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Review

Prediabetes and COVID-19 severity, an underestimated risk factor: A systematic review and meta-analysis

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ABSTRACT

Background and aims: The novel coronavirus disease 2019 (COVID-19) has rapidly spread through the whole globe. Since the beginning of the outbreak, some individuals were more likely to manifest more severe outcomes. Diabetic patients were of that sort; however, the severity of COVID-19 in prediabetic ones remained less identified. This study aimed to systematically review and conduct a meta-analysis of the previously published observational studies investigating the severity of COVID-19 in prediabetic patients.

Methods: Medline/PubMed, Scopus, EMBASE, Web of Science, Cochrane library, and google scholar databases were queried to identify relevant studies concerning prediabetes and serious COVID-19 outcomes. The Newcastle-Ottawa scale was used to assess the quality of the included studies. Odds ratio (OR) and 95% confidence interval (CI) were used to evaluate the likelihood of severe presentations in prediabetic patients.

Results: A total of 3027 patients were included in the meta-analysis. A random-effects model was used regarding the high heterogeneity (I^2 = 55%). Prediabetes was significantly associated with adverse outcomes of COVID-19 with an OR of 2.58 (95%CI, 1.46–4.56).

Conclusion: Prediabetes could act as a risk factor for the severity of COVID-19. Early detection of prediabetic patients might be helpful to adopt preventive and protective strategies to improve the prognosis of the infected individuals.

1. Introduction

The ongoing pandemic of Coronavirus Disease-2019 (COVID-19) has led to plenty of limitations and difficulties for people and healthcare systems from the beginning of the crisis in December 2019, in Wuhan, China, where a cluster of cases with pneumonia was recognized [1]. The development and wide distribution of various vaccines and their promising results in trials have brought hope that we are probably so close to the end of the pandemic. However, we should not be blinded by the light at the end of the pandemic tunnel, as many aspects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are still unknown.

Since the very early worldwide outbreak of the COVID-19, the management and outcome of the infected patients with underlying comorbidities, such as cardiovascular diseases, hypertension, and diabetes mellitus (DM), have been a matter of major importance [2]. Previous studies had demonstrated a high frequency of DM in those with COVID-19, and strikingly, worse COVID-19 outcomes and poor clinical profiles were associated with diabetes patients, regardless of the type [3,4]. However, considering the higher frequency of type 2 DM in older adults who are highly vulnerable to COVID-19 infection, the association between type 2 DM and COVID-19 is more significant than type 1. The exact pathomechanisms behind this association are yet to be fully comprehended, but several factors are assumed to account for serious COVID-19

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Table 1
Assessment of the qualified studies using Newcastle-Ottawa scale; a cohort study can be awarded a maximum of 4 scores for Selection, 2 for Comparability, and 3 for Outcome/Exposure section.

Study, year	Number of stars			Overall score
	Selection	Comparability	Outcome/Exposure	
Zhang et al. (2020) [25]	4	2	2	8
Alahmad et al. (2020) [26]	3	2	2	7
Vargas-vazquez et al. (2021) [27]	4	2	3	9
Li et al. (2020) [28]	4	2	2	8
Tee et al. (2020) [29]	3	1	3	7
Subramanian et al. (2021) [30]	3	1	3	7

episodes or even death in diabetes patients. Innate and adaptive immunity defects along with cardiovascular complications in DM could potentially explain severe COVID-19 outcomes [5]. Another responsible factor is the downregulation of the angiotensin-converting enzyme 2 (ACE2) receptor following the attachment with the spike protein of SARS-CoV-2. ACE2 receptors had been recognized to be the major entry receptors for the virus [6]. Corroborating findings from several studies have suggested the prominent role of ACE2 receptors in the homeostasis of inflammation, but the expression of these receptors is extensively reduced upon the SARS-CoV-2 invasion [7–10]. Moreover, chronic hyperglycemia can downregulate the expression of ACE2 receptors, which, considering their anti-inflammatory role, aggravation of COVID-19 symptoms can be justified in diabetic patients [11].

