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A prospective study of the impact of glycaemic status on clinical outcomes and anti-SARS-CoV-2 antibody responses among patients with predominantly non-severe COVID-19

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ABSTRACT

Aims: We carried out this prospective study of predominantly non-severe COVID-19 patients, to evaluate the influence of glycaemic status on clinical outcomes and neutralising antibody (Nab) responses, potentially relevant to the COVID-19 vaccination programme.

Methods: We included consecutive adults admitted to Queen Mary Hospital for COVID-19 from July 2020–May 2021. Glycaemic status was defined by admission HbA1c. Clinical deterioration was defined by radiological progression/new oxygen requirement/intensive care requirement/death. COVID-19 survivors had Nab measurements at 1-month, 2-month, 3-month and 6-month post-discharge.

Results: Among 605 patients (96.9% non-severe COVID-19; 325 normoglycaemia, 185 prediabetes, 95 diabetes), 74 (12.2%) had clinical deterioration, more likely with worse glycaemic status and higher HbA1c ($p < 0.001$). Older age ($p < 0.001$), higher viral loads ($p < 0.001$), higher C-reactive protein (CRP) ($p < 0.001$) and symptomatic presentation ($p = 0.008$), but not glycaemic status/HbA1c, independently predicted clinical deterioration. Older age ($p = 0.001$), higher CRP ($p = 0.038$), elevated lactate dehydrogenase ($p = 0.046$) and interferon treatment ($p = 0.001$), but not glycaemic status/HbA1c, independently predicted Nab titres. Rate of Nab titre decline was comparable across glycaemic status.

Conclusions: COVID-19 patients with worse glycaemic status were more likely to deteriorate clinically, mediated through the association of worse glycaemic status with older age, more severe inflammation and higher viral loads. Importantly, Nab responses did not differ across glycaemic status.

1. Introduction

Coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected over 220 million people worldwide, causing >4.5 million fatalities [1]. Notably, diabetes is one of the most important risk factors for severe COVID-19, contributed by older age, a proinflammatory and hypercoagulable state, hyperglycaemia and the associated comorbidities [2]. Less is known about the influence of prediabetes, a precursor to diabetes, on the clinical outcomes of COVID-19 patients. Chandrasekaran *et al.* reported a relatively high rate of severe adverse outcomes among 102 COVID-19 patients with prediabetes in India [3]. Results from case-control studies were mixed: a retrospective cohort of 843 COVID-19 patients in the United States reported no significant difference in outcomes in 110 patients with prediabetes compared with control [4], while a Mexican cohort of 317 COVID-19 patients [5] and a selected cohort of 240 migrant workers in Singapore [6] showed that prediabetes conferred a greater risk of severe COVID-19. These were patients with more severe diseases or from a selected sub-population. Hence, the influence of prediabetes on the clinical outcomes of COVID-19 patients, in

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general, remained to be clarified.

Moreover, there are concerns about the potential adverse impacts of diabetes on the antibody response to the SARS-CoV-2 vaccine, given the impaired antibody response to influenza and hepatitis vaccine [7,8]. Studies of SARS-CoV-2 antibody responses among patients who recovered from COVID-19 may provide insights. An early report of a small cohort of 31 non-severe patients showed that patients with diabetes were more likely to be negative for anti-SARS-CoV-2 antibodies [9]. On the other hand, a subsequent larger Italian cohort of hospitalised COVID-19 patients [10] showed that patients with diabetes had robust and sustained neutralising antibodies (Nab) to SARS-CoV-2 [11]. Hence, it is worthwhile to evaluate the anti-SARS-CoV-2 antibody responses in a cohort of predominantly non-severe COVID-19 patients representative of the general population.

We carried out this prospective study of COVID-19 patients, predominantly of non-severe disease, to evaluate the influence of glycaemic status on their clinical outcomes and Nab responses.

2. Material and Methods

The public health ordinance in Hong Kong required all patients tested positive for COVID-19 to be admitted to the hospital, including those detected on contact tracing and the Universal Community Testing Programme, regardless of symptoms [12]. Queen Mary Hospital is one of the major centres in Hong Kong receiving confirmed COVID-19 patients. Our previous publication has demonstrated that characteristics of COVID-19 patients admitted to Queen Mary Hospital were largely similar to those admitted to other centres in Hong Kong. Hence, our cohort is representative of COVID-19 patients in Hong Kong [13]. Consecutive adult patients (aged $\geq$ 18 years) admitted to Queen Mary Hospital for COVID-19 between 21 July 2020 and 20 May 2021 were prospectively recruited. The presence of SARS-CoV-2 was confirmed in all patients by reverse transcription-polymerase chain reaction (RT-PCR) from the nasopharyngeal swab (NPS) or deep throat saliva (DTS), using the LightMix SarbecoV E-gene assay (TIB Molbiol, Berlin, Germany), which targeted the envelope protein (E) gene of SARS-CoV-2 [12,14]. Each patient had baseline blood tests taken within 24 h after admission before starting COVID-19 treatments. Basic haematology and biochemistry panel, including random glucose (RG), glycated haemoglobin (HbA1c) and C-reactive protein (CRP), were measured. Abnormal laboratory parameters were defined according to their respective reference ranges [12]. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in all individuals [15]. Exclusion criteria included (i) history of SARS-CoV-2 vaccination, (ii) admission episode for re-infection by SARS-CoV-2, and (iii) pregnancy.

The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. Written consent has been obtained from each patient or subject after fully explaining the purpose and nature of all procedures used.

