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Review Article

Underreporting of treatment outcomes in hospitalized COVID-19 infected diabetes patients: a systematic review, meta-analysis, and meta-regression

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Abstract

Background: Prolonged inpatient care requirements and time constraints of research and researchers lead to the non-reporting of the treatment outcome of certain COVID-19 infected diabetes patients in published manuscripts. This study aims to quantify its global burden.

Methods: A search for citations addressing the above outcome ensued chiefly in the PubMed, Embase, and Scopus databases, irrespective of the publication date and geographical region. Recruited studies were critically appraised with the National Heart, Lung, and Blood Institute's tool. Using the random-effects meta-analysis with an exact binomial method and Freeman-Tukey double arcsine transformation, the overall and subgroup-wise weighted pooled prevalence of the missing treatment outcome data was determined. The heterogeneity and publication bias assessment utilized I^2 and Chi^2 statistics, and funnel plot, and Egger's test, respectively.

Results: Ten publications (primarily case series; 70.0%) included in this review sourced data from 6687 COVID-19 infected inpatient diabetes patients from Asia, Australia, Europe, and North America. The global pooled prevalence of missing treatment outcome data among these patients was 33.0% (95% CI: 15.0-53.0%; I^2: 99.53%; P of Chi^2: <0.001). It was highest in Europe (63%; 95% CI: 61.0-66.0%). Publication bias assessment was not suggestive of any small study effect.

Conclusion: A considerable proportion of crucial prognosis information of hospitalized COVID-19 patients with diabetes goes underreported. It increases the risk of biasing the contemporary COVID-19-diabetes literature. The reporting of these data in the post-publication era or postponing the primary publication until the availability of all patients' treatment outcome data, when feasible, is recommended to address this enigma.

Keywords: Coronavirus Infection, Diabetes Mellitus, Type 1, Type 2, Systematic Review, Meta Analysis, India

Background

The ongoing coronavirus disease (COVID-19) pandemic started in December 2019 in Wuhan, China [1–3]. As of April 08, 2021, almost 132 million confirmed cases of COVID-19 cases got reported globally, including about 2.8 million deaths [4]. One of the most commonly reported comorbidities determining the morbidity and mortality risk in COVID-19 patients is diabetes. Deaths among hospitalized COVID-19 patients with diabetes are substantial (almost 20% globally) and about two times higher than COVID-19 patients without diabetes [5]. Among hospitalized severe COVID-19 patients, deaths are commoner in those with diabetes than those without diabetes [5]. In the past, during the 2009-H1N1 pandemic influenza and the Middle East Respiratory Syndrome, diabetes was also a crucial determinant of death [6, 7]. The poor disease outcome in COVID-19 patients with diabetes is plausibly attributable to the damage of pancreatic islet cells caused by SARS-CoV-2 entry into the host cell via the angiotensin-converting enzyme-2 receptor [8–10]. Presently, little is known about the clinical outcomes and treatments of inpatient COVID-19 infected diabetes patients, and we must depend heavily on first-hand observational and case series studies for it. The entire COVID-19 infected inpatient diabetes patient population's treatment outcome data (e.g., morbidity, mortality, recovery, and discharge) remain unavailable in some of these studies since some of these patients remain hospitalized when these studies' manuscripts are prepared or published. Such non-reporting may be due to the time constraints imposed by the study funder, the end of the pre-defined follow-up period of the study, and referral of severe COVID-19 cases to different health facilities

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making their tracking difficult or impossible for the primary investigators. Quantifying the burden of such patients whose prognostic data go missing from the contemporary COVID-19 literature is crucial to ensure the comprehensiveness and rigor of this literature. This systematic review and meta-analysis aim to quantify this burden by estimating its pooled prevalence.

Methods

Registration

This systematic review is pre-registered in the PROSPERO (CRD42020197319) [11] and reported here according to The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)2020 statement (Supplementary Table S1) [12]. A pre-published protocol does not exist.

Inclusion criteria

We included studies that fulfilled the following inclusion criteria:

1. Study population: Hospitalized COVID-19 infected diabetes patients of any age or gender.
2. Study design: Observational studies, including case series conducted in any country.
3. Outcome: The outcome of interest is the number of patients whose post-hospitalization treatment outcome (i.e., discharge from hospital or death) was not reported in the published manuscript.

Exclusion criteria

1. Studies conducted on pregnant patients.
2. Experimental study designs, case reports, letters, and editorials.
3. Studies that were reporting of treatment outcomes of its entire sample population.

Data Source:

We searched the title and abstract of eligible citations published in the English language in three electronic databases (PubMed, Embase, and Scopus) irrespective of the publication date or geographical boundary. Subsequent search terms were used to search the PubMed database: "diabetes mellitus, type 2"(MeSH Major Topic) OR "diabetes mellitus, type 1"(MeSH Major Topic) OR "diabetes mellitus"(MeSH Major Topic) AND "coronavirus infections"(MeSH Major Topic) AND diabetes AND SARS-CoV-2 OR Coronavirus OR COVID-19 NOT "Middle East respiratory syndrome" NOT MERS. Table S2 provides the detailed search strategy used to search different databases. Additional searches ensued in the bibliography of the articles included in this review and the 'Google' search engine.

Study selection and data abstraction

After uploading the retrieved citations from the database search and additional searches to a reference management software, the review authors independently skimmed through it to identify dubious and seemingly eligible articles for full-text reading and subsequently finalized the list of articles to be reviewed. Data abstraction from the studies included in this review happened for the following components - the nation and continent of the conduct of the study, follow-up duration of the study, the total number of inpatient COVID-19 infected diabetes patients, the total number of these patients whose prognosis data did not get reported in the article, type of diabetes detected in the study population, diagnostic guideