Incidence, Risk and Clinical Course of New-Onset Diabetes after COVID-19: Protocol for a Systematic Review and Meta-Analysis of Cohort Studies

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Article

Incidence, Risk and Clinical Course of New-Onset Diabetes after COVID-19: Protocol for a Systematic Review and Meta-Analysis of Cohort Studies

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Abstract: Coronavirus disease 2019 (COVID-19), an infectious disease pandemic, affected millions of people globally, resulting in high morbidity and mortality. Causing further concern, significant proportions of COVID-19 survivors suffer from the lingering health effects of severe acute respiratory syndrome virus 2 (SARS-CoV-2), the pathogen that causes COVID-19. One of the diseases manifesting as a post-acute sequela of COVID-19 is new-onset diabetes. This systematic review and meta-analysis will perform a comprehensive and systematic literature search to estimate the burden of new-onset diabetes after COVID-19. Specifically, this study will estimate the magnitude of the incidence, risk, and population-attributable fraction of new-onset diabetes. The study will also explore and summarize the data on the natural history or clinical course of the new-onset diabetes cases. Five bibliographic databases, including PubMed, MEDLINE, Embase, Scopus, and Web of Science, will be searched for eligible studies. The World Health Organization COVID-19 Research Database, preprint servers, and conference abstracts will also be searched. Cohort studies of COVID-19 patients of all ages providing data on new cases of diabetes in the post-acute phase of the illness will be included. The comparators to estimate the pooled risk ratio will be those with no diagnosis of COVID-19 or those infected with other respiratory tract infections. The findings of this study will likely inform clinical practice, public health guidelines, and policies for early detection and treatment of new-onset diabetes cases in the long-COVID phase. This protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO: No.CRD42020200432).

Keywords: COVID-19; SARS-CoV-2; diabetes; new-onset diabetes; long-COVID; postacute sequelae of SARS-CoV-2

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome virus 2 (SARS-CoV-2) has had devastating effects on people's health and livelihoods, health systems, and the global economy [1,2]. Globally, as of September 25, 2023, there have been >770 million confirmed cases of COVID-19, including nearly 7.7 million deaths [2]. In 2020, global gross domestic product (GDP) fell by 3.4%, while the initial forecast was 2.9% GDP growth [1].

While COVID-19 is an infectious disease, it appears to have a bilateral relationship with a chronic disease, diabetes, which is of significant concern [3–5]. Diabetes is a major global pandemic that has been ongoing for several decades [6], and it is projected that 1.31 billion people will be living with diabetes in 2050 [7]. Studies have well established that people with diabetes (pre-existing or newly diagnosed diabetes) are at an increased risk of having severe COVID-19 illness characterized by requiring intensive care unit admission, endotracheal intubation, or mortality [3,8,9]. On the other hand, a recent systematic review and meta-analysis showed that incidence rates of type 1 diabetes in

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children and adolescents were higher during the pandemic than in the pre-pandemic years [10]. These are further supported by existing and emerging evidence that increasingly demonstrates a positive association between COVID-19 and the new onset of diabetes during the acute phase of illness [4,11,12] and after recovery [13], the so-called "long COVID" [14]. Most importantly, some studies have shown that the incidence of diabetes was higher than that observed in people with no SARS-CoV-2 infection [15] or with other respiratory tract infections such as influenza [16]. Further, some reports show that a significant proportion of COVID-19 survivors with new-onset diabetes tend to remain diabetic in the long-COVID phase [16,17].

Although there have been systematic reviews and meta-analyses reporting the incidence [18,19] or risk [18,20–23] of developing diabetes in COVID-19 patients, these studies are limited by the following: incomplete or non-up-to-date searches [18,20,22], lack of meta-analysis [23], focused only on type 1 diabetes [21], use of only one definition of diabetes (e.g., ICD-10 codes) [18], or no simultaneous reporting of incidence and risk of new-onset diabetes [19–22]. Moreover, none of the studies have provided data on the clinical course of new-onset diabetes and estimated the population-attributable fraction (PAF) for COVID-19 as a risk factor for new-onset diabetes. PAF is defined as the proportion of all cases of a specific disease in a population that is attributable to a specific exposure [24].

To address these research gaps, this systematic review and meta-analysis will comprehensively and systematically synthesize to achieve the following objectives: 1) estimate the incidence of new-onset diabetes in COVID-19 patients; 2) estimate the excess risk of developing diabetes in COVID-19 patients compared to those without COVID-19; 3) examine the clinical course or natural history of new-onset diabetes cases; and 4) estimate the PAF for COVID-19 as a risk factor for new-onset diabetes.

2. Materials and Methods

This protocol was developed in accordance with the standard guidelines, including the Cochrane Handbook for Systematic Reviews [25] and the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) [26]. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO: No.CRD42020200432) [27].

2.1. Inclusion and Exclusion Criteria

We will follow the PECOS (Population, Exposure, Comparator, Outcome, and Study Design) framework [28] to formulate the eligibility criteria for the proposed systematic review and meta-analysis.

Population: Patients of any age diagnosed with COVID-19, either clinically, using diagnostic codes (e.g., ICD-10 [29] codes), or by a positive SARS-CoV-2 test.

Exposure: COVID-19.

Comparators: Comparators will be those with no diagnosis of COVID-19 or with other respiratory tract infections, such as influenza.

Outcomes: The primary outcomes include: **a)** New-onset diabetes (no prior history of diabetes with fasting plasma glucose ≥126 mg/dl, 2-hour plasma glucose ≥200 mg/dl, random blood glucose ≥200 mg/dl, or HbA1c ≥6.5% or diagnosed using ICD-10 [29] or similar codes) [30] after ≥30 days of COVID diagnosis [14] or after discharge from the hospital, and **b)** The natural history or clinical course of new-onset diabetes cases: glycemic status at follow-up (regression to normoglycemia or prediabetes, persistence of diabetes, and glycemic control), treatment status (taking oral hypoglycemic drugs or insulin), development of diabetes complications and deaths.

