0.03). There were no significant differences in the risk of SAR among different DM statuses.

Conclusion: The transmissibility of SARS-CoV2/WA-1/2020 was high (79.3%) among household members without PPE who had "Three Cs" exposure. Although pre-DM and established DM did not confer a risk for transmissibility, higher BMI was associated with an increased risk of SAR.

Trial Registration: UMIN Clinical Trials Registry, UMIN0000 50905.

Keywords: obesity, pre-diabetes, SARS-CoV-2 transmission

Introduction

Since the two studies that identified a novel coronavirus-associated infectious disease,[1,2] there have been reports of single-center experiences involving a small number of patients in China. Subsequently, multicenter experiences from various regions worldwide, starting from Asia,[3–5] followed by Europe and the USA, mirrored the spread of the pandemic's epicenter.

Received: 30 November 2023
Accepted: 14 June 2024
Published: 20 June 2024

Since early 2020, many countries have experienced the coronavirus disease (COVID-19) pandemic, with under-reported cases of severe respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and related deaths.[6] Throughout 2020 and 2021, the pandemic has been extensively studied, examining various epidemiological factors, including age, sex, ethnicity, and comorbidities in the population.[7,8]

Previous studies have consistently identified older age, male sex, obesity, hypertension, diabetes mellitus (DM), cardiovascular disease, chronic lung disease, renal disease, and cerebrovascular disease as risk factors for COVID-19 mortality.[9–12] Mild hyperglycemia (>7.0 mM [126 mg/dl]) upon hospital admission, without a known diagnosis of DM, has also been associated with poor outcomes and increased mortality.[13] Also, observational study which reported the different COVID-19 outcomes between BMI and the state of obesity, adiposity related metabolic dysfunctions are associated with enhanced inflammation and metabolic imbalance. These are leading to pro-inflammatory state and associated with worse viral infection outcomes and poor defense mechanisms.[14]

Similar to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), COVID-19 can be transmitted from person to person through direct contact with contaminated surfaces or objects, as well as through inhalation of respiratory droplets from infected individuals.[1]

Only a limited number of studies have utilized routinely collected surveillance data from smaller urban areas, focusing on both hospitalized and non-hospitalized individuals who tested positive for SARS-CoV-2.

DM is a risk factor for severe COVID-19, and well-controlled blood glucose (BG) levels have been shown to reduce the risk of severe COVID-19.[9,11,15] However, limited data are available regarding whether patients with DM are more susceptible to contracting COVID-19 compared to those without DM. Researchers have investigated potential mechanisms linking COVID-19 and DM,[9,10] such as the impact of SARS-CoV-2 on glucose metabolism,[13] inflammation and insulin resistance,[16] immune reactivity,[17] the severity of COVID-19,[18] the relationship to certain types of DM medications,[19] and the amenability to new-onset DM.[20] However, there is the scarcity of retrospective analyses on COVID-19 transmission within households and close contacts.

This gap must be addressed from a public health perspective by focusing on the magnitude of glycemia within close contacts in indoor settings. Transmission data from environmental and experimental studies provide evidence of the biological plausibility of high-risk infections in individuals with DM.[21] In this study, we examined glycemia levels to evaluate the potential for human-to-human transmission of SARS-CoV-2 in indoor community settings and assessed the impact of potential modifying factors on this transmission. We propose that the degree of glucose tolerance plays a role in modulating the rate of COVID-19 infection among household members and individuals in close airborne contact within indoor community settings.

Methods

Patients

This retrospective observational cohort study included a total of 539 patients who were anticipated for the SARS-CoV-2/WA-1/2020 infection at Toho University Medical Center Omori Hospital from February 1 to May 31 2020. They had upper respiratory symptoms and/or "Three Cs" condition: crowded places between distance< 6 feet, closed spaces indoor and close contact settings who contacted >15min with tested positive for SARS-CoV-2/WA-1/2020 without PPE. We excluded children 0 to 17 years old. Of the 374 patients, those infected with other confirmed pathogens were excluded. The remaining 54 patients were selected in this study (Supplement). All these patients have been tested SARS-CoV-2/WA-1/2020 PCR. No statistical sample size calculations were conducted due to the exploratory retrospective cohort study. The study protocol was reviewed by the Japanese authorities in accordance with local regulations, followed by review and approval by the Ethics Committee of Toho University Omori Medical Center (M20263, 20135). This study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. This study was registered at the National University Hospital Medical Information Network (UMIN Clinical Trials Registry: UMIN0000 50905).