Prediabetes is a long-lasting state with impaired glucose tolerance preceding type 2 DM. Concerning the pathophysiology of prediabetes and alterations in the immune system of the affected individuals [12], a similar outcome of COVID-19 in prediabetes would be plausible. However, this association is far from being understood, considering the relatively small number of studies in this regard and their conflicting results. Elucidating the severity of COVID-19 in prediabetic patients is of crucial value as prediabetes diagnosis has not been established in the vast majority of the population. Taking the importance of the aforementioned association into account, we sought to investigate the clinical outcome of COVID-19 in patients with prediabetes by conducting a systematic review and meta-analysis to address this gap in the literature.

2. Methods

2.1. Protocol and registration

To ensure the quality of the study, Preferred Items for Systematic Reviews and Meta-Analysis (PRISMA) [13] guidelines were utilized, and the review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42021272282).

2.2. Search strategy

In accordance with PRISMA, the Medline/PubMed, Scopus, EMBASE, Web of Science, Cochrane library, and google scholar databases were queried without language restrictions, covering the period between January 2020 and July 2021. We used the following search terms to identify and extract relevant studies: ("COVID-19" OR "coronavirus disease" OR "SARS-CoV-2") AND ("prediabetes" OR "prediabetic state" OR "impaired fasting glucose" OR "impaired glucose tolerance"). Furthermore, the references of the retrieved article were screened to find additional studies.

2.3. Eligibility criteria and study selection

According to PICO [14], the framework of this study was: Population: patients with COVID-19; Intervention: prediabetes; Comparisons: COVID-19 infected patients without normal blood glucose; Outcomes: severity of COVID-19.

In order to assess the association of prediabetes and COVID-19 severity, comparative (prediabetic vs. normoglycemic) studies were considered eligible types of studies to be recruited.

We included the studies defining the following criteria for diagnosis of prediabetes:

- Fasting plasma glucose 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L), or
- Oral glucose tolerance test 2-h plasma glucose 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L), or
- Hemoglobin A1C 5.7–6.4% (39–47 mmol/mol) [14].

The severity of COVID-19 was defined as a poor or critical outcome, refractory to treatment, need for mechanical ventilation, admission to intensive care unit (ICU), and eventually death.

The following exclusion criteria were applied for this study:

- Studies not comparing the odds of severe COVID-19 outcomes in prediabetes vs. normoglycemia
- Case reports/series, review articles, and studies that did not provide sufficient data.
- Low-quality studies based on the score of Newcastle-Ottawa assessment scale (NOS) (however, all studies had high quality and none of them was excluded) [15].
- Unavailable studies (although we contacted the corresponding author to obtain the full text of the article, no response was received).

2.4. Quality assessment

Following the qualification of the studies, two independent reviewers (D.SH, D.S) evaluated the quality and internal validity of the included studies by means of NOS for cohort studies which is represented in Table 1. The NOS scoring range is from 0 to 9, with higher scores signifying a higher quality of the article. Base on the scores, studies were classified as those with low risk of bias (7–9), high risk of bias (4–6), and very high risk of bias (0–3). Discrepancies in the quality assessment were solved by joint discussion or by the third reviewer (M.H).

2.5. Data extraction

Two reviewers (D.SH, D.S) independently carried out data extraction from the qualified studies to minimize the risk of reporting and data collection bias. The extracted data were added

to the previously prepared table (Table 1), including the first author's name, publication date, location of the study, type, and title of the study, total population (prediabetes), and mean age of the patients as the indices. The third reviewer (M.H) scrutinized the extracted data and resolved any inconsistency in the data. In case of incomplete data in the retrieved articles, the corresponding author was contacted. If the authors had not responded, another E-mail was sent five days later.

2.6. Statistical analysis

The association between prediabetes and COVID-19 severity was expressed as odds ratio (OR) with a 95% confidence interval (CI). Heterogeneity among the studies was evaluated by I^2 statistic, with $I^2 > 75\%$ indicating extreme heterogeneity, I^2 between 50% and 75% high heterogeneity, I^2 between 25% and 50% moderate heterogeneity, and $I^2 < 25\%$ no heterogeneity [16,17]. A random-effects model was applied in case of high heterogeneity ($I^2 > 75\%$); otherwise, a fixed-effects model was used. A random-effects model was used regarding the high heterogeneity ($I^2 = 55\%$) in this meta-analysis. All statistical analyses were performed using STATA 14. The statistical level of significance was set at P-value < 0.05.

