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Predictive value of HbA1c for in-hospital adverse prognosis in COVID-19: A systematic review and meta-analysis

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ARTICLE INFO

ABSTRACT

Background and aims: Clinical and laboratory predictors of adverse clinical course and death in COVID-19 patients urgently need to be identified. So far, the association between HbA1c and in-hospital mortality of COVID-19 remains a controversial issue. The aim of this study is to analyze predictive value of HbA1c for adverse prognosis in COVID-19.

Methods: Both Chinese and English databases were systematically searched using specific keywords associated with the aims until November 21th, 2020. The Newcastle-Ottawa Scale (NOS) was used for quality assessment. A Statistical analysis was carried out using Review Manager 5.3 and STATA 15.1.

Results: Nine clinical trials were included in this study involving 2577 subjects. The results indicate that the association between elevated HbA1c referred as a continuous variable and adverse prognosis of COVID-19 was not significant (OR, 1.02; 95%CI, 0.95–1.09). However, higher HbA1c levels regarded as a dichotomous variable contributed to an increase mortality of COVID-19 (OR, 2.300; 95%CI, 1.679–3.150). Results were stable in a sensitivity analysis. More studies are needed to demonstrate the effect of HbA1c on hospital mortality.

Conclusion: Prolonged uncontrolled hyperglycemia increases the risk of adverse prognosis in COVID-19. Patients with higher HbA1c should be monitored strictly to minimize the risk of adverse prognosis in COVID-19.

Contents

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1. Introduction

The epidemic of COVID-19 has spread rapidly worldwide [1–3]. The manifestations of severe cases with COVID-19 can develop into acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) [1]. Identifying the risk factors associated with the progress of COVID-19 is essential to guide clinicians to carry out targeted therapy. Data has showed that patients with poor glucose control have a higher mortality of other viral epidemics such as H1N1 flu and SARS [4,5]. Currently, the inclusion of diabetes status estimation is strongly supported by the evidence on the risk management of COVID-19 patients. Glycosylated hemoglobin (HbA1c) is a stable index of long-term glucose control and provides an average value of the past 3 months [6]. It can be used to assess diabetes status to identify high-risk individuals of COVID-19 with low awareness of diabetes [7]. Compared with several risk elements identified for COVID-19-related mortality such as advanced age, HbA1c can be improved through health-care interventions and easily available in daily practice [8]. Thus, HbA1c may be used for efficient risk assessment of COVID-19. So far, some studies have found that HbA1c is independently associated with hospital mortality [7,9], while others got opposite results [10,11]. In conclusion, the relationship between HbA1c and severe COVID-19 in diabetic and non-diabetic individuals is still unclear. The predictive value of HbA1c for adverse prognosis in patients with COVID-19 needs to be examined. This study therefore carried out the meta-analysis of retrospective and prospective cohort studies to estimate if higher HbA1c levels are associated with adverse prognosis of COVID-19 patients.

2. 2 Material and Methods

2.1. Search strategy

This study was carried on and the results were reported in accordance with Preferred reporting items for systematic reviews and meta-analyses checklist (PRISMA) [12]. Relevant studies were searched from databases, including Wanfang Database, China National Knowledge Infrastructure (CNKI), Chinese Biomedicine Literature Database (CBM-SinoMed), Weipu Database, Embase, Cochrane Central Register, PubMed and Web of Science from inception to 21 November 2020 without language restrictions. MeSH terms for COVID-19, Glycated Hemoglobin A, glycemic control and corresponding synonyms were included into the searching strategy (Supplementary List S1). Reference lists to retrieved articles were also reviewed to further identify relevant studies. The study was not approved and informed by the Institutional Review Committee, because of a systematic review of the literature, thus this study was limited to published information and did not come into contact with any human subjects.

2.2. Eligibility criteria

The protocol was not registered. All titles and full-text versions of all relevant studies were screened for eligibility by two independent reviewers (Zheng Zhu and Yaqian Mao) and disagreements were settled by discussion. Studies were eligible for inclusion if they fulfilled the following criteria: (a) peer-reviewed prospective or retrospective original reports; (b) all patients were diagnosed as COVID-19; (c) outcome indicators were adverse prognosis (fatal and/or critical outcomes). Mechanical ventilation, intensive care unit and shock were found in critical COVID-19 illnesses [13]. Since most studies identified diabetes status by self-reporting, undetected diabetes might be ignored. This study was not limited to the inclusion of diabetes to avoid selection bias. As 7% HbA1c level was the most widely used threshold in numbers of studies, and it was proposed by the American Diabetes Association (ADA) as a standard of medical care for diabetes in 2020 [14], a cutoff value of 7% was preferred. Alternative cutoff was those closest to 7%.

2.3. Quality assessment

Quality assessment of risk of bias of all selected articles was performed using the Newcastle-Ottawa Scale (NOS) for nonrandomized studies [15]. They were rated according to three main aspects: selection, comparability, and exposure. The highest score for each study was 9, studies with a score above 7 were considered to be of high quality, excluding articles of poor quality (0–3).

2.4. Data extraction

Two investigators (ZZ and YM) extract the following data from eligible studies: authors, journal, country, study period and sample size, the following potential risk factors were recorded independently: baseline demographic characteristics, glucose metabolic states (DM or all included), comorbidities (hypertension, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease), number of patients in control or case group, maximally adjusted effect estimates (HR and OR) and corresponding 95% confidence intervals (95%CIs), and adjustment factors. The data mentioned were either extracted from the manuscript or converted from the tables and figures provided. Any variances were resolved by consensus.