Study design: We will only consider cohort studies with follow-up data available on new-onset diabetes in COVID-19 patients. Cross-sectional and case-control studies, randomized controlled trials, case reports, case series, letters, editorials, opinion articles, and comments will be excluded. No language restrictions will be applied to the search.

2.2. Data Sources, Search Terms, and Search Strategy

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We will systematically search PubMed, MEDLINE, Embase, Scopus, and Web of Science bibliographic databases for the eligible studies. A comprehensive search strategy for each bibliographic database will be developed using a mix of subject headings and text words according to the PECOS framework, as given in Table 1. We will also hand-search the reference list of selected studies and relevant narrative and systematic reviews. Gray literature, such as government reports, preprint servers, and conference abstracts, will also be searched.

Table 1. Key terms for developing a comprehensive search strategy for each bibliographic database.

Population (P)	Exposure (E)	Comparator (C)	Outcome (O)	Study design (S)
COVID-19	COVID-19	People with no diagnosis of COVID-19 or those with other respiratory tract infections	New-onset diabetes	Cohort study
SARS-CoV-2			New-onset hyperglycemia	
Coronavirus disease 2019			Newly diagnosed diabetes	
Severe acute respiratory syndrome coronavirus 2			Incident diabetes	

2.3. Study Selection

Two independent reviewers (A.T., N.B) will screen the titles and abstracts of studies retrieved from the database search. Afterward, they will screen the full text of the selected studies using the inclusion and exclusion criteria to identify eligible studies. Conflicts in study selection between the reviewers will be resolved by discussion or by a third reviewer (T.S). The percent agreement for study selection between the two reviewers will be presented.

2.4. Data Extraction

Data will be summarized as means (standard deviations) or medians (inter-quartile ranges) for continuous variables and as frequencies (%) for categorical variables. We will design a data extraction form as per the Cochrane Handbook for Systematic Reviews [25]. Two independent reviewers (A.T., N.B) will extract the following data: first author's name, country, data source(s), study design, study setting (community or hospital), number of participants with COVID-19, number of participants without COVID-19 or with other respiratory tract infections, age, sex, follow-up time, post-COVID period, number of new cases of diabetes, diagnostic criteria for COVID-19, diagnostic criteria for diabetes, reported risk estimates, type of diabetes, covariates adjusted in regression models, and level of COVID-19 severity. The reviewers will also collect data on the clinical course of new-onset diabetes cases, including the number (%) of participants who regressed to normoglycemia or prediabetes, remained diabetic, continued taking oral hypoglycemic drugs or insulin, developed diabetes complications, and died, and glycemic control (as determined by HbA1c levels). Disagreements in the data extraction between the reviewers will be resolved by discussion or by a third reviewer (TS).

2.5. Data Management

Articles retrieved from databases and other sources will be imported into EndNote software, and a separate EndNote file will be created for each data source. These EndNote files will then be exported as "XML" files, which will be imported into the web-based Covidence platform [31]. Covidence will be used to remove duplicate records, screen articles, resolve disagreements between the reviewers, conduct data extraction using a customized template, perform risk of bias assessment,

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create a PRISMA flowchart, and export the eligible studies for conducting meta-analysis in Review Manager (RevMan) and Stata softwares.

2.6. Risk of Bias and Certainty of Evidence

Two independent reviewers (A.T., N.B) will assess the risk of bias in included studies using the Newcastle-Ottawa Scale (NOS) [32], and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [33] framework will be used to determine the certainty of the evidence. Consensus between the reviewers will be achieved by discussion or by a third reviewer (TS).

2.7. Data Synthesis

We will stabilize the variances of incidence proportions (%) using the Freeman–Turkey Double Arcsine Transformation method [34]. The random-effects DerSimonian-Laird models [35] will then be used to pool the proportions and the incidence rate of diabetes (per 1000 person-years) across studies [35]. The pooled risk estimates for diabetes incidence will be expressed as risk ratios (and 95% CIs), which will be obtained using the one-stage DerSimonian-Laird random-effects meta-analysis [35]. We will perform a sensitivity analysis to assess the impact of unmeasured confounding on the risk ratios with "E-value" [36,37] using the methodology proposed by VanderWeele and Ding [38]. PAF in each study will be estimated using the formula [24] below, and the PAFs across studies will be pooled using the random-effects models [35].

$$PAF = \frac{P'(RR-1)}{P'(RR-1)+1}$$

P′ = Proportion of patients with COVID-19 in the entire study population.

RR = Risk Ratio

The degree of between-study heterogeneity will be 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%) [39]. Based on the data availability, we will perform sub-group analysis by age, sex, follow-up time, pandemic phase, time since the diagnosis of diabetes, type of diabetes, comorbidities, glycemic status (normal glucose tolerance or prediabetes), controls (general population or with respiratory tract infections), race or ethnicity, and country. We will assess for publication bias if 10 or more studies are included in the analysis by funnel plots [40] and Egger's test [41]. A two-sided $p<0.05$ will be considered statistically significant. Analyses will performed using RevMan version 5.4.1 and Stata software version 17.0 (StataCorp, College Station, TX, USA).

3. Discussion

This systematic review and meta-analysis aims to estimate the pooled incidence rate, risk ratio, and PAF of new-onset diabetes as a post-acute sequela of COVID-19. We will also provide data on the clinical course of new-onset diabetes cases in COVID-19 patients. The findings of this study will likely inform clinical practice, public health guidelines, and policies for early detection and treatment of new-onset diabetes in COVID-19 survivors.

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