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Proportion of newly diagnosed diabetes in COVID-19 patients: a systematic review and meta-analysis

Running title: Newly diagnosed diabetes in COVID-19

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The world is currently grappling with a dual pandemic of diabetes mellitus and coronavirus disease 2019 (COVID-19). Several articles published in the recent issues of

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Diabetes, obesity and Metabolism and elsewhere have raised concerns about a bi-directional relationship between these two health conditions.[1-8] It is now undoubtedly proven that diabetes is associated with a poor prognosis of COVID-19.[6,9-13] On the other hand, COVID-19 patients with diabetes frequently experience uncontrolled hyperglycemia and episodes of acute hyperglycemic crisis, requiring exceptionally high doses of insulin.[1,2,5,7,9,14] More intriguingly, recent reports show that newly diagnosed diabetes is commonly observed in COVID-19 patients.[2,3,5,15] However, this has not been systematically studied before. Therefore, we performed a systematic review and meta-analysis to examine the proportion of newly diagnosed diabetes in COVID-19 patients.

This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[16] and Meta-analyses Of Observational Studies in Epidemiology (MOOSE)[17] guidelines (see S Figure 1 and S Table 1 for checklists), and is registered with PROSPERO (registration no. CRD42020200432). Two authors (TS and YC) independently searched PubMed, MEDLINE, Embase, and Scopus databases and preprint servers (medRxiv and Research Square) until Nov 02, 2020. We considered observational studies providing data on the number or proportion of COVID-19 patients (laboratory-confirmed or clinically diagnosed) with newly diagnosed diabetes. We excluded observational studies that were conducted only among patients with diabetes, case reports, case series, letters, editorials, commentaries, and review articles. Newly diagnosed diabetes was defined as new-onset diabetes (no prior history of diabetes with fasting plasma glucose (FPG) ≥7.0 mmol/l or random blood glucose (RBG) ≥11.1 mmol/l and HbA1c <6.5%) or

previously undiagnosed diabetes (FPG ≥7.0 mmol/l or RBG ≥11.1 mmol/l and HbA1c ≥6.5% or HbA1c ≥6.5% only).[18] We used the search terms “new-onset diabetes”, “newly diagnosed diabetes”, “incident diabetes”, “transient hyperglycemia”, and “secondary hyperglycemia” in conjunction with “COVID-19” (see Supplement file for search strategies). No language restrictions were applied. We also checked the reference list of relevant articles to identify additional eligible studies. If the study cohorts overlapped (i.e., patients from the same hospital with similar time periods of data collection), then the study with the largest sample size was selected. Data on first author name, country, study design, hospital name, study period, age, sex, total number of patients, number of patients with newly diagnosed diabetes, definition of newly diagnosed diabetes, time of diagnosis, and type of diabetes were extracted independently by the same two authors (TS and YC) using a data extraction form that was adapted from the Cochrane Collaboration.[19] We did not contact the authors of the included studies to obtain missing data due to time constraints. The National Institutes of Health Quality Assessment Tool for observational studies was used to assess the quality of the included studies.[20] Disagreements in study selection, data extraction, and quality assessment were resolved by consensus between the two authors (TS and YC) or by discussion with a third author (RJT).

We pooled the proportion of newly diagnosed diabetes across studies with the DerSimonian and Laird random-effects model.[21] The variances of the proportions were stabilized with the Freeman-Turkey Double Arcsine Transformation method.[22] 95% confidence interval (CI) for the proportion in individual studies was calculated using the

exact method. Heterogeneity between the studies was assessed using the Cochran's Q Test ($p<0.01$ for heterogeneity) and Higgins I^2 statistic (low: <25%, moderate: 25-50%, and high: >50%).[23] To investigate the sources of between-study heterogeneity, we did a subgroup analysis by the country of origin of studies and univariate random effects meta-regression models[19] were fitted for mean age (median age was used if mean was not reported), sex (proportion of males), and sample size of studies. We did not assess for publication bias, as there were fewer than ten studies in this meta-analysis.[19,24] Analyses were performed using Stata software version 16.1 (StataCorp, College Station, TX, USA).

A total of 148 studies were retrieved during the search, of which 100 studies were duplicates, and 30 were case reports, case series, letters, commentaries, or review articles. After full-text review, a further 10 studies were excluded, including three overlapping cohorts, three studies that were conducted only among patients with diabetes, and four that did not satisfy the criteria of newly diagnosed diabetes. A total of eight studies were included in the final analysis[4,25-31] (see S Figure 2 for the PRISMA flow diagram).