2.5. Statistical analysis

The statistical analysis was carried out using Review Manager 5.3 and STATA 15.1. Because of the different statistical methods used in the collected studies, studies were analyzed that analyzed the measured HbA1c values as continuous variables and dichotomous variables, respectively. The maximally adjusted HR and OR with 95%CI were used to estimate the strength of the association between HbA1c levels and adverse outcome of COVID-19 by using the generic inverse variance method. If the ORs and 95% CIs were
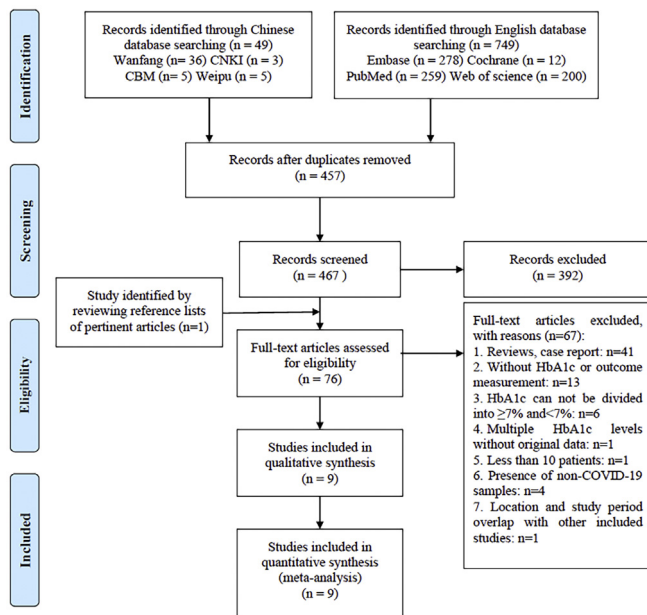
Fig. 1. PRISMA flow diagram of study selection process.

not published in the paper, the original data was used for the calculation of ORs. For studies reporting multiple HbA1c levels, this study extracted the number of events and patients with HbA1c< or ≥7%, and calculated the relative crude OR with 95% CIs. Chi-squared test (Chi2) and I-squared statistic (I2) were used to evaluate the degree of heterogeneity among the included studies [16]. For Chi2 test, a Cochrane's Qp value of <0.10 was considered significant. The I2 statistics thresholds of 75%, 50% and 25% were used to indicate high, moderate and low heterogeneity. When the I2 > 50%, the random-effect model (Inverse Variance) was chosen to calculate the pooled effect, otherwise the fixed-effect model (I–V) was used instead. The sources of heterogeneity were explored by subgroup analysis. In order to determine the stability of the summarized results, the sensitivity analysis of the in-hospital mortality was conducted using two techniques, respectively ignoring studies one by one, repeating meta-analysis by using a random-effects model. Publication bias was tested by Begg rank correlation test and Egger linear regression test [17,18], with p < 0.1 representing publication bias. The statistical significance level of the two-sided test was p < 0.05 unless otherwise specified.

2.6. Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of the results. We do plan to disseminate the results of the research to the relevant patient communities.

3. Results

3.1. Study identification and selection

Our comprehensive retrieval identified 798 records from the electronic databases, and 467 studies were remained after removing duplications. After scanning the titles, abstracts, reading full texts and handsearching the reference lists of articles, this study finally got 9 retrospective studies [7,10,19–25] (flow diagram and the detailed reasons for the exclusion were shown in Fig. 1) includ-

ing a total of 2577 COVID-19 to evaluate the associations between HbA1c level and their in-hospital mortality and/or intubation rate. As the location and study period of the two studies overlapped [6,10], the one with a larger sample size were included [10]. One excluded study contained multiple HbA1c levels without original data, and approximately one-third of the studied population did not provide data on HbA1c [11].

3.2. Study characteristics

The characteristics of eligible studies were summarized in Table1. All studies derived the data from the electronic health records of institutions or hospitals. Three studies were conducted in Europe [20,24,25], two in the USA [10,23], and remaining four in Asia [7,19,21,22]. The study period of eligible studies ranged from 7 [25] to 118 [24] days. The sample size of eligible study ranged from 29 [19] to 1279 [10]. The mean age of participants included in the studies varied from 63.6 years [7] to 68.0 years [23]. The proportion of male in each study ranged from 48.3% [19] to 62% [7]. Most of the eligible studies were of high quality with an average quality score as 7.11 (Supplementary Table S1). The samples included in these four studies were all COVID-19 with diabetes [10,19,24,25], and six studies described co-morbidities such as hypertension [7,10,19–22]. Only five studies reported the adjusted OR or HR [7,10,19,21,25], while six studies provided the original number of events [19–24]. The sample size of these five studies reached 1618 [7,10,19,21,25], and their effect values at least adjusted for confounders of age. The two studies also adjusted the confounding factors of hypertension [10,21]. Three studies only involved patients with diabetes (n = 1520), and the other six included 427 patients with diabetes and 711 patients without diabetes. Among them, one study reported that 36.4% of patients in the high HbA1c group were not previously known to have diabetes [23].