3. Results

3.1. Study selection

As depicted in the PRISMA flowchart (Fig. 1), a total of 134 records were initially identified through the primary search on the mentioned databases. Forty-eight of which were removed because of duplication. Titles and abstracts of the remaining 86 studies were screened, and 75 more articles were eliminated according to the exclusion criteria. Of the remaining 11 studies, 5 were excluded due to unavailable full text or insufficient data. Finally, 6 studies met the inclusion criteria and were selected for quality assessment.

In the six final studies, a total number of 3027 prediabetes patients aged between 47.7 and 62 years were presented. Features of these studies are comprehensively represented in Table 2.

3.2. Meta-analysis

Strikingly, as depicted in Fig. 2, prediabetes is associated with severe COVID-19 outcomes with an OR of 2.58 (95%CI, 1.46–4.56), which is statistically significant. Respecting the limited number of included studies, data analyses were not carried out separately sorted by the location of the study, sex, age, and duration of the hospitalization.

Meta-regression analysis (Fig. 3) displayed a negative correlation between the impact of prediabetes on COVID-19 outcomes and the sample size of the studies; however, the correlation was not significant (P-value: 0.187).

The sensitivity analysis (Fig. 4), conducted by eliminating each study in turn and re-evaluating the remained effect sizes, demonstrated that the study by Li et al. had the most influence on the results of the meta-analysis as upon the elimination of this study, the OR decreased to 0.73.

4. Discussion

4.1. Principle findings

This systematic review and meta-analysis included six studies and assessed the odds of presenting the severe form of COVID-19 in patients with prediabetes. Our results showed a statistically significant association between COVID-19 severity and prediabetic state (OR: 2.58; 95%CI, 1.46–4.56). However, this finding should be considered cautiously considering the small number of studies included in the analyses. The scant data in this regard potentially stem from the obscure status of prediabetes in a large proportion of COVID-19 infected patients. Between-study heterogeneity was high

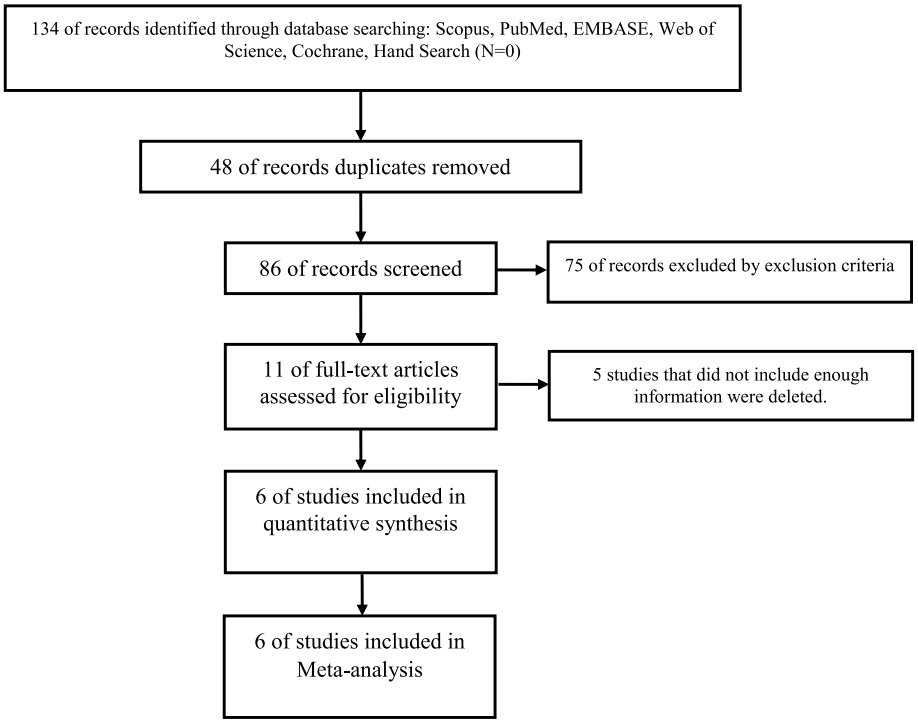

Fig. 1. PRISMA flow diagram.

Table 2
Characteristics of the included studies.