2.1. Definition of glycaemic status

HbA1c was measured in whole blood using cation-exchange high-performance liquid chromatography. The assay was certified by National Glycohemoglobin Standardization Programme and standardised to Diabetes Control and Complications Trial reference assay.

Participants were classified to have diabetes if they had a documented diagnosis of diabetes before admission for COVID-19 (fasting glucose [FG] $\geq$ 7.0 mmol/L or HbA1c $\geq$ 6.5% [48 mmol/mol]; or use of anti-diabetic agents), or if their HbA1c on admission was $\geq$ 6.5% (48 mmol/mol).

If participants did not have a known diagnosis of diabetes, they were classified as having prediabetes if HbA1c was between 5.7% (39 mmol/mol) and 6.4% (47 mmol/mol) (inclusive) [16], and normoglycaemia if HbA1c $<$ 5.7% (39 mmol/mol).

2.2. Definition of covariates

Demographics and significant comorbidities were recorded. Obesity was defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 278.0. Hypertension was defined by the use of anti-hypertensive medications at baseline, or patients' report of known physician-diagnosed hypertension. Cancer was defined by patients' reported history of cancer. COVID-19-related symptoms were evaluated with a standard checklist. Respiratory rate, baseline oxygen saturation by pulse oximetry, and oxygen requirement on admission were captured. Cycle threshold (Ct) values were obtained from the qualitative LightMix SarbecoV E-gene assay (TIB Molbiol, Berlin, Germany) performed on specimens from NPS or DTS (whichever was lower) on admission. The Ct value represents the number of cycles required for a gene target or a PCR product to be detected. While viral loads were not directly measured with a dedicated quantitative RT-PCR assay in this analysis, studies have shown a good correlation between Ct values and SARS-CoV-2 viral loads [17,18], such that the lower the Ct values, the higher the viral loads. COVID-19 severity was classified according to the 'Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition)' published by the Chinese National Health Commission (NHC) [19]. Mild disease was defined by mild clinical symptoms without manifestations of pneumonia on imaging. Moderate disease was defined by fever and respiratory symptoms, and manifestations of pneumonia on imaging. Severe disease was defined by any of the following: respiratory rate $\geq$ 30/min, SpO2 $\leq$ 93% at rest, and $>$ 50% progression in 48 h on imaging. Critical disease was defined by respiratory failure requiring mechanical ventilation, shock, and intensive care unit (ICU) admission. Each patient's clinical outcomes, including radiological progression, supplementary oxygen requirements, ICU admission and death, were captured. For patients treated for COVID-19, one or more of the following were given: clofazimine [20], ribavirin, interferon beta-1b, or remdesivir [21]. Dexamethasone [22] was added at physicians' discretion as clinically indicated.

2.3. Definition of clinical deterioration

Clinical deterioration was defined as worsening in $\geq$ 1 category of clinical severity according to the Chinese NHC guideline. Hence, the definition of clinical deterioration incorporated radiological deterioration, new-onset oxygen requirement, ICU admission, and death.

2.4. Nab measurement by microneutralisation (MN) assay

Virus culture and MN assay were performed as previously described [23]. Briefly, serum samples were serially diluted in 2-folds with minimum essential medium from 1:10 to 1:320. Diluted sera were mixed with 100 $TCID_{50}$ of SARS-CoV-2 and incubated at 37 °C for 1 h. The mixture was added to VeroE6 cells and incubated at 37 °C and 5% CO_2. Cytopathic effects were determined under inversion microscopy. The MN antibody titre was determined as the highest dilution showing 50% inhibition of cytopathic effects [24]. Titres of $\geq$ 20 were considered positive. MN antibody titres correlated well with both anti-SARS-CoV-2-nucleoprotein (NP) and anti-SARS-CoV-2-spike protein receptor-binding domain (RBD) IgG levels ($R^2 > 0.9$) [24].

2.5. Serial assessments of Nab titres

According to the study protocol, follow-up visits in a dedicated COVID-19 clinic were arranged at 1-month, 2-month, 3-month and 6-month from admission for blood tests for Nab titres. Data were captured until 30 June 2021.

2.6. Statistical analyses

All statistical analyses were performed with IBM® SPSS® version 26. Two-sided p-values < 0.05 were considered statistically significant. Values not normally distributed were logarithmically transformed before analyses. Data were presented as median with interquartile range (IQR) or number with percentage as appropriate. Between-group comparisons were performed with one-way ANOVA for continuous variables as appropriate, and Chi-square test for categorical variables as appropriate. Multivariable stepwise logistic regression analysis was used to identify the independent determinants of clinical deterioration. Nab titres were categorised into four quartiles. Multivariable ordinal logistic regression analysis was used to identify the independent determinant of Nab titres. All variables with statistical significance ($p < 0.05$) in the univariate analysis were included in the multivariable regression analysis. General linear model with repeated measures was used to compare the Nab titres at the four time points upon follow-up according to different glycaemic status. Sensitivity analyses were performed using admission HbA1c or RG as continuous variables instead of glycaemic status as a categorical variable.

2.7. Sample size calculation

The R package "devtools" was used to calculate the sample size and power of the study. From our recent study [25], the anticipated distribution of included subjects was in the ratio of 3:2:1 for normoglycaemia: prediabetes:diabetes. In order to detect a difference of 10% in clinical deterioration between each group at a significance level of 5% in combination with Bonferroni's correction, the total sample size required was 520 to achieve the power of 90%. Hence, the required sample size in each group was 274, 164, and 82 for normoglycaemia, prediabetes, and diabetes respectively according to the anticipated ratio.