In addition, the baseline characteristics and laboratories values of the high and low HbA1c groups after admission were shown in tables 2 [19–24]. All p-values > 0.05, which meant that there was no significant difference in indicators between the two groups, which might be related to the lack of available data. However, only from the numerical value, the high HbA1c group had a higher proportion of comorbidities and the elderly than low HbA1c group. Patients with the high HbA1c levels had more fever, cough, and higher levels of inflammation markers (i.e. C-reactive protein, procalcitonin, ferritin, interleukin-6, tumor necrosis factor-a), D-dimer and fibrinogen. Most notably, the frequencies of ICU admission and mechanical ventilation were significantly higher in high HbA1c group than low HbA1c group. In addition, indicators with different units were not pooled together. In these researches [20–22], compared with the low HbA1c group, leukocytes, neutrophils increased and lymphocytes decreased in the high HbA1c group.

3.3. Pooled analysis

When HbA1c was regarded as a continuous variable [7,10,19,21,25], the pooled analysis without statistical heterogeneity across different studies (I2 = 0%; p = 0.63) did not find the correlation between the higher HbA1c and the reduced adverse prognosis of COVID-19 (OR 1.02 [0.95–1.09]; p = 0.63) (Supplementary Fig. 2A). However, six studies referred HbA1c as a dichotomous variable, involving a sum of 1180 subjects and 301 deaths, and showed that higher HbA1c was significantly related to increased hospital mortality compared with groups with lower HbA1c (OR 2.300 [1.679–3.150]; p = 0.000, I2 = 48%; p = 0.087) (Supplementary Fig. 2B). Because of the moderate heterogeneity, sensitivity analysis was carried out. After ignoring studies one by one, there was no substantial alterations in the pooled ORs, confirming that this result was robust and reliable (Supplementary Fig.

Table 1
Characteristics of included studies.

First author	Study period	Diabetic status/N	Age (mean ± SD)/(%)	Male (%)	HTN (%)	CVD (%)	CKD (%)	COPD (%)	OR1/HR1	Confounder	HbA1c		QS
											Low (N/n)	High (N/n)	
Agarwal	March 11–May 7	DM 1279	67.9 ± 13.7	49.3	90.9	58	42.5	13.5	OR1 1.01 (0.94, 1.09)	Age, sex, BMI, insurance, insulin regimen, HNT, CVD, CK, COPD	NR	NR	8
Chung	28 Day	DM 29	66.3 ± 8.9	48.3	55.2	17.2	NR	6.9	OR1 1.26 (0.52, 3.06)	Age, sex, smoking status, serum glucose levels	21/10	8/3	86
		WDM 81											
Conway	March 23–April 4	DM 16	Age ≥ 65:73.2	57.7	45.1	33.8	12.7	33.8	NR	NR	55/19	16/4	6
		WDM 55											
Liu, Z.	February 3–February 26	DM 64	Stratified by HbA1c:	54.2	58.9	NR	0.5	NR	OR1 3.29 (1.19–9.13)	Maximum of the blood glucose in-hospital, lymphocyte, C-reactive protein, prothrombin time. The control group was closely matched to the case group in age, sex, and comorbidities	128/10	64/12	8
		WDM 128	DM66.0 (59.0–71.0) WDM67.0 (59.3–71.0)										
Yan	January 10–February 24	DM 48	64 (49–73)	59.1	37.8	16.1	2.1	7.3	NR	NR	145/69	48/39	6
		WDM 145											
Liu, L.	During February	DM 28	63.6 ± 3.6	62	42	20	9	10	HR1 1.36 (1.08–1.72)	Age, sex, and the presence of cardiovascular and chronic respiratory disease.	NR	NR	8
		WDM 49											
Saand	March–May	DM 242	68 (58–77)	58.4	NR	NR	NR	NR	NR	NR	253/42	242/76	7
		WDM 253											
Shestakova	February 1–April 27	DM 200	NR	NR	NR	NR	NR	NR	NR	NR	89/5	111/12	6
Wargny	7 Day	DM 41	NR	NR	NR	NR	NR	NR	OR1 0.46 (0.17–1.21)	Age	NR	NR	7

CI: confidence interval; NR, not reported; P, prospective; R, retrospective; DM, patients diagnosed with diabetes mellitus; WDM, patients without diabetes; OR, maximally adjusted odds ratio was provided (OR1, OR of continuous variables; OR2, OR of dichotomous variable); HR, maximally adjusted hazard ratio was provided (HR1, HR of continuous variables; HR2, HR of dichotomous variable) QS, quality scores; HTN, hypertension; CVD, cardiovascular disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; N/A, not available; N, number of samples; n, number of outcomes.

Table 2
Baseline characteristics of the low and high HbA1c group.