The patients were divided into two groups: 43 SARS-CoV-2 PCR-positive cases (79.6%) and 11 SARS-CoV-2 PCR-negative cases (20.4%). We analyzed the close contacted secondary attack rate (SAR) and the risk of SAR. SAR defined as the probability that an infection occurs among susceptible people within a specific group, as households, close contacts or co-workers.

All patients had close contact with individuals who tested positive for SARS-CoV-2, either within their families or their environment (workplace, school, etc.) as Figure 1 shows. Patients were further categorized into non-DM (hemoglobin A1c [HbA1c] < 5.6%), pre-DM (HbA1c, 5.7–6.4%), and DM (HbA1c > 6.5%) groups, following the American Diabetes Association Guidelines for the Degree of Diagnosis.[22]

Testing Transmissibility

Samples were collected using throat or nasal swabs. Total viral RNA was extracted from the swabs using a QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany) or BD MAXTM ExK TNA-3 (swab; Becton Dickinson, Franklin Lakes, NJ, USA). To estimate the concentration of the virus in the samples, PCR tests were used, which are widely employed for confirming COVID-19 infections. These tests detect the genetic material of the virus by amplifying the DNA until it becomes detectable as a fluorescent signal in chemiluminescence microparticle immunoassays, including chemiluminescent immunoassays (CLIAs) and enzyme-linked immunoassays (ELISAs).

The cycle threshold (Ct) value, indicating the number of amplification cycles required to obtain a detectable signal, served as a proxy for the viral concentration. A lower Ct value corresponds to a higher viral genetic material presence. SARS-CoV-2 PCR positivity was defined as Ct values below 35.

Study Design

For each evaluated case, data on age, sex, height, body weight, body mass index (BMI), HbA1c level, date of sampling, presence of various symptoms at the time of testing, and chronic comorbidities including hypertension, smoking, and alcohol habits were collected. All data on symptom onset, presence of symptoms, and comorbidities were self-reported by the patients. All participants were unvaccinated at the time of their arrival at the hospital.

Statistical Analysis

Quantitative variables were presented as mean ± standard deviation (SD), and qualitative variables were presented as number (percentage). *T*-tests were used to compare the averages of continuous variables, and chi-squared tests were used to compare the proportions of categorical variables between the groups. Statistical significance was set at P-values < 0.05. All analyses were conducted using JMP version 15 (www.JMP.com). A multiple logistic regression model was

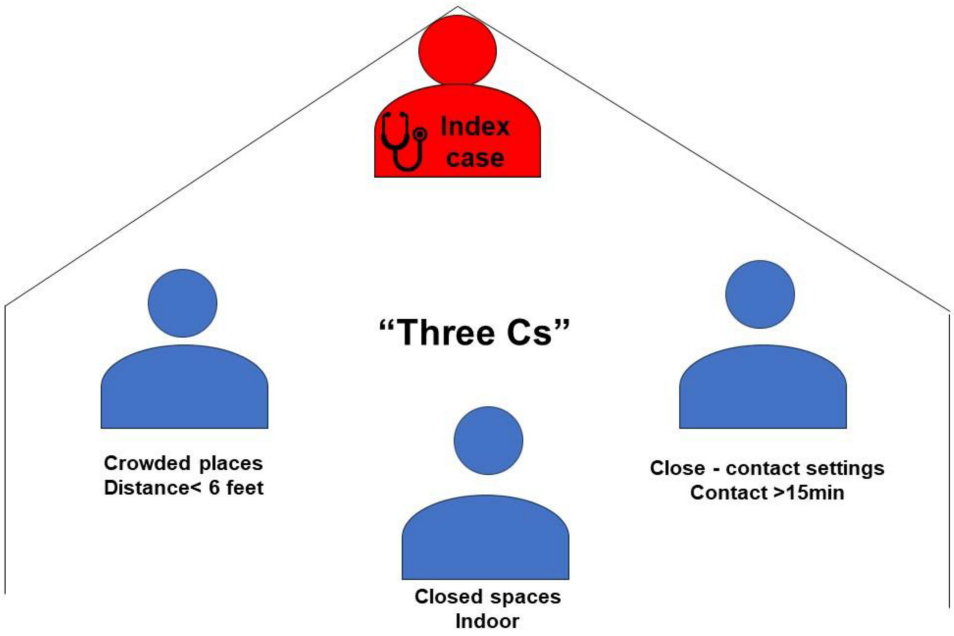

Figure 1 The figure shows the study subjects obtained by "Three Cs" in the SARS-CoV-2/WA-1/2020 era without any personal protective equipment. "Three Cs" defined as continued to share the circumstances with an index case which contains crowded places distance< 6 feet, indoor closed-spaces with poor air ventilation and shared close-contact settings more than 15 min.

utilized to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to identify PCR positivity rates and assess the impact of COVID-19 aggravating factors, such as high BMI, abnormal HbA1c level, and older age.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Results

No statistical sample size calculations were conducted due to the exploratory retrospective cohort study. However, a sample size of 54 subjects gave post hoc powers of 4.00 (1.24–13, 95% CI) and 94% (82%-98%, 95% CI) to detect positive likelihood ratio and positive test posterior probability, respectively. Due to the small sample size and the measurement error in root segmentation, we also calculated negative likelihood ratio and negative test posterior probability, as 0.25 (0.13–0.49, 95% CI) and 48% (33–65%, 95% CI). The characteristics of the patients are summarized in Table 1. Between February and May 2020, we observed 43 patients with positive SARS-CoV-2 infection (PCR-positive) and 11 with negative SARS-CoV-2 infection (PCR-negative). The male/female ratio in the PCR-positive and negative groups was 21/22 and 7/4, respectively (P = 0.38). No statistically significant differences were found in terms of age (P = 0.95), height (P = 0.80), and body weight (P = 0.10) between the PCR-positive and negative groups. However, the BMI of the PCR-negative group was significantly lower than that of the PCR-positive group (P = 0.03). Furthermore, there were no significant differences in terms of HbA1c levels (P = 0.14), hypertension (P = 0.19), cigarette smoking (P = 0.84), and alcohol consumption (P = 0.29) between the PCR-positive and negative groups.

The results of univariate and multivariate analyses of risk factors associated with testing positive for SARS-CoV-2 are shown in Table 2. Univariate analyses demonstrated that male sex (odds ratio (OR) 0.54 [95% Cl 0.13–2.13]), age (OR 0.99 [0.96–1.03]) and HbA1c (OR 2.59 [0.66–10.11]) were not considered to be risk factors. BMI (OR 1.24 [1.02–1.51], P=0.03) was a statistically significant correlated to the testing positive rates for SARS-CoV-2. In multivariate analysis, adjusted for sex, age and HbA1c, BMI was independently correlated with testing positive rates for SARS-CoV-2 (adjusted odds ratio 1.28, 95% Cl 1.02–1.60, P=0.03).

The following factors were examined: sex, age, HbA1c level, and BMI. To further analyze the relationship between BMI and COVID-19 risk, patients were divided into three groups: a low BMI group (14 < BMI < 20.8), middle group (20.9 < BMI < 25.3), and high group (25.5 < BMI < 35.8). Each group was divided equally among 18 patients. Eighteen of 54 patients were obese (BMI of 25 kg/m2 or higher). Compared to the lower BMI group, the middle group had a risk ratio of 1.16 (95% CI, 0.78–1.64; P = 0.45) for developing COVID-19, while the higher group had a risk ratio of 1.41 (95% CI, 1.02–1.59; P = 0.03) (Table 3).

Table 1 Characteristics of 54 Individuals Tested for SARS-CoV-2

Characteristic	Total	PCR-Positive	PCR-Negative	P-value
N (%)	54 (100.0)	43 (79.6)	11 (20.4)	N/A
Male, Female	28, 26	21, 22	7, 4	0.38
Age (years)	54 ± 17.3	54 ± 17.8	54.2 ± 15.4	0.95
Height (cm)	164.2 ± 8.78	163.9 ± 9.06	165.1 ± 7.49	0.8
Body weight (kg)	63.1 ± 15.7	64.8 ± 15.7	56.3 ± 13.4	0.1
BMI (kg/m^2)	23.2 ± 4.55	23.9 ± 4.49	20.4 ± 3.6	0,03*
Diabetes, Pre-Diabetes, Non-Diabetes (N)	11, 25, 18	10, 19, 14	1, 6, 4	N/A
HbA1c (%)	6.21 ± 1.40	6.32 ± 1.53	5.78 ± 0.41	0.14
Hypertension (%)	24.1	27.9	9	0.19
Smoke (%)	20.4	21	18	0.84
Alcohol (%)	20.4	23.2	9	0.29

Notes: Data are presented as mean ± standard deviation. *P < 0.05 represents a significant difference between groups.
Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; PCR, polymerase chain reaction.

Table 2 Univariate and Multivariate Analyses of Risk Factors for Testing Positive for SARS-CoV-2

Risk Factor	Univariate Analysis	P-value	Multivariate Analysis	P-value
	Odds ratio (95% CI)		Odds ratio (95% CI)	
Sex (Male)	0.54 (0.13–2.13)	0.38	0.29 (0.05–1.65)	0.29
Age	0.99 (0.96–1.03)	0.97	1.00 (0.94–1.06)	0.96
HbA1c	2.59 (0.66–10.11)	0.17	3.43 (0.45–26.06)	0.16
BMI	1.24 (1.02–1.51)	0,03*	1.28 (1.02–1.60)	0,03*

Notes: Data were adjusted for sex, age, HbA1c, and BMI. *P < 0.05 represents a significant difference between groups.
Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c; BMI, body mass index.

Table 3 Association Between Aggravating Factors of SARS-CoV-2 and BMI

BMI Group (n=54)	BMI (kg/m2)	Risk Ratio (95% CI)	P-value
Low Group (n=18)	14.0–20.8	1.0	–
Middle Group (n=18)	20.9–25.3	1.16 (0.78–1.64)	0.45
High Group (n=18)	25.5–35.8	1.41 (1.02–1.59)	0,03*

Note: *P < 0.05 represents a significant difference between groups.
Abbreviations: CI, confidence interval; BMI, body mass index.

Discussion

Main Findings

This study aimed to investigate the pure transmissibility of SARS-CoV-2/WA-1/2020 among households and co-workers reliance on "Three Cs" condition in Japanese epicenter. We found that the overall positive transmission rate was 79.3% (Table 1), which was significantly higher than the overall secondary attack rate (SAR) of 15.6% reported at the first epicenter of COVID-19 in Wuhan, China.[23] In our risk factor analysis, we did not find a significant association between glycemic status (non-DM, pre-DM, and DM) and the risk of SARS-CoV-2 transmission to household and community close contacts. Although no significant risk was found for various DM statuses in relation to SARS-CoV-2/WA-1/2020 SAR, the highest BMI tertile was associated with an increased SAR. The study highlights the significance of implementing comprehensive contact tracing strategies to evaluate the strict SAR in "Three Cs". Obesity, as indicated by a BMI > 25 in Asians, was associated with an elevated risk of SARS-CoV-2/WA-1/2020 SAR in East Asian epicenter.

Pure Transmissibility in the Close Community Contact-Tracing

Airborne transmission has been observed in various respiratory viruses, including influenza virus, respiratory syncytial virus, human-rhinovirus, adenovirus, SARS-CoV, SARS-CoV-2, and MERS-CoV. This highlights the importance of investigating and implementing preventive measures to address airborne transmission.[24,25] Close contacts with the highest risk of transmission typically include household members, extended caregivers, and colleagues, with SARs ranging from 4 to 35%.[26,27] The classification of contact tracing by the Centers for Disease Control and Prevention (CDC) aligns with the Japanese guideline, which includes six categories: household contacts, closed settings, healthcare settings, professional contacts, public or shared transport, and other well-defined settings with specific exposure time and social distancing measures.[28] Although the risk of different DM statuses with SARS-CoV-2/WA-1/2020 SAR was not significant (Table 2), BMI was associated with increased SAR. This study highlights the importance of implementing comprehensive contact tracing strategies to accurately evaluate the true SAR. Reducing the average daily number of contacts per participant by 74% (from 10.8 to 2.8) through the implementing of lockdown measures has been shown to effectively decrease the basic reproduction number (R0) from 2.6 to 0.62 (95% CI, 0.37–0.89) and 0.37 (95% CI, 0.22–0.53) based on all types of contact and physical contact, respectively.[29]