Author	Year of Publication	Country	Sample Size of prediabetes	Number of females in prediabetic patients	Number of males in prediabetic patients	Age group in prediabetic patients (year)	Date	Study design	Prediabetes		
									OR	Low	Up
Subramanian et al. [30]	2021	UK	2546	2546	0	–	between January 31, 2020 and July 22, 2020	cohort study	1.31	0.86	2
Vargas-Vázquez et al. [27]	2021	Mexico	125	45	80	50	from 16 March to July 1, 2020	cohort study	4.15	1.29	16.75
Tee LY et al. [29]	2020	Singapore	21	0	21	47.7	from April 21 to June 1, 2020.	cohort study	6.137	1.605	28.51
Alahmad et al. [26]	2020	Kuwait	82	–	–	–	between February and May 2020	cohort study	1.69	0.63	4.05
Zhang et al. (severity) [25]	2020	China	62	28	34	62	from Jan 1 to Mar 17, 2020	cohort study	1.42	0.53	3.81
Zhang et al. (mortality) [25]	2020	China	62	28	34	62	from Jan 1 to Mar 17, 2020	cohort study	4.11	1.15	14.74
Li et al. [28]	2020	China	129	61	68	51.9	from January 22, 2020 to March 17, 2020	cohort study	9.42	2.18	40.7

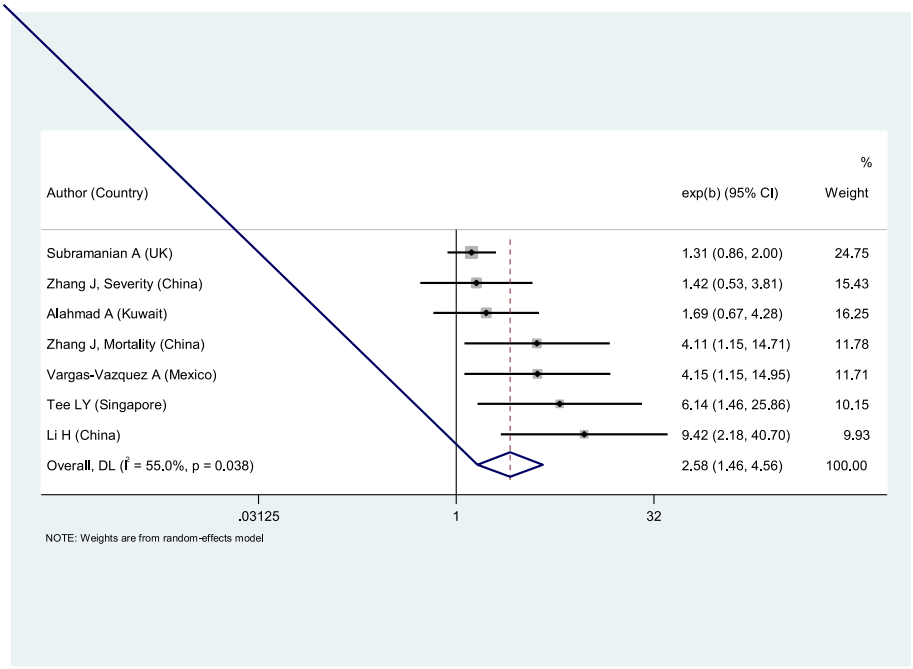

Fig. 2. Forest plot random effect model for COVID-19 severity in prediabetic patients.

($I^2 = 55\%$) in this meta-analysis.

4.2. Pathophysiological background of the association

The association of coronavirus and prediabetes, or in general, hyperglycemia, was first noticed in the SARS-CoV pandemic in 2003. The literature generated at the time implied derangement in the islets of Langerhans following infection. This detrimental phenomenon was explained by the overexpression of ACE2 receptors in the Langerhans islets [18] and was speculated to take place in the COVID-19 infected individuals as well. Accordingly, Wang et al. presented COVID-19 patients with mild pancreatic injury [19]. Even SARS-CoV-2 was presumed to trigger the development of type 2 diabetes in prediabetic patients. Type 2 DM has a well-established role in suppressing the immune system and promoting inflammation, which could worsen the COVID-19 symptoms. Moreover, observational and experimental evidence has revealed the increased interleukin-6 and C-reactive protein levels in prediabetes. These inflammatory markers have a well-documented role in developing a destructive phenomenon termed "cytokine storm syndrome" and the following devastating outcomes [20,21]. In addition to the mentioned points, the potential role of CD147 and the dipeptidyl peptidase-4 (DPP-4) enzyme in inducing severe COVID-19 outcomes should not be disregarded. CD147 is a transmembrane complex, identified to be a binding site for spike protein of the SARS-CoV-2 and facilitate the viral entry. The expression of this supramolecular compound is upregulated in hyperglycemia and DM, rendering hyperglycemic patients prone to worse and more severe COVID-19 symptoms [22].