3. Results

In total, 605 COVID-19 patients were included in this analysis. The study flow diagram is shown in Fig. 1. Their baseline characteristics are summarised in Table 1. The mean age was 50.2 ± 17.1 years. 45.1% were men. Hypertension (21.0%) was the most common comorbidity. Most (96.9%) of the participants had non-severe COVID-19 on admission, and most (69.8%) were symptomatic on presentation. The median Ct value on admission was 24.62 (18.20 – 31.39).

Regarding their glycaemic status: 325 (53.7%) were normoglycaemic, 185 (30.6%) had prediabetes, and 95 (15.7%) had diabetes. Of the patients with diabetes in this cohort, 34 (35.8%) were newly diagnosed upon admission with their median blood glucose 9.93 mmol/L (IQR: 7.22 – 12.98); none had symptoms of hyperglycaemia or ketosis. Among those with known diabetes, all had type 2 diabetes according to the judgement of their attending physicians [16]: 7 (7.4%) were on diet control, 43 (45.3%) were treated with oral anti-diabetic agents, and 11 (11.6%) were treated with insulin (all confirmed to be type 2 diabetes on the electronic health record). An increasing trend of age and comorbidities (hypertension, obesity, cardiovascular diseases and cancer) was observed with worsening in glycaemic status. The severity of COVID-19 on admission was worse in prediabetes and diabetes, accompanied by higher CRP levels. The initial SARS-CoV-2 viral load was also higher in

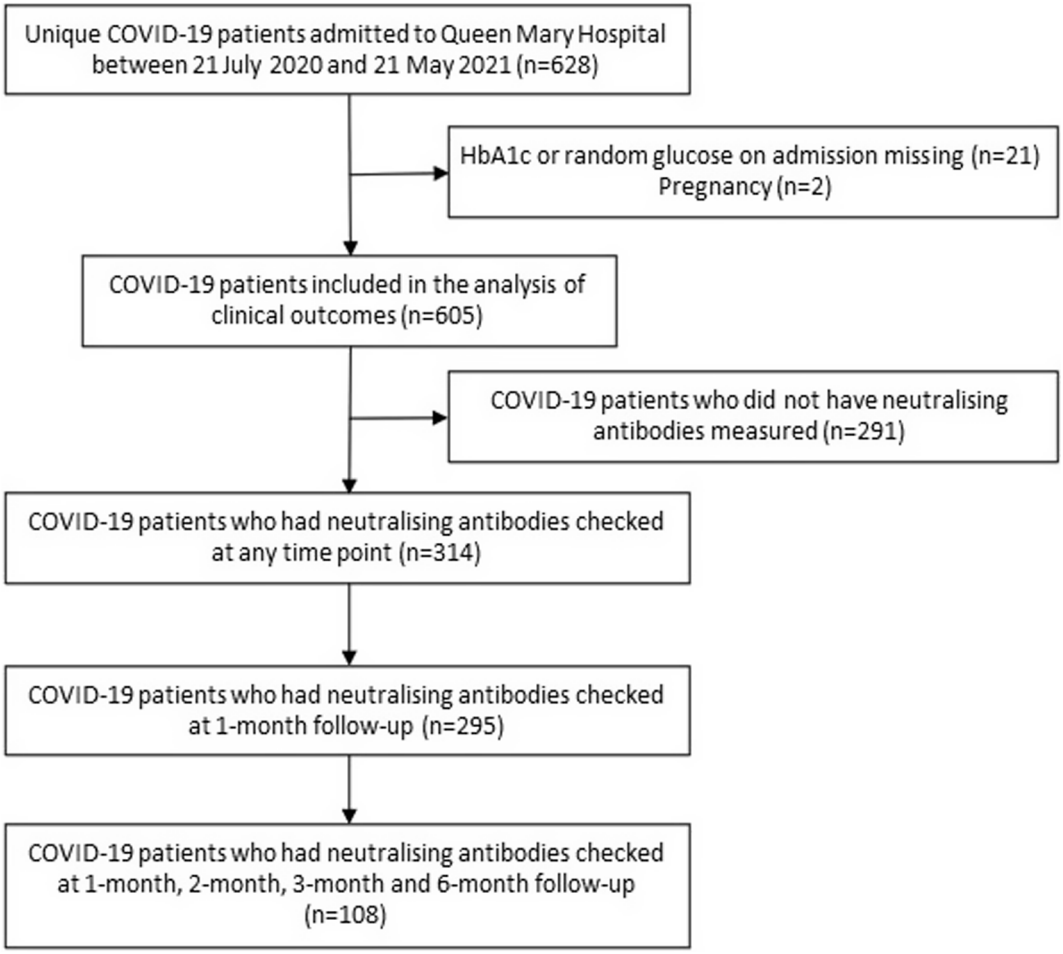

Fig. 1. Study flow diagram.

Table 1
Baseline characteristics of the cohort.