Parameter	Studies	Low HbA1c		High HbA1c		p-Value
	N	N	(mean)/ (%)	N	(mean)/ (%)	
Age (year)	4 [19,21–23]	607	61.63	383	67.83	0.107
Male (%)	5 [19–23]	662	56.52%	399	57.36%	0.891
Comorbidities						
HNT (%)	4 [19,20,21,22]	409	38.88%	157	59.50%	0.062
CVD (%)	3 [19,20,22]	281	17.10%	93	27.27%	0.363
CKD (%)	3 [20–22]	328	3.03%	128	12.50%	0.493
COPD (%)	3 [19,20,22]	281	13.43%	93	19.67%	0.698
Presentation						
Fever (%)	4 [19–22]	409	66.15%	157	72.55%	0.572
Fatigue (%)	2 [21,22]	273	36.85%	112	40.85%	0.873
Cough (%)	3 [19,21,22]	354	64.80%	141	59.70%	0.693
Diarrhea (%)	3 [19,21,22]	354	19.00%	141	13.80%	0.507
Laboratories values						
Leukocyte count (×109/L)	3 [19,22,23]	479	6.4	319	8.1	0.039
Hb (g/L)	2 [21,22]	273	127.75	112	128.25	0.846
PLT (×109/L)	3 [19,21,22]	354	225.77	141	211.9	0.726
PT (s)	2 [21,22]	273	13.9	112	14.05	0.804
APTT (s)	2 [21,22]	273	39.2	112	38.45	0.532
Fbg (g/L)	2 [22,23]	398	4.96	290	5.06	0.896
D-dimer (mg/L)	3 [21,23]	526	1.14	354	1.6	0.473
CRP (mg/L)	2 [19,21,23]	462	7.95	335	11.45	0.471
PCT (ng/mL)	3 [19,21,22]	354	0.13	141	0.49	0.376
Ferritin (μg/L)	2 [22,23]	398	688.75	290	1134.9	0.210
Interleukin-6 (pg/mL)	3 [21,23]	526	26.24	354	36.63	0.645
TNFα (pg/mL)	2 [21,22]	273	8.15	112	9.55	0.509
Creatinine (μmol/L)	2 [21,22]	273	74.50	112	76	0.873
Urea nitrogen (mmol/L)	2 [21,22]	273	4.90	112	6.65	0.340
ALT (U/L)	2 [21,22]	273	21.00	112	22.75	0.232
AST (U/L)	2 [21,22]	273	27.00	112	29.5	0.718
Triglyceride (mmol/L)	2 [22,23]	398	4.08	290	5.01	0.846
ICU admission (%)	4 [19–22]	409	17.40%	157	27.88%	0.546
Mechanical ventilation (%)	2 [22,23]	398	43.10%	290	65.65%	0.310

HbA1c, glycated hemoglobin; HTN, hypertension; CVD, cardiovascular disease; CK, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Hb, hemoglobin; PLT, platelet count; PT, prothrombin time; APTT, activated partial thromboplastin time; Fbg, fibrinogen; CRP, C-reactive protein; PCT, procalcitonin; TNFα, tumor necrosis factor-a; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

1S). Pooled ORs from the fixed-effects model and random-effects model were virtually similar (Supplementary Fig. 2S).

3.4. Subgroup analysis

Because there were moderate differences between individual studies, this research conducted a subgroup analysis in accordance with the study period, sample size, age, sex, diabetic status, incidence of hypertension (Table 3). Significant correlations between higher HbA1c and adverse prognosis remained in age subgroups. Subgroup analysis by diabetic status and the incidence of hypertension showed that HbA1c level was associated with adverse prognosis among COVID-19 patients included diverse diabetic status (OR 2.45[1.75–3.42]; p = 0.000), but not in COVID-19 patients with diabetes (OR 1.46[0.59–3.62]; p = 0.416) or high incidence of hypertension (OR 1.98[0.90–4.37]; p = 0.092). Subgroup analysis categorized by study period did not show any significant relation between HbA1c and primary outcome among studies period <30days. Similarly, the significant relation could not be replicated among female patients or from smaller sample size studies.

3.5. Publication bias

No publication bias was found by Begg's and Egger's test among the studies (all p > 0.05) (Supplementary Fig. 3SA, SB).

4. Discussion

Nine clinical trials were included in this study involving 2577 subjects. The study did pooled analysis of all studies of in-hospital

mortality or critical illnesses for COVID-19, and found that elevated HbA1c levels contributed to an increase in-hospital mortality in patients with COVID-19, when it was regarded as a dichotomous variable. Incidence of hypertension and diabetic status were the main source of moderate heterogeneity. However, when HbA1c was referred as a continuous variable, this association was not significant.

The meta-analysis of HbA1c as a dichotomous variable has the moderate heterogeneity, but the I2 < 50% was acceptable, and the sensitivity analysis showed that the result was robust and reliable. In two previous population-based studies, one showed that COVID-19-related mortality was higher in people with HbA1c>7.5% [26], and another identified that mortality in people with type 1 and type 2 diabetes was significantly and independently related to the HbA1c [8]. In addition, a study of 80 patients with type 2 diabetes from India even found that COVID-19 patients with HbA1c > 8% exhibited a excessive uncontrolled inflammatory responses, hypercoagulable state, and severe symptomatic presentation [27]. Besides, A similar outcome was found in 44 COVID-19 patients admitted to an intensive care unit in Austria [28]. From another point of view, based on the results of a study of 806 diabetes patients in Saudi Arabia, it was found that high HbA1c level were independently associated with hospitalization, compared with low HbA1c level [29]. This evidently indicated that patients especially of the poorly-controlled group associated to a significantly higher risk of severe COVID-19 requiring hospitalization.

Severe COVID-19 could be accompanied by fatal complications, such as acute respiratory distress syndrome, pneumonia, disseminated intravascular coagulation, and eventually lead to death [30,31]. In the present study, more severe lung involvement and

Table 3
Subgroup analyses of the pooled ORs for associations between HbA1c level and the adverse prognosis of COVID-19.