Table 1 presents the characteristics of the included studies. All eight studies were retrospective cohort studies, including four from China,[4,29-31] two from Italy,[25,26] and the remaining two from the USA.[27,28] All studies were conducted during the first six months of the pandemic (i.e., between January and May 2020). The mean or median age of patients in these studies varied from 47 to 64.9 years. All studies (except two with no

data on sex)[29,30] had more males than females, with the proportion of males ranging from 53.3 to 80%. Data on new-onset diabetes were available in two studies[4,31] and three studies (or cohorts) had previously undiagnosed diabetes cases.[4,28,30] In six studies (or cohorts),[4,25-29] HbA1c was not performed for all participants, so it was not possible to differentiate between new-onset and previously undiagnosed diabetes. In the majority of studies (n=5),[25,26,28,30,31] the exact time of detection of newly diagnosed diabetes was not reported, whereas, in three studies,[4,27,29] the diagnosis was made within 24 hours to three days after hospital admission. Only one study reported on the type of diabetes (i.e., type 2 diabetes).[27] The quality of studies was either fair or good, with most (n=6, 75%) studies were of good quality. With a total of 3711 COVID-19 patients with 492 cases of newly diagnosed diabetes from eight studies, the random-effects meta-analysis estimated a pooled proportion of 14.4% (95% CI: 5.9-25.8%) with a high degree of heterogeneity (I^2: 98.6%, p<0.001). The pooled proportion was non-significantly lower in China than in other countries (13.4% vs. 15.4%, p=0.87, See S Figure 3). Meta-regression models found no significant association between the pooled proportion and mean study age (p=0.84), the proportion of males (p=0.89), and sample size (p=0.81) (see S Table 2).

While newly diagnosed diabetes in COVID-19 patients could be due to the stress response associated with severe illness or treatment with glucocorticoids, the diabetogenic effect of COVID-19 should also be considered.[3] This is supported by reports showing exceptionally high insulin requirement in severely or critically ill COVID-19 patients with diabetes. These appear disproportionate when compared with critical

illness caused by other conditions.[5,7] Further, it has been noted that diabetic ketoacidosis and hyperosmolar hyperglycemic state are unusually common in COVID-19 patients with diabetes.[1,2,5,9,14] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, by attaching to angiotensin-converting enzyme-2 (ACE2) receptors in beta cells of the pancreas, could cause acute impairment in insulin secretion.[3] Indeed, an organoid study has shown that SARS-CoV-2 can enter and damage the pancreatic beta cells.[32] SARS-CoV-2 may also injure the beta cells by triggering a plethora of proinflammatory cytokines (e.g., Interleukin-6) or by enhancing autoimmunity in genetically predisposed people.[3] In addition to defective insulin secretion, COVID-19 patients also present with a high degree of insulin resistance, particularly those with severe illness.[5] It is not known whether this is due to insulin receptor defects in the key metabolic organs associated with glucose metabolism or interference with the insulin receptor signaling by the virus. ACE2 receptors are expressed in the liver, adipose tissue, and skeletal muscle, and binding of SARS-CoV-2 to these receptors may impair responses to insulin.[3] The insulin receptor signaling could be impaired by the proinflammatory cytokines induced by SARS-CoV-2 or by enhanced actions of angiotensin II, resulting from the downregulation of ACE2 after the virus entry into the cells.[3,5,9] Similar mechanisms with other viral infections, such as Hepatitis C, leading to type 2 diabetes have been described before.[33]

This is the first systematic review and meta-analysis to study the extent of newly diagnosed diabetes in COVID-19 patients. We used robust and standard methods, the search was comprehensive (includes grey literature too), literature search, study

screening, selection, data extraction, and quality assessment were performed independently by two researchers, and the quality of most studies was good. Finally, we removed overlapping cohorts in our analysis, which was not commonly performed in many other systematic reviews and meta-analyses conducted in COVID-19 patients. However, our study has some limitations. The true proportion is unknown as all studies were hospital-based, and the patients were mostly severely or critically ill. Further, of the eight studies, 50% were from China, and the rest were from only two other countries, which limits the generalizability of the findings. Finally, the subgroup and meta-regression analyses lack sufficient power to detect associations between variables, as they are limited to the use of study-level data, and the number of studies was small.[19,24] These limitations clearly emphasize the need for more studies with larger samples, including those conducted in community settings where mild cases are treated, from several regions of the world.