DPP-4 enzyme was previously indicated to be capable of the

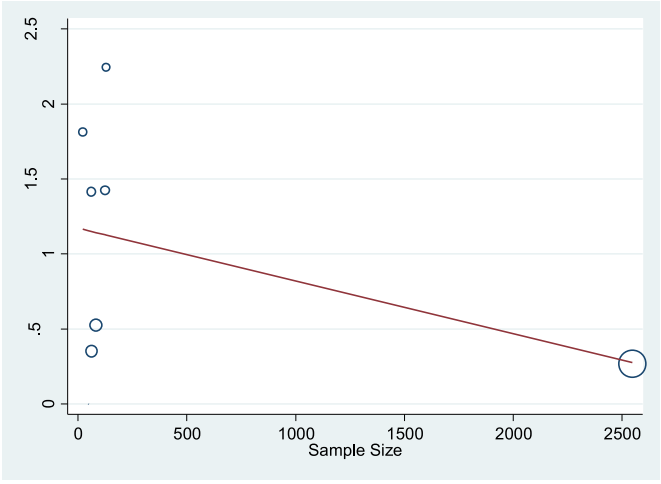

Fig. 3. Meta-regression for association of sample size and prediabetes effect on COVID-19 outcomes.

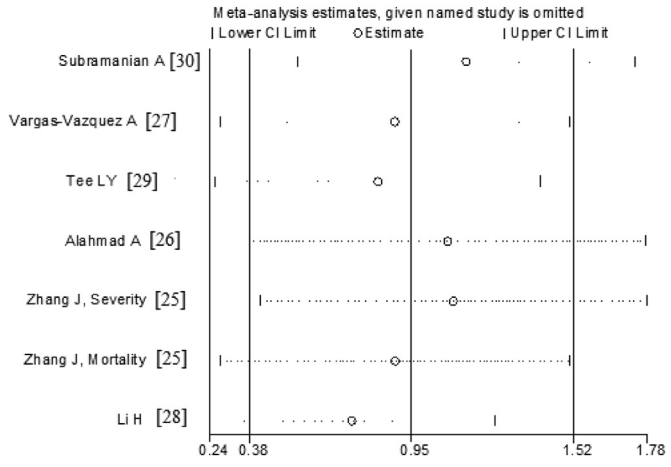

Fig. 4. Sensitivity analysis of the considered studies.

binding middle east respiratory syndrome (MERS)-CoV (another type of human coronaviruses), and notably, this serine protease could potentially bind and cleavage SARS-CoV-2 as well, according to the *in-silico* findings [23,24]. Considering the increased expression and activity of DPP-4 following hyperglycemia and the pivotal role of DPP-4 in stimulating the immune system and inflammatory reactions, prediabetic patients are probably vulnerable to severe outcomes of COVID-19. Overall, COVID-19 could potentially induce hyperglycemia and even type 2 DM, and on the other hand, prediabetic cases are probably more likely to develop more severe forms of COVID-19. Hence, a reciprocal association might be a reasonable term to express how these two pathologic states are related.

4.3. Implications for practice and conclusion

According to the meta-analysis, a prediabetic state was significantly likely to increase the risk of serious COVID-19 symptoms. However, further research is warranted to confirm this deleterious effect of prediabetes on COVID-19 severity and to yield robust evidence in this regard. Taken together, screening patients with COVID-19 for prediabetes might be a good option to detect those with prediabetes, although no therapeutic drug or medication has been approved for its treatment yet. Early identification of prediabetic patients infected with COVID-19 could enable healthcare professionals to adopt stringent preventive and protective strategies for these individuals who comprise a large proportion of the total population, and still, the majority of them are not detected.

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Ethical approval

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Declaration of competing interest

The authors declare no relative competing interests.