	All	Normoglycaemia	Prediabetes	Diabetes	p-value
Number of patients	605	325	185	95	—
HbA1c, %	5.84 ± 1.00	5.30 ± 0.29	5.93 ± 0.19[a]	7.51 ± 1.49[a,b]	<0.001
HbA1c, mmol/mol	40.3 ± 10.9	34.4 ± 3.2	41.4 ± 2.1[a]	58.6 ± 16.3[a, b]	<0.001
Admission RG, mmol/L	5.91 (5.13 – 7.35)	5.45 (4.88 – 6.35)	6.18 (5.44 – 7.36)[a]	8.98 (6.88 – 12.66)[a,b]	<0.001
Age, years	50.2 ± 17.1	42.4 ± 15.8	57.0 ± 14.0[a]	63.3 ± 13.0[a,b]	<0.001
Male	273 (45.1%)	134 (41.2%)	91 (49.2%)	48 (50.5%)	0.050
Comorbidities					
Hypertension	127 (21.0%)	31 (9.5%)	46 (24.9%)[a]	50 (52.6%)[a,b]	<0.001
Obesity	28 (4.6%)	8 (2.5%)	9 (4.9%)	11 (11.6%)[a]	0.005
IHD/CHF	28 (4.6%)	4 (1.2%)	9 (4.9%)[a]	15 (15.8%)[a,b]	<0.001
Stroke/TIA	14 (2.3%)	3 (0.9%)	6 (3.2%)	5 (5.3%)[a]	0.021
Cancer	28 (4.6%)	10 (3.1%)	10 (5.4%)	8 (8.4%)	0.045
Symptomatic	422 (69.8%)	215 (66.2%)	136 (73.5%)	71 (74.7%)	0.066
COVID-19 severity					<0.001
Mild	445 (73.6%)	273 (84.0%)	116 (62.7%)[a]	56 (58.9%)[a]	
Moderate	142 (23.5%)	48 (14.8%)	57 (30.8%)[a]	37 (38.9%)[a]	
Severe	9 (1.5%)	4 (1.2%)	2 (1.1%)[a]	3 (3.2%)[a]	
Ct value*	24.62 (18.20–31.39)	24.90 (17.62–31.65)	25.59 (19.94–31.42)	21.30 (17.50–28.19)[b]	0.038
CRP*, mg/dL	0.52 (0.31–2.03)	0.31 (0.31–1.08)	1.11 (0.35–3.42)[a]	1.05 (0.36–3.53)[a]	<0.001
Abnormal neutrophil counts	189 (31.2%)	99 (30.5%)	56 (30.3%)	34 (35.8%)	0.737
Lymphopenia	216 (35.7%)	106 (32.6%)	72 (38.9%)	38 (40.0%)	0.094
Thrombocytopenia	126 (20.8%)	62 (19.1%)	38 (20.5%)	26 (27.4%)	0.099
eGFR < 60 mL/min	26 (4.3%)	2 (0.6%)	8 (4.3%)[a]	16 (16.8%)[a,b]	<0.001
Elevated ALT	86 (14.2%)	41 (12.6%)	33 (17.8%)	12 (12.6%)	0.562
Elevated AST	146 (24.1%)	61 (18.8%)	58 (31.4%)[a]	27 (28.4%)	0.006
Elevated LDH	206 (34.0%)	90 (27.7%)	79 (42.7%)[a]	37 (38.9%)	0.003
Elevated CK	69 (11.4%)	28 (8.6%)	30 (16.2%)	11 (11.6%)	0.112
Elevated TnT	62 (10.2%)	14 (4.3%)	20 (10.8%)[a]	28 (29.5%)[a,b]	<0.001
Treatment	349 (57.7%)	153 (47.0%)	117 (63.2%)[a]	79 (83.2%)[a,b]	<0.001
Clofazimine	6 (1.0%)	4 (1.2%)	1 (0.5%)	1 (1.1%)	0.625
Ribavirin	159 (26.3%)	87 (26.8%)	42 (22.7%)	30 (31.6%)	0.893
Interferon	267 (44.1%)	133 (40.9%)	80 (43.2%)	54 (56.8%)[a]	0.028
Remdesivir	153 (25.5%)	45 (13.8%)	62 (33.5%)[a]	46 (48.4%)[a,b]	<0.001
Dexamethasone	94 (15.5%)	22 (6.8%)	44 (23.8%)[a]	28 (29.5%)[a]	<0.001
Clinical deterioration	74 (12.2%)	20 (6.2%)	34 (18.4%)[a]	20 (21.1%)[a]	<0.001
Radiological deterioration	44 (7.3%)	15 (4.6%)	19 (10.3%)[a]	10 (10.5%)	0.012
New oxygen requirement	42 (6.9%)	10 (3.1%)	16 (8.6%)[a]	16 (16.8%)[a]	<0.001
ICU admission	16 (2.6%)	3 (0.9%)	9 (4.9%)[a]	4 (4.2%)	0.012
Death	4 (0.7%)	2 (0.6%)	0 (0%)	2 (2.1%)	0.576

Abbreviations: RG, random glucose; IHD, ischaemic heart disease; CHF, congestive heart failure; TIA, transient ischaemic attack; COVID-19, coronavirus disease 2019; Ct, cycle threshold; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; TnT, troponin T; ICU, intensive care unit

* logarithmically transformed before analysis

[a] $p < 0.05$ compared with normoglycaemia.

[b] $p < 0.05$ compared with prediabetes (with Bonferroni correction for multiple comparison).

the diabetes group. There were more biochemical abnormalities observed in both the prediabetes and diabetes groups, including renal impairment (eGFR) and raised levels of tissue injury markers (aspartate aminotransferase [AST], lactate dehydrogenase [LDH] and troponin T [TnT]).

3.1. Clinical course of COVID-19 patients according to glycaemic status

The median length of hospitalisation was 8 days (IQR: 5 – 12). 57.7% of all patients received treatments, more among patients with prediabetes and diabetes. Interferon beta-1b was the most common treatment. Overall, 74 patients had clinical deterioration (12.2%), among whom 16 required ICU admission and 4 died. Of note, we observed an increasing trend of clinical deterioration among patients with progressively worse glycaemic status ($p < 0.001$), and specifically, the rate of clinical deterioration rose starting from prediabetes ($p < 0.05$), mainly driven by new oxygen requirement.