In conclusion, this meta-analysis of eight studies with more than 3700 patients shows a pooled proportion of 14.4% for newly diagnosed diabetes in hospitalized COVID-19 patients. Recent reports have shown that newly diagnosed diabetes may confer a greater risk for poor prognosis of COVID-19 than no diabetes or pre-existing diabetes.[4,13] Therefore, COVID-19 patients with newly diagnosed diabetes should be managed early and appropriately and closely monitored for the emergence of full-blown diabetes and other cardiometabolic disorders in the long term. In this regard, the establishment of the CoviDiab Registry (covidiab.e-dendrite.com)[2] is timely and should provide valuable insights into issues regarding COVID-related diabetes. We are now

seeing a classic example of a lethal intersection between a communicable and non-communicable disease!

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Contribution statement: TS conceived the idea, conducted the literature search, screened, selected, and quality assessed the articles, and wrote the first draft of the manuscript. NK reviewed and edited the manuscript. YC conducted the literature search and study screening, selection, data extraction, and quality assessment. She also reviewed and edited the manuscript. RJT resolved any disagreements between TS and YC with the selection and quality assessment of the studies. RJT also helped TS in addressing the reviewers' comments and revising the manuscript. PZ conceived the idea along with TS and reviewed and edited the manuscript.

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Table 1: Study characteristics.

Author & country	Study design	Study period	Study setting	Age (years), mean (SD or range) or median (IQR)	Male, %	N[†]	n[‡] (%)	Definition of newly diagnosed diabetes	Time of diagnosis	Type of diabetes	Study quality[§]
New-onset diabetes											
Li H et al,[4] China	Retrospective cohort	Jan 22 to Mar 17, 2020	Wuhan Union Hospital	61.0 (49-48)	59	453	25 (5.5)	No prior diabetes history, FPG ≥7.0 mmol/l and HbA1c <6.5%	Within 3 days after hospital admission	NR	Good
Zhou W et al,[31] China	Retrospective cohort	Jan to Mar 2020	Anhui Provincial Hospital	47.0 (35-56)	80	80	22 (27.5)	No prior diabetes history, RBG ≥11.1 mmol/l and HbA1c<6.5%	Exact time of diagnosis not reported	NR	Good
Previously undiagnosed diabetes											
Li H et al,[4] China	Retrospective cohort	Jan 22 to Mar 17, 2020	Wuhan Union Hospital	61.0 (49-48)	59	453	38 (8.4)	No prior diabetes history, FPG ≥7.0 mmol/l and HbA1c ≥6.5%	Within 3 days after hospital admission	NR	Good
Yi H et al,[30] China	Retrospective cohort	Jan to Feb, 2020	Jinyintan Hospital in Wuhan, Ruijin Hospital in Shanghai, Tongren Hospital in Anhui, and Tongling People's Hospital in Anhui	NR	NR	521	3 (0.6)	No prior diabetes history and HbA1c ≥6.5%	Exact time of diagnosis not reported	NR	Good
Smith SM et al,[28] USA	Retrospective cohort	Mar 16 to May 2, 2020	Saint Barnabas Medical Center	64.4 (range: 21-100)	53.3	184	85 (46.2)	No prior diabetes history and HbA1c ≥6.5%	Exact time of diagnosis not reported	NR	Fair
New-onset or previously undiagnosed diabetes[¶]											
Li H et al,[4] China	Retrospective cohort	Jan 22 to Mar 17, 2020	Wuhan Union Hospital	61.0 (49-48)	59	453	31 (6.8)	No prior diabetes history and FPG ≥7.0 mmol/l	Within 3 days after hospital admission	NR	Good
Wang S et al,[29] China	Retrospective cohort	Jan 24 to Feb 10, 2020	Wuhan Union West Hospital and Wuhan Red Cross Hospital	NR	NR	1101[a]	176 (16.0)	No prior diabetes history and FPG ≥7.0 mmol/l	Within 24 hours after hospital admission	NR	Fair
Fadini GP et al,[25] Italy	Retrospective cohort	Feb to April, 2020	Hospital in North-East Italy	64.9 (15.4)	59.3	413	21 (5.1)	No prior diabetes history, HbA1c ≥6.5% or RBG	Exact time of diagnosis not reported	NR	Good