References

[1] Organization, W.H., Pneumonia of unknown cause—China. Available at: who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/; 2020. Accessed April, 2020. 1.
[2] Chen Y, et al. Effects of hypertension, diabetes and coronary heart disease on COVID-19 diseases severity: a systematic review and meta-analysis. MedRxiv; 2020.
[3] Apicella M, et al. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. The lancet Diabetes & endocrinology; 2020.
[4] Myers AK, et al. Predictors of mortality in a multiracial urban cohort of persons with type 2 diabetes and novel coronavirus 19. J Diabetes 2021;13(5):430–8.
[5] Bornstein SR, et al. Practical recommendations for the management of diabetes in patients with COVID-19. The lancet Diabetes & Endocrinology 2020;8(6):546–50.
[6] Cuervo NZ, Grandvaux N. ACE2: evidence of role as entry receptor for SARS-CoV-2 and implications in comorbidities. Elife 2020;9:e61390.
[7] Hamming I, et al. The emerging role of ACE2 in physiology and disease. J Pathol: A J Pathol Soc Great Britain Ireland 2007;212(1):1–11.
[8] Clarke NE, Turner AJ. Angiotensin-converting enzyme 2: the first decade. Int J Hypertens 2012. 2012.
[9] Datta PK, et al. SARS-CoV-2 pandemic and research gaps: understanding SARS-CoV-2 interaction with the ACE2 receptor and implications for therapy. Theranostics 2020;10(16):7448.
[10] Hoffmann M, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181(2):271–80.e8.
[11] Bindom SM, Lazartigues E. The sweeter side of ACE2: physiological evidence for a role in diabetes. Mol Cell Endocrinol 2009;302(2):193–202.
[12] Mzimela NC, Ngubane PS, Khathi A. The changes in immune cell concentration during the progression of pre-diabetes to type 2 diabetes in a high-fat high-carbohydrate diet-induced pre-diabetic rat model. Autoimmunity 2019;52(1):27–36.
[13] Moher D, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4(1):1–9.
[14] Hostalek U. Global epidemiology of prediabetes-present and future perspectives. Clinical Diabetes Endocrinol 2019;5(1):1–5.
[15] Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000. Oxford.
[16] Bowden J, et al. Quantifying, displaying and accounting for heterogeneity in the meta-analysis of RCTs using standard and generalised Q statistics. BMC Med Res Methodol 2011;11(1):1–12.
[17] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539–58.
[18] Yang J-K, et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47(3):193–9.
[19] Wang F, et al. Pancreatic injury patterns in patients with coronavirus disease 19 pneumonia. Gastroenterology 2020;159(1):367–70.
[20] Grossmann V, et al. Profile of the immune and inflammatory response in individuals with prediabetes and type 2 diabetes. Diabetes Care 2015;38(7):1356–64.
[21] Tang Y, et al. Cytokine storm in COVID-19: the current evidence and treatment strategies. Front Immunol 2020;11:1708.
[22] Radzikowska U, et al. Distribution of ACE2, CD147, CD26, and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors. Allergy 2020;75(11):2829–45.
[23] Valencia I, et al. DPP4 and ACE2 in diabetes and COVID-19: therapeutic targets for cardiovascular complications? Front Pharmacol 2020;11:1161.
[24] Vankadari N, Wilce JA. Emerging COVID-19 coronavirus: glycan shield and

structure prediction of spike glycoprotein and its interaction with human CD26. Emerg Microb Infect 2020;9(1):601–4.
[25] Zhang J, et al. Impaired fasting glucose and diabetes are related to higher risks of complications and mortality among patients with coronavirus disease 2019. Front Endocrinol 2020;11:525.
[26] Alahmad B, et al. Fasting blood glucose and COVID-19 severity: nonlinearity matters. Diabetes Care 2020;43(12):3113–6.
[27] Vargas-Vázquez A, et al. Impact of undiagnosed type 2 diabetes and prediabetes on severity and mortality for SARS-CoV-2 infection. BMJ Open Diabetes Research and Care 2021;9(1):e002026.
[28] Li H, et al. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. Diabetes Obes Metabol 2020;22(10):1897–906.
[29] Tee LY, et al. COVID-19 and undiagnosed pre-diabetes or diabetes mellitus among international migrant workers in Singapore. Frontiers in public health 2020;8.
[30] Subramanian A, et al. Increased COVID-19 infections in women with polycystic ovary syndrome: a population-based study. Eur J Endocrinol 2021;184(5):637–45.