3.2. Variables associated with clinical deterioration

We compared the baseline clinical characteristics of patients who did and did not have clinical deterioration. (Table 2) Those who developed clinical deterioration had worse glycaemic status, and higher HbA1c and admission RG. They were older and had more comorbidities. Regarding the clinical course of COVID-19, factors associated with clinical deterioration included more severe disease, higher initial SARS-CoV-2 viral loads, symptomatic presentation, higher CRP levels and more adverse profiles of haematological and biochemical parameters.

Compared with normoglycaemia, both prediabetes (unadjusted OR 3.43, 95% CI 1.91 – 6.17, $p < 0.001$) and diabetes (unadjusted OR 4.07, 95% CI 2.08 – 7.94, $p < 0.001$) were associated with a higher risk of clinical deterioration. When adjusted for age and comorbidities (hypertension, obesity, stroke/TIA), glycaemic status was no longer an independent predictor of clinical deterioration ($p = 0.067$). In the multivariable stepwise logistic regression analysis (Table 3), the independent determinants of clinical deterioration were age (adjusted OR 1.04, 95% CI 1.02 – 1.06, $p < 0.001$), symptomatic presentation (adjusted OR 3.06, 95% CI 1.29 – 7.30), Ct value (adjusted OR 0.10, 95% CI 0.04 – 0.29, $p < 0.001$) and CRP levels (adjusted OR 2.11, 95% CI 1.56 – 2.85, $p < 0.001$). Glycaemic status was not an independent determinant of clinical deterioration.

We repeated the analysis using HbA1c as a continuous variable instead of glycaemic status as a categorical variable. Higher A1c levels were associated with higher odds of clinical deterioration (for each % increase, unadjusted OR 1.40, 95% CI 1.16 – 1.70; for each mmol/mol increase, unadjusted OR 1.03, 95% CI 1.01 – 1.05; both $p < 0.001$). In

Table 2
Baseline characteristics of patients who did and did not have clinical deterioration.

	No Clinical Deterioration	Clinical Deterioration	P-value
Number of patients	531	74	—
Glycaemic status			<0.001
Normal	305 (57.4%)	20 (27.0%)	
Prediabetes	151 (28.4%)	34 (45.9%)	
Diabetes	75 (14.1%)	20 (27.0%)	
HbA1c, %	5.78 ± 0.93	6.26 ± 1.35	0.005
HbA1c, mmol/mol	39.7 ± 10.1	44.9 ± 14.7	0.005
Admission RG, mmol/L	5.82 (5.07 – 7.10)	6.87 (5.73 – 8.83)	0.001
Age, year	48.6 ± 17.0	61.5 ± 13.2	<0.001
Male	298 (56.1%)	34 (45.9%)	0.099
Baseline clinical severity			0.002
Mild	398 (75.0%)	46 (62.2%)	
Moderate	121 (22.8%)	21 (28.4%)	
Severe	12 (2.3%)	7 (9.5%)	
Comorbidities			
Hypertension	98 (18.5%)	29 (39.2%)	<0.001
Obesity	20 (3.8%)	8 (10.8%)	0.007
IHD/CHF	23 (4.3%)	5 (6.8%)	0.352
Stroke/TIA	9 (1.7%)	5 (6.8%)	0.007
Cancer	25 (4.7%)	3 (4.1%)	0.999
Symptomatic	355 (66.9%)	67 (90.5%)	<0.001
Ct value*	25.51 (18.60 – 31.71)	20.00 (16.09 – 24.33)	<0.001
CRP*, mg/dL	0.43 (0.31 – 1.58)	1.87 (0.71 – 4.83)	<0.001
Abnormal neutrophil counts	90 (16.9%)	11 (14.9%)	0.686
Lymphopenia	176 (33.1%)	40 (54.1%)	<0.001
Thrombocytopenia	101 (19.0%)	25 (33.8%)	0.003
eGFR < 60 mL/min	19 (3.6%)	7 (9.5%)	0.019
Elevated alanine aminotransferase	74 (13.9%)	12 (16.2%)	0.595
Elevated aspartate aminotransferase	122 (23.0%)	24 (32.4%)	0.075
Elevated lactate dehydrogenase	172 (32.4%)	34 (45.9%)	0.021
Elevated creatine kinase	54 (10.2%)	15 (20.3%)	0.010
Elevated troponin T	48 (9.0%)	14 (18.9%)	0.009

Abbreviations: RG, random glucose; IHD, ischaemic heart disease; CHF, congestive heart failure; TIA, transient ischaemic attack; COVID-19, coronavirus disease 2019; Ct, cycle threshold; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate
* logarithmically transformed before analysis

Table 3
Variables associated with clinical deterioration in the final model of the multivariable stepwise logistic regression analysis.

	Adjusted Odds Ratio (95% CI)	P-value
Age, years	1.04 (1.02 – 1.06)	<0.001
Symptomatic presentation	3.06 (1.29 – 7.30)	<0.001
COVID-19 severity		0.081
Mild	Reference	—
Moderate	0.45 (0.21 – 0.96)	0.040
Severe	1.04 (0.30 – 3.65)	0.948
Ct value*	0.10 (0.04 – 0.29)	<0.001
C-reactive protein*, mg/dL	2.11 (1.56 – 2.85)	<0.001
Elevated creatine kinase	2.01 (0.96 – 4.20)	0.065

Abbreviations: COVID-19, coronavirus disease 2019; Ct, cycle threshold
* logarithmically transformed before analysis
The regression model included glycaemic status, age, hypertension, obesity, stroke/transient ischaemic attack, symptomatic presentation, Ct value, C-reactive protein, lymphopenia, thrombocytopenia, eGFR < 60 mL/min, elevated lactate dehydrogenase, elevated creatine kinase, elevated troponin T and baseline COVID-19 severity

the multivariable stepwise logistic regression analysis, however, HbA1c level was not an independent predictor of clinical deterioration (data not shown). We also repeated the analysis using admission RG as a continuous variable. Higher admission RG levels were associated with higher odds of clinical deterioration (unadjusted OR 4.15, 95% CI 2.02 – 8.54, p < 0.001). In the multivariable stepwise logistic regression analysis, however, admission RG levels were not an independent predictor of clinical deterioration (data not shown).