Subgroups	No. of studies	OR (95% CI)	Z-value	pa	Heterogeneity	
					I2 (%)	pb
Study period						
<30d	3	1.43 (0.73,2.80)	1.05	0.295	54.6	0.11
≥30d	3	2.63 (1.84,3.75)	5.32	0	27.3	0.25
Sample size						
<100	2	0.64 (0.23,1.75)	0.86	0.387	0	0.97
100 ≤ n < 200	2	3.73 (2.06,6.77)	4.33	0	0	0.36
200 ≤ n < 300	2	2.26 (1.52,3.37)	4.02	0	0	0.84
Age						
<65y	1	4.77 (2.16,10.57)	3.85	0	N/A	N/A
≥65y	4	2.01 (1.40,2.88)	3.78	0	48	0.12
Sex						
Male	4	2.45 (1.75,3.42)	5.23	0	58.8	0.06
Female	1	0.66 (0.12,3.50)	0.49	0.625	N/A	N/A
Diabetic status						
DM	2	1.46 (0.59,3.62)	0.81	0.416	18.9	0.27
AI	4	2.45 (1.75,3.42)	5.23	0	58.8	0.06
HTN						
<50%	2	2.69 (1.37,5.26)	2.88	0.004	85.9	0.01
≥50%	2	1.98 (0.90,4.37)	1.69	0.092	53.4	0.14

CI: confidence interval; N/A, not applicable; DM, patients diagnosed with diabetes mellitus; AI, all included with or without diabetes; OR, odds ratio; HTN, hypertension; pa, p-value for Z test; pb, p-value for Q test.

higher levels of coagulation and inflammation markers were more specific in the high HbA1c group. Similarly, a previous study conducted by Wang et al. pointed out that HbA1c was associated with low SaO2, hypercoagulability, and inflammation in COVID-19 patients [6]. Fever and cough occurred more often in the higher HbA1c group, and the fundamental cause of such manifestation might be the early and extensive lung involvement of COVID-19 infection caused by glucose variability [27]. Moreover, compared with patients with controlled glucose, increased leukocytes, neutrophils and decreased lymphocytes in patients with uncontrolled glucose, suggesting that viral infection was more serious and was easy to be accompanied by bacterial infection [22]. It is widely known that, in the pathophysiological process of severe infection, the increased cytokines released by elevated neutrophils could lead to cytokine storms and multiple organ dysfunction [32–34]. The elevated neutrophils were positively correlated with the increased risk of death of COVID-19 [34,35]. Meanwhile, the absolute count of lymphocytes among COVID-19 was negatively correlated with viral RNA load, occurrence of ARDS, need of ICU care, severity and mortality [34–37]. A study conducted by Evangelos et al. showed that the elevated CRP was positively related with the occurrence of ARDS, myocardial injury and death, and the increase of ferritin was related to the poor prognosis of COVID-19 [38]. Simultaneously, it is reported that hyperglycemia aggravates inflammation by raising the release of TNF-α and interleukin [39–41], which can result in inflammatory storm, and is judged to be one of the principal causes of poor prognosis in patients with COVID-19 [42]. Therefore, the causality between the characteristics of HbA1c groups and the pooled ORs of this study could be explicated.

Some biological mechanisms have been raised to explain the potential causal relationship between prolonged uncontrolled hyperglycaemia and increased mortality in COVID-19 patients. Impaired immune response to viral infections is the main cause [43]. Particularly, hyperglycemia may inhibit intracellular destruction of microbes, neutrophil chemotaxis, and phagocytosis, thereby providing higher affinity for cellular binding and effective virus entry, and reducing viral clearance [44]. In addition, it can also cause direct glycosylation of proteins, thus changing the structure of complements [45,46]. Chronic hyperglycemia downregulates the expression of ACE2 possessing anti-inflammatory property through glycosylation, making cells vulnerable to viral inflammation and destruction, which might interpret higher predisposition

of COVID-19 with chronic hyperglycemia to ARDS [47,48]. Furthermore, endotheliitis might be a possible mechanism leading to organ dysfunction causing critical illness in COVID-19, which might be exacerbated by endothelial dysfunction associated with chronic hyperglycemia [49]. Notably, HbA1c is as much a marker of ambient glucose as it is of oxidative stress. It is an early step in the production of advanced glycation end products. Perhaps the sickest of the ICU/intubated COVID-19 patients had a great deal of oxidative stress. High HbA1c may be associated with a large amount of oxidative stress for critical illness in COVID-19.

Advanced age, hypertension and diabetes are not only risk factors for poor prognosis of COVID-19, but also confounding factors for HbA1c [23]. Among patients with severe COVID-19, more non- survivors were male [22]. Thus, age, sex, diabetic status, and the incidence of hypertension are possible effect modifiers of the HbA1c-mortality association. However, the results of our age-stratified subgroup analysis did not furnish evidence to support this hypothesis. There was moderate heterogeneity among these studies, which was solved according to diabetic status and the incidence of hypertension through subgroup analysis. Some of the inconsistencies in these findings could partly be explained by discrepancy in dietary patterns, lifestyle habits, antidiabetic or antihypertensive drugs, ICU length of stay, and better compliance with doctor's advice before and after infection with COVID-19. Besides, compared with studies of large sample size, small sample size studies were more likely to be affected by selection bias. Similarly, the significant relation could not be replicated among female patients or short study periods. Therefore, these results should be explicated with caution to a certain extent. Significantly, stress hyperglycemia (HbA1C < 6.5%, transient hyperglycemia) may have a worser outcome than previously diagnosed diabetes [50]. Limited studies have ruled out our attempt to study admission glucose as a potential modifier through subgroup analysis. Therefore, more research is needed to determine whether stress hyperglycemia can change the correlation of HbA1c- mortality.