								≥11.1 mmol/l with signs and symptoms of hyperglycemia			
Smith SM et al,[28] USA	Retrospective cohort	Mar 16 to May 2, 2020	Saint Barnabas Medical Center	64.4 (range: 21-100)	53.3	184	29 (15.8)	No prior diabetes history, persistently elevated FPG ≥7.0 mmol/l and requiring insulin therapy	Exact time of diagnosis not reported	NR	Fair
Sieglie J et al,[27] USA	Retrospective cohort	Mar 11 to April 30, 2020	Massachusetts General Hospital	63.9 (16.5)	58.3	450	13 (2.9)	No prior diabetes history and HbA1c ≥6.5% or RBG ≥11.1 mmol/l	Within 24 hours after hospital admission	Type 2 diabetes	Good
Lampasona V et al,[26] Italy	Retrospective cohort	Feb 25 to Apr 19, 2020	IRCCS San Raffaele Hospital	64.0 (56.2-71.5)	66.2	509	49 (9.6)	No prior diabetes history and mean FPG ≥7.0 mmol/l during hospitalization	Exact time of diagnosis not reported	NR	Good

SD, standard deviation; IQR, inter-quartile range; FPG, fasting plasma glucose; RBG, random blood glucose; NR, not reported. †Number of COVID-19 patients. ‡Number of newly diagnosed diabetes cases. §Study quality was assessed using the National Institutes of Health Quality Assessment Tool. ¶HbA1c was not performed for all participants, so it was not possible to differentiate between new-onset and previously undiagnosed diabetes.

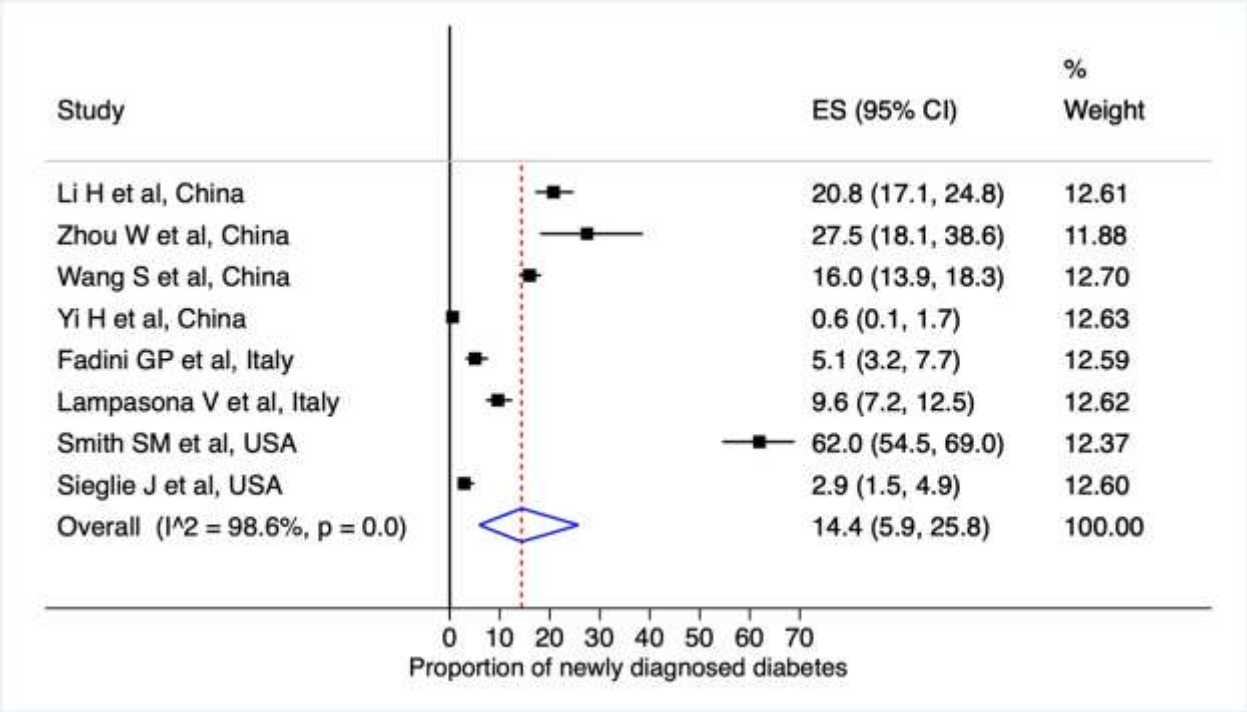

Figure 1: Forest plot for pooled proportion of newly diagnosed diabetes in COVID-19 patients.