3.3. Nab titres upon follow-up

Among the entire cohort of 605 patients, 314 patients (51.9%) had Nab titres measured at any time point upon follow-up. Patients who had Nab titres checked were slightly older (51.9 ± 16.1 years vs 48.4 ± 18.0, p = 0.014) and more likely to be men (51.5% vs 38.1%, p < 0.001), but otherwise comparable COVID-19 severity (p = 0.181), Ct values (p = 0.380), glycaemic status (p = 0.291) and HbA1c (p = 0.846). 295 patients had Nab titres checked at 1-month follow-up, 227 at 2-month follow-up, 207 at 3-month follow-up, and 122 at 6-month follow-up. Most of the patients were Nab positive throughout the 6-month follow-up: 94.9% at 1-month, 93.8% at 2-month, 87.4% at 3-month, and 80.3% at 6-month.

3.4. Variables associated with Nab titres upon 1-month follow-up

We compared the clinical characteristics of patients according to quartiles of Nab titres at 1-month follow-up (quartile 1: <10 – 10; quartile 2: 20 – 40; quartile 3: 80 – 160; quartile 4: 320 – >320) (Table 4). Towards higher quartiles of Nab titres, we observed older age, worse glycaemic status, higher prevalence of hypertension, and worse COVID-19 course (clinical severity, CRP levels and symptomatic presentation and requirement of COVID-19 treatments). Neither HbA1c nor admission RG levels significantly differed across the quartiles of Nab titres. In the multivariable ordinal logistic regression analysis, the independent factors associated with higher quartiles of Nab titres included older age (adjusted OR 1.03, 95% CI 1.01 – 1.05, p = 0.001), higher CRP levels (adjusted OR 1.32, 95% CI 1.02 – 1.70, p = 0.038), interferon treatment (adjusted OR 2.12, 95% CI 1.34 – 3.37, p = 0.001) and elevated LDH (adjusted OR 1.69, 95% CI 1.01 – 2.83, p = 0.046) (**Supplementary** Table S1). Glycaemic status did not independently predict Nab titres.

Apart from Nab titres, we repeated the analysis of factors associated with Nab positivity. Among glycaemic status, HbA1c levels and admission RG levels, none independently predicted Nab positivity (data not shown).

3.5. Kinetics of Nab titres according to glycaemic status

108 patients had Nab titres measured at all the four time points (1-month, 2-month, 3-month and 6-month follow-up). Comparison of the trends of Nab titres according to glycaemic status revealed no statistically significant difference over the 6-month follow-up period (p = 0.280) (Fig. 2). The trend of Nab positivity over the 6-month follow-up did not differ by glycaemic status (p = 0.840).

4. Discussion

In this cohort of predominantly non-severe COVID-19 patients, those with prediabetes and diabetes had a higher risk of clinical deterioration than those with normoglycaemia. While older age, symptomatic COVID-19, higher viral loads and levels of inflammatory markers independently predicted clinical deterioration, glycaemic status was not an independent predictor of clinical deterioration. More importantly, glycaemic status was not an independent predictor of Nab responses at 1-month, and Nab responses to SARS-CoV-2 were not different across glycaemic status over 6 months of follow-up. As there was a previous report of 31 non-severe COVID-19 patients showing that patients with diabetes were more likely to be negative for anti-SARS-CoV-2 antibodies [9], our results derived from a larger cohort of predominantly non-severe COVID-

Table 4
Comparison of baseline clinical characteristics of COVID-19 patients with different levels of neutralising antibody responses at 1-month follow-up (n = 295).