Nevertheless, when HbA1c was referred as a continuous variable, this association was not significant. Several reasons should be considered. First of all, there may be several confounding factors that interfere with this result, such as age, sex, diabetic status, and the incidence of hypertension. Secondly, as reported by Agarwal et al. [10], when the mortality rate in the cohort was such high, the effect of glucose control on mortality might be relatively

too small to be detected. Thirdly, the HbA1 might have an effect on in-hospital glucose levels and could not independently predict mortality, which may be affected by hospitalization factors, such as hospitalization insulin treatment, other hyperglycemia-inducing hospital interventions, and severity of illness, and need to be further investigated. Last but not least, a small number of patients with relatively short study periods should be taken into consideration, as HbA1c is generally considered to be a long-term predictor of mortality in patients with diabetes.

The current meta-analysis has some inevitable limitations. Firstly, although this study extracted the adjusted OR (if they are available), confounding factors such as demographic characteristics, BMI, comorbidities, and post-hospital treatment might still interfere with the results due to the inability to obtain data for individual participants. Therefore, this result should be interpreted carefully in clinical practice. Besides, excluding several studies that did not report the necessary data for HbA1c-mortality analysis may lead to publication bias. Lastly, due to the inherent limitations of observational studies, this research failed to establish a causal link between HbA1c and adverse outcome of COVID-19, when HbA1c was referred as a continuous variable. More studies are needed to use HbA1c as a continuous variable to demonstrate its effect on hospital mortality. The number of included studies was relatively small to reach a definite conclusion. Further studies need to be conducted through highly powered, multi-centered, prospective controlled trials.

While recognizing the built-in limitations of the original data, we insist that this meta-analysis has its merits and clinical significance. In this study, we searched 8 databases for the relationship between HbA1c and poor prognosis of COVID-19, and there was no language restriction. In addition, the stabilization and reliability of this results were further verified by the sensitivity analysis. For all we know, this study is the first systematic review and meta-analysis of the predictive value of pre-admission hba1c on the short-term prognosis of COVID-19. Though there is a resemble review regarding a mixed population with and without diabetes [51], it only included in two studies and all patients of them were Chinese. According to this meta-analysis, we proposed people at high-risk of COVID-19 without (known) diabetes to control and monitor HbA1c levels. The effect of HbA1c on the hospitalization rate, in-hospital glucose levels, the glucose variation, and the influence of new-onset diabetes on the prognosis of COVID-19 are worth exploring in the future.

The elevation of HbA1c is a predictor of COVID-19's in-hospital mortality. The COVID-19 high-risk population with elevated HbA1c should comply with doctor's advice, strictly monitor and control hyperglycemia. For clinicians, HbA1c can represent a clinical tool for early risk assessment of COVID-19, which is vital for targeted therapy and needs more attention. As for researchers, further prospective studies and much larger samples size are needed to verify these findings.

Author contributions

Gang Chen conceived and designed this study. ZZ and YM collected the data and performed the literature search. ZZ was involved in the writing of this paper. All of the authors read and approved the final version of this paper.

Ethical approval

Not required.

Conflicts of interest

The authors declare no conflict of interests.

Dissemination to participants and related patient and public communities

We will disseminate our findings to patient organisations and media outlets.

Data sharing

No additional data available.

References

[1] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (2020) 507–513, http://dx.doi.org/10.1016/S0140-6736(20)30211-7.

[2] B.E. Young, S.W.X. Ong, S. Kalimuddin, J.G. Low, S.Y. Tan, J. Loh, O.-T. Ng, K. Marimuthu, L.W. Ang, T.M. Mak, S.K. Lau, D.E. Anderson, K.S. Chan, T.Y. Tan, T.Y. Ng, L. Cui, Z. Said, L. Kurupatham, M.I.C. Chen, M. Chan, S. Vasoo, L.-F. Wang, B.H. Tan, R.T.P. Lin, V.J.M. Lee, Y.-S. Leo, D.C. Lye, T. for the Singapore Novel Coronavirus Outbreak Research, Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore, JAMA 323 (2020) 1488–1494, http://dx.doi.org/10.1001/jama.2020.3204.

[3] C. Rothe, M. Schunk, P. Sothmann, G. Bretzel, G. Froeschl, C. Wallrauch, T. Zimmer, V. Thiel, C. Janke, W. Guggemos, Transmission of 2019-nCoV infection from an asymptomatic contact in Germany, N. Engl. J. Med. 382 (2020) 970–971.

[4] J.K. Yang, Y. Feng, M.Y. Yuan, S.Y. Yuan, H.J. Fu, B.Y. Wu, G.Z. Sun, G.R. Yang, X.L. Zhang, L. Wang, Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS, Diabet. Med. 23 (2006) 623–628.

[5] A. Badawi, S.G. Ryoo, Prevalence of diabetes in the 2009 influenza A (H1N1) and the Middle East respiratory syndrome coronavirus: a systematic review and meta-analysis, J. Public Health Res. 5 (2016).

[6] Z. Wang, Z. Du, F. Zhu, Glycosylated hemoglobin is associated with systemic inflammation, hypercoagulability, and prognosis of COVID-19 patients, Diabetes Res. Clin. Pract. 164 (2020), 108214.

[7] L. Liu, W. Wei, K. Yang, S. Li, X. Yu, C. Dong, B. Zhang, Glycemic control before admission is an important determinant of prognosis in patients with coronavirus disease 2019, J. Diabetes Investig. 12 (2021) 1064–1073.