Potential Mechanisms Related to Glycaemia and BMI with Infection

Coronaviruses have been shown to up-regulate the expression and production of interferon-gamma (INFγ), which activates natural killer (NK) and killer T cells as defensive mechanisms.[30] In the context of glucose metabolism, there is a relationship between the immune response, NK cell activity, and glucose management with type 2 DM. Significant heterogeneity was found among studies of COVID 19 SAR, age, sex, contact frequency and environments were determinants.[31] However, in our study of entirely symptomatic cases from the Japanese epicenter, the estimated SAR was profoundly increased, making it difficult to interpret the precise risk factors.[23] Result from previous observational study which reported the different clinical outcomes between the spectrum of BMI, obesity induced metabolic dysfunctions are associated with enhanced inflammation and metabolic imbalance,[14] which may disrupt the prompt response to the defense mechanisms to COVID-19 infections, resulting in a pro-inflammatory state and worse outcomes to the post-infection surveillance.[32] Insofar as putative mechanism of increase the rate of SARS-CoV-2 viral infection associated with higher BMI, upper-respiratory and pulmonary cell entry of the virus is dependent on angiotensin-converting enzyme 2 protein, which had increased expression with the patient percentage of body fat mass and BMI.[33]

Higher infection rates in this study may be attributed to overcome the magnitude of each risks to the SAR, leading to the ascertain whether glycemic status may be influenced to SARS-CoV2/WA-1/2020 SAR. Given the increased risk to glycemic status, future studies might compare in different ethnicities, age and sex matched controls and viral loads at the time of symptom onset.

Limitations

Our study had several limitations. The most notable is the small number of participants. Although statistical sample size calculation was not conducted due to the exploratory retrospective cohort study, the small sample size and the measurement error in root segmentation should be interpreted with caution. We selected limited subjects because of; 1) we wish to focus on the transmissibility of most lethal genotype SARS-CoV-2/WA-1/2020 in Japan, 2) we forced to select the patients within February to May 2020, which allowed us to eliminate the effect of widespread access to personal protective equipment. While we traced individuals, who had close contact with household members and patients, there may still be a confounding bias that we could not completely rule out. Rates of SAR also varied across geographic locations, type of working office and tertiary transmission which cannot be ignored. Additionally, contact with different patients concurrently may have impacted the accuracy of contact tracing. Furthermore, we did not specifically examine incubation periods or unforeseen factors that could influence virus transmission. Lastly, although this study evaluated the transmission rate in urban areas of Japan, the dynamics of SARS-CoV2/WA-1/2020 infections in the global population may be more complex than expected.

Conclusions

During the early days of SARS-CoV2/WA-1/2020 in East Asia, specifically in Tokyo, Japan, the secondary infection rate was remarkably high, reaching approximately 80%. This transmission primarily occurred during the incubation period among individuals in households and close contact settings without personal protective equipment. Surprisingly, the extent of glucose status did not show a clear association with the risk of transmission. However, implementing comprehensive contact tracing among individuals with a high BMI who have household and close contact relationships with infected individuals could be an effective strategy to reduce secondary transmission. Although a large number of participants and repeated study in different regions are warranted, the study highlights the significance of implementing comprehensive contact tracing strategies to evaluate the strict SAR in “Three Cs”. Obesity, as indicated by a BMI > 25 in Japanese, was associated with an elevated risk of SARS-CoV-2/WA-1/2020 SAR in Japanese epicenter.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics/Ethical Approval

The study protocol was reviewed by the Japanese authorities in accordance with local regulations, followed by review and approval by the Ethics Committee of Toho University Omori Medical Center (M20263, 20135). This study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. This study was registered at the National University Hospital Medical Information Network (UMIN Clinical Trials Registry: UMIN0000 50905).

Written informed consent was obtained from all participants.

Acknowledgments

We are grateful to all the individuals who participated in this study. We would like to thank Editage (www.editage.com) for English language editing.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure

Dr Fukumi Yoshikawa reports personal fees from Novo Nordisk Pharma Ltd., during the conduct of the study. All authors declare no other competing interests in this work.

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