	Neutralising antibody titres				P-value
	<10 – 10	20 – 40	80 – 160	320 – >320	
Number of patients (%)	15 (5.1%)	78 (26.4%)	118 (40.0%)	84 (28.5%)	—
Glycaemic status					0.007
Normoglycaemia	13 (86.7%)	47 (60.3%)	70 (59.3%)	8 (9.5%)	
Prediabetes	2 (13.3%)	23 (29.5%)	32 (27.1%)	16 (19.0%)	
Diabetes	0 (0%)	8 (10.3%)	16 (13.6%)	12 (14.3%)	
HbA1c, %	5.27 ± 0.30	5.76 ± 0.68	5.80 ± 1.10	5.90 ± 0.82	0.090
HbA1c, mmol/mol	34.0 ± 3.3	39.4 ± 7.4	39.9 ± 12.0	41.0 ± 8.9	0.090
Admission RG, mmol/L	5.25 (4.94 – 7.35)	5.86 (5.11 – 7.45)	6.17 (5.31 – 7.23)	6.28 (5.58 – 7.74)	0.444
Age, years	39.5 ± 17.2	47.5 ± 16.9	52.5 ± 16.1	56.5 ± 13.5	<0.001
Male	8 (53.3%)	42 (53.8%)	56 (47.5%)	47 (56.0%)	0.845
Comorbidities					
Hypertension	1 (6.7%)	15 (19.2%)	25 (21.2%)	24 (28.6%)	0.046
Obesity	0 (0%)	6 (7.7%)	5 (4.2%)	8 (9.5%)	0.332
IHD/CHF	1 (6.7%)	4 (5.1%)	3 (2.5%)	6 (7.1%)	0.718
Stroke/TIA	0 (0%)	1 (1.3%)	2 (1.7%)	3 (3.6%)	0.236
Abnormal neutrophil counts	3 (20.0%)	12 (15.4%)	25 (21.2%)	11 (13.1%)	0.614
Lymphopenia	6 (40.0%)	25 (32.1%)	44 (37.3%)	45 (53.6%)	0.015
Thrombocytopenia	2 (13.3%)	18 (23.1%)	34 (28.8%)	21 (25.0%)	0.429
eGFR < 60 mL/min	0 (0%)	1 (1.3%)	5 (4.2%)	4 (4.8%)	0.156
Elevated ALT	1 (6.7%)	12 (15.4%)	19 (16.1%)	15 (17.9%)	0.375
Elevated AST	1 (6.7%)	20 (25.6%)	32 (27.1%)	28 (33.3%)	0.058
Elevated LDH	0 (0%)	25 (32.1%)	43 (36.4%)	45 (53.6%)	<0.001
Elevated CK	1 (6.7%)	7 (9.0%)	24 (20.3%)	8 (9.5%)	0.658
Elevated TnT	1 (6.7%)	3 (3.8%)	7 (5.9%)	11 (13.1%)	0.046
Worst COVID-19 severity					<0.001
Mild	14 (93.3%)	60 (76.9%)	68 (57.6%)	44 (52.4%)	
Moderate	1 (6.7%)	17 (21.8%)	35 (29.7%)	27 (32.1%)	
Severe	0 (0%)	1 (1.3%)	12 (10.2%)	9 (10.7%)	
Critical	0 (0%)	0 (0%)	2 (16.9%)	4 (4.8%)	
Ct value*	21.77 (17.26 – 36.38)	22.93 (17.73 – 29.15)	25.01 (18.78 – 29.61)	24.65 (18.32 – 31.19)	0.512
CRP*, mg/dL	0.31 (0.30 – 0.31)	0.43 (0.31 – 1.32)	0.62 (0.31 – 2.36)	1.34 (0.36 – 4.09)	<0.001
Symptomatic presentation	8 (53.3%)	58 (74.4%)	95 (80.5%)	70 (83.3%)	0.016
Immunomodulatory treatment					
Interferon	7 (4.7%)	38 (48.7%)	70 (59.3%)	60 (71.4%)	0.002
Dexamethasone	0 (0%)	3 (3.8%)	21 (17.8%)	20 (23.8%)	<0.001

Abbreviations: RG, random glucose; IHD, ischaemic heart disease; CHF, congestive heart failure; TIA, transient ischaemic attack; COVID-19, coronavirus disease 2019; Ct, cycle threshold; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; TnT, troponin T
* logarithmically transferred before analysis

19 patients clarified concerns about impaired antibody response against SARS-CoV-2 among patients with impaired glucose metabolism.

Mounting evidence has shown that patients with type 2 diabetes are more likely to have severe COVID-19 (variably defined as requirement of ICU admission, mechanical ventilation or mortality), contributed by cardiometabolic comorbidities and hyperinflammation [2]. Our study extended the current understanding of the relatively less well-known impact of prediabetes on the clinical course of COVID-19. A recent Indian cohort characterised 102 COVID-19 patients with prediabetes, demonstrating relatively high mortality of 30%, where non-survivors had higher levels of inflammatory markers and coagulation dysfunction [3]. However, a control group was not available in that study [3]. A single-centre retrospective study in the United States showed the rate of severe COVID-19 was not increased in patients with prediabetes, where prediabetes was defined by HbA1c checked anytime within one year of admission [4]. On the contrary, a recent Mexican retrospective cohort study analysing COVID-19 patients with HbA1c checked on admission based on attending physicians' discretion showed that prediabetes was associated with a higher risk of severe COVID-19 [5]. The conflicting results could be explained by the inherent selection bias in the above studies. Furthermore, all these studies focused on hospitalised patients with moderate to severe disease, potentially limiting the generalizability of the results to the general COVID-19 population, predominantly of non-severe disease [26]. With consecutive assessment of HbA1c on admission in our representative cohort of predominantly non-severe COVID-19 patients, we observed that the risk of clinical deterioration increased starting from prediabetes and, consistently, with increasing HbA1c levels. Nonetheless, the independent predictors of clinical deterioration were older age, symptomatic COVID-19, higher viral loads and higher levels of inflammation, but not glycaemic status or HbA1c on admission.

One and a half years since the declaration of this COVID-19 pandemic, at this stage, vaccination hopefully can bring an end to this fight against COVID-19. Data are limited specifically for patients with diabetes in the clinical trials of vaccines. While some preliminary data demonstrate similar vaccine efficacy in this subgroup [27], insights could be obtained from the existing studies of the Nab response among COVID-19 survivors. To date, there were only reports from two groups of investigators addressing this issue. An Italian group studying 150 hospitalised patients with at least moderate COVID-19 showed that anti-SARS-CoV-2 antibody responses among patients with diabetes were superimposable to those without diabetes in terms of both kinetics and durability [11]. In that study, glycaemic status was defined by FG on admission, where the possibility of stress hyperglycaemia could not be entirely excluded. Furthermore, the results may not be generalised to the population as this study focused on non-mild COVID-19 patients. An Indian study of 31 COVID-19 patients with a milder disease spectrum found a lower rate of seroconversion at 2 weeks post-discharge among patients with diabetes [9]. In that study, HbA1c was not measured among patients without known diabetes. With the relatively small sample size, possible misclassification or bias may explain the difference in seroconversion rate. Quantitative measurement and longitudinal follow-up results were also not available. Our results thus filled the current knowledge gaps. We demonstrated that Nab responses were comparable across glycaemic status over 6 months of follow-up among patients with predominantly non-severe COVID-19. Interestingly, we identified several independent determinants of Nab responses: older age, higher levels of inflammation, and exposure to interferon treatment. Higher antibody response with advancing age has been reported in other studies as well [28–30], which may be partly contributed by the more severe COVID-19 clinical course. Indeed, invariably, symptomatic presentation, hospitalisation or more severe COVID-19 have been reported to be associated with higher anti-SARS-CoV-2 antibody response

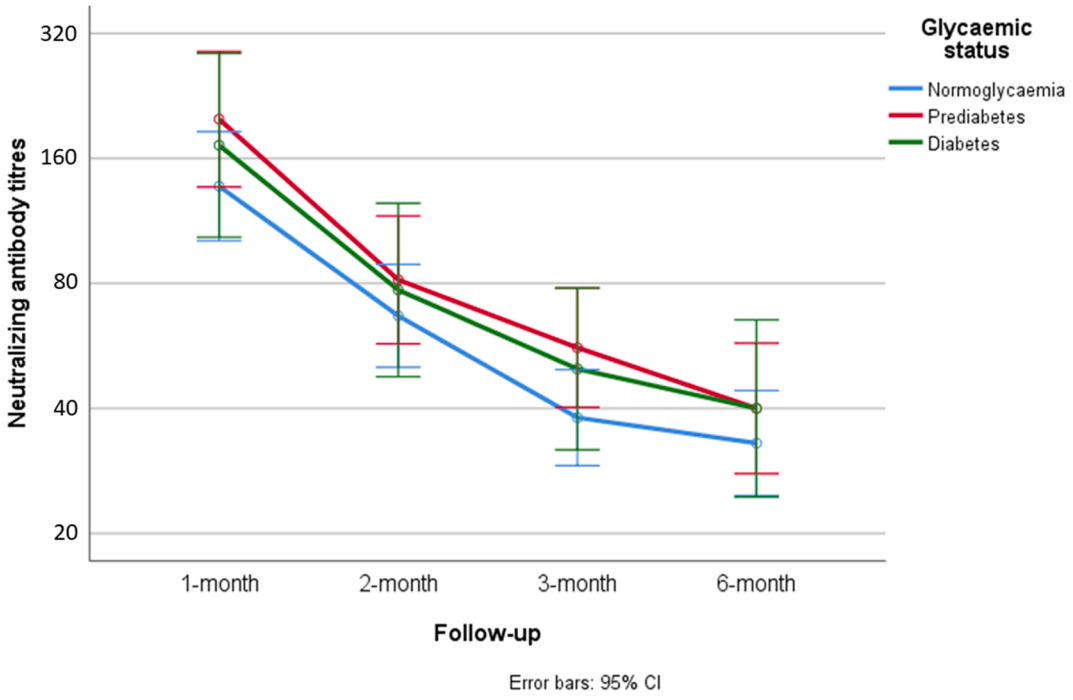

Fig. 2. Neutralising antibody titres upon follow-up categorised according to glycaemic status (normoglycaemia, n = 54; prediabetes, n = 35; diabetes, n = 19). Comparison of the trends of neutralising antibody titres according to glycaemic status, using general linear model with repeated measures, revealed no statistically significant difference over the 6-month follow-up period (p = 0.280).

[31]. Consistent with these factors, our study showed that higher levels of CRP and LDH were associated with higher anti-SARS-CoV-2 antibody response, supporting the theory of a more pronounced inflammatory state favouring an early maturation of the antibody response [32]. It is not surprising that interferon beta-1b exposure correlated with higher Nab titres, as the use of interferon beta-1b probably jump-started or improved the antiviral response of patients, resulting in shortening virus shedding, alleviating symptoms, and facilitating discharge of patients with mild to moderate COVID-19 [33].

Our data had enhanced the existing literature regarding the impact of glycaemic status on the clinical outcomes and Nab responses among COVID-19 patients. Nonetheless, our results should be interpreted bearing the following limitations. Firstly, as our cohort comprised mainly mild to moderate COVID-19 patients and thus had a low mortality rate, our study was not powered to identify predictors of mortality. Secondly, SARS-CoV-2 viral loads were represented by Ct values. Despite a good correlation [17,18], direct quantitative measurements of viral loads would have been preferred if available. Thirdly, obesity, increasingly recognised as an important risk factor for COVID-19-related morbidity and mortality [34], was defined by ICD-9-CM diagnostic code in our study as a categorical variable, instead of body mass index as a continuous variable, and was likely to be underreported.

5. Conclusions

We observed a higher likelihood of clinical deterioration in those with dysglycaemia in this cohort of predominantly non-severe COVID-19 patients, starting from prediabetes, likely secondary to the association of dysglycaemia with older age, symptomatic COVID-19, higher viral loads and levels of inflammation, which independently predicted clinical deterioration. Glycaemic status did not adversely impact the anti-SARS-CoV-2 antibody responses upon 6 months of follow-up.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Disclosure

The author has no conflict of interest to declare.

Ethical statements

The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. Written consent has been obtained from each patient or subject after fully explaining the purpose and nature of all procedures used.

Data Availability

Datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.109232.

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