[8] N. Holman, P. Knighton, P. Kar, J. O'Keefe, M. Curley, A. Weaver, E. Barron, C. Bakhai, K. Khunti, N.J. Wareham, Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study, Lancet Diabetes Endocrinol. 8 (2020) 823–833.

[9] L. Zhu, Z.-G. She, X. Cheng, J.-J. Qin, X.-J. Zhang, J. Cai, F. Lei, H. Wang, J. Xie, W. Wang, H. Li, P. Zhang, X. Song, X. Chen, M. Xiang, C. Zhang, L. Bai, D. Xiang, M.-M. Chen, Y. Liu, Y. Yan, M. Liu, W. Mao, J. Zou, L. Liu, G. Chen, P. Luo, B. Xiao, C. Zhang, Z. Zhang, Z. Lu, J. Wang, H. Lu, X. Xia, D. Wang, X. Liao, G. Peng, P. Ye, J. Yang, Y. Yuan, X. Huang, J. Guo, B.-H. Zhang, H. Li, Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes, Cell Metab. 31 (2020), http://dx.doi.org/10.1016/j.cmet.2020.04.021, 1068–1077.e3.

[10] S. Agarwal, C. Schechter, W. Southern, J.P. Crandall, Y. Tomer, Preadmission diabetes-specific risk factors for mortality in hospitalized patients with diabetes and coronavirus disease 2019, Diabetes Care 43 (2020) 2339–2344.

[11] B. Cariou, S. Hadjadj, M. Wargny, M. Pichelin, A. Al-Salameh, I. Allix, C. Amadou, G. Arnault, F. Baudoux, B. Bauduceau, Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study, Diabetologia 63 (2020) 1500–1515.

[12] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Int. J. Surg. 8 (2010) 336–341.

[13] C. National Health, Diagnosis and treatment protocol for novel coronavirus pneumonia (Trial Version 7), Chin. Med. J. 133 (2020) 1087–1095.

[14] A.D. Association, 6. Glycemic targets: standards of medical care in diabetes—2020, Diabetes Care 43 (2020) S66–S76, http://dx.doi.org/10.2337/dc20-S006.

[15] J. Peterson, V. Welch, M. Losos, P. Tugwell, The Newcastle-ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses, Ottawa Ottawa Hosp. Res. Inst., 2011, pp. 1–12.

[16] J.P.T. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Stat. Med. 21 (2002) 1539–1558.

[17] C.B. Begg, M. Mazumdar, Operating characteristics of a rank correlation test for publication bias, Biometrics (1994) 1088–1101.

[18] M. Egger, G.D. Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, BMJ 315 (1997) 629–634.

[19] S.M. Chung, Y.Y. Lee, E. Ha, J.S. Yoon, K.C. Won, H.W. Lee, J. Hur, K.S. Hong, J.G. Jang, H.J. Jin, The risk of diabetes on clinical outcomes in patients with coronavirus disease 2019: a retrospective cohort study, Diabetes Metab. J. 44 (2020) 405–413.

[20] J. Conway, A. Gould, R. Westley, S.A. Raju, A. Oklopcic, A. Broadbent, A.H. Abdel-hafiz, A.J. Sinclair, Characteristics of patients with diabetes hospitalised for COVID-19 infection-a brief case series report, Diabetes Res. Clin. Pract. 169 (2020), 108460.

[21] Z. Liu, X. Bai, X. Han, W. Jiang, L. Qiu, S. Chen, X. Yu, The association of diabetes and the prognosis of COVID-19 patients: a retrospective study, Diabetes Res. Clin. Pract. 169 (2020), 108386.

[22] Y. Yan, Y. Yang, F. Wang, H. Ren, S. Zhang, X. Shi, X. Yu, K. Dong, Clinical characteristics and outcomes of patients with severe covid-19 with diabetes, BMJ Open Diabetes Res. Care 8 (2020), e001343.

[23] A.R. Saand, M. Flores, T. Kewan, S. Alqaisi, M. Alwakeel, L. Griffiths, X. Wang, X. Han, R. Burton, M.J. Al-Jaghbeer, Does inpatient hyperglycemia predict a worse outcome in COVID-19 intensive care unit patients? J. Diabetes 13 (2021) 253–260.

[24] M.V. Shestakova, O.K. Vikulova, M.A. Isakov, I.I. Dedov, Diabetes and COVID-19: analysis of the clinical outcomes according to the data of the russian diabetes registry, Probl. Actuels Endocrinol. Nutr. 66 (2020) 35–46.

[25] M. Wargny, P. Gourdy, L. Ludwig, D. Seret-Bégué, O. Bourron, P. Darmon, C. Amadou, M. Pichelin, L. Potier, C. Thivolet, Type 1 diabetes in people hospitalized for COVID-19: new insights from the CORONADO study, Diabetes Care 43 (2020) e174–e177.

[26] E.J. Williamson, A.J. Walker, K. Bhaskaran, S. Bacon, C. Bates, C.E. Morton, H.J. Curtis, A. Mehrkar, D. Evans, P. Inglesby, OpenSAFELY: factors associated with COVID-19 death in 17 million patients, Nature 584 (2020) 430.

[27] S. Bhandari, G. Rankawat, A. Singh, V. Gupta, S. Kakkar, Impact of glycemic control in diabetes mellitus on management of COVID-19 infection, Int. J. Diabetes Dev. 40 (2020) 340–345.

[28] S.J. Klein, D. Fries, S. Kaser, S. Mathis, C. Thomé, M. Joannidis, Unrecognized diabetes in critically ill COVID-19 patients, Crit. Care 24 (2020) 1–4.

[29] A.A. Al Hayek, A.A. Robert, A. Bin Matar, A. Algarni, H. Alkubedan, T. Alharbi, A. Al Amro, S.A. Alrashidi, M. Al Dawish, Risk factors for hospital admission among COVID-19 patients with diabetes: a study from Saudi Arabia, Saudi Med. J. 41 (2020) 1090.

[30] D.S. Hui, E.I. Azhar, T.A. Madani, F. Ntoumi, R. Kock, O. Dar, G. Ippolito, T.D. McHugh, Z.A. Memish, C. Drosten, The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—the latest 2019 novel coronavirus outbreak in Wuhan, China, Int. J. Infect. Dis. 91 (2020) 264–266.

[31] S. Murthy, C.D. Gomersall, R.A. Fowler, Care for critically ill patients with COVID-19, JAMA 323 (2020) 1499–1500.

[32] G. Chen, D.I. Wu, W. Guo, Y. Cao, D. Huang, H. Wang, T. Wang, X. Zhang, H. Chen, H. Yu, Clinical and immunological features of severe and moderate coronavirus disease 2019, J. Clin. Invest. 130 (2020) 2620–2629.

[33] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) 497–506.

[34] C. Wu, X. Chen, Y. Cai, X. Zhou, S. Xu, H. Huang, L. Zhang, X. Zhou, C. Du, Y. Zhang, Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China, JAMA Intern. Med. 180 (2020) 934–943.

[35] X. Yang, Y. Yu, J. Xu, H. Shu, H. Liu, Y. Wu, L. Zhang, Z. Yu, M. Fang, T. Yu, Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study, Lancet Respir. Med. 8 (2020) 475–481.

[36] Y. Liu, W. Liao, L. Wan, T. Xiang, W. Zhang, Correlation between relative nasopharyngeal virus RNA load and lymphocyte count disease severity in patients with COVID-19, Viral Immunol. 34 (2021) 330–335.

[37] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China, JAMA 323 (2020) 1061–1069.

[38] E. Terpos, I. Ntanasis-Stathopoulos, I. Elalamy, E. Kastritis, T.N. Sergentanis, M. Politou, T. Psaltopoulou, G. Gerotziafas, M.A. Dimopoulos, Hematological findings and complications of COVID-19, Am. J. Hematol. 95 (2020) 834–847.

[39] N. Ouchi, J.L. Parker, J.J. Lugus, K. Walsh, Adipokines in inflammation and metabolic disease, Nat. Rev. Immunol. 11 (2011) 85–97.

[40] D. Mathis, Immunological goings-on in visceral adipose tissue, Cell Metab. 17 (2013) 851–859.

[41] C. Xia, X. Rao, J. Zhong, Role of T lymphocytes in type 2 diabetes and diabetes-associated inflammation, J. Diabetes Res. 2017 (2017).

[42] W. Guo, M. Li, Y. Dong, H. Zhou, Z. Zhang, C. Tian, R. Qin, H. Wang, Y. Shen, K. Du, Diabetes is a risk factor for the progression and prognosis of COVID-19, Diabetes. Metab. Res. Rev. 36 (2020) e3319.

[43] J.A. Critchley, I.M. Carey, T. Harris, S. DeWilde, F.J. Hosking, D.G. Cook, Glycemic control and risk of infections among people with type 1 or type 2 diabetes in a large primary care cohort study, Diabetes Care 41 (2018) 2127–2135.

[44] R. Muniyappa, S. Gubbi, COVID-19 pandemic, coronaviruses, and diabetes mellitus, Am. J. Physiol. Metab. 318 (2020) E736–E741.

[45] N. Jafar, H. Edriss, K. Nugent, The effect of short-term hyperglycemia on the innate immune system, Am. J. Med. Sci. 351 (2016) 201–211.

[46] Q. Wang, P. Fang, R. He, M. Li, H. Yu, L. Zhou, Y. Yi, F. Wang, Y. Rong, Y. Zhang, O-GlcNAc transferase promotes influenza A virus–induced cytokine storm by targeting interferon regulatory factor–5, Sci. Adv. 6 (2020) eaaz7086.

[47] S.R. Bornstein, F. Rubino, K. Khunti, G. Mingrone, D. Hopkins, A.L. Birkenfeld, B. Boehm, S. Amiel, R.I.G. Holt, J.S. Skyler, Practical recommendations for the management of diabetes in patients with COVID-19, Lancet Diabetes Endocrinol. 8 (2020) 546–550.

[48] J.-K. Yang, S.-S. Lin, X.-J. Ji, L.-M. Guo, Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes, Acta Diabetol. 47 (2010) 193–199.

[49] Z. Varga, A.J. Flammer, P. Steiger, M. Haberecker, R. Andermatt, A.S. Zinkernagel, M.R. Mehra, R.A. Schuepbach, F. Ruschitzka, H. Moch, Endothelial cell infection and endotheliitis in COVID-19, Lancet 395 (2020) 1417–1418.

[50] A.K. Singh, R. Singh, Does poor glucose control increase the severity and mortality in patients with diabetes and COVID-19? Diabetes Metab. Syndr. Clin. Res. Rev. 14 (2020) 725–727.

[51] J. Chen, C. Wu, X. Wang, J. Yu, Z. Sun, The impact of COVID-19 on blood glucose: a systematic review and meta-analysis, Front. Endocrinol. (Lausanne) 11 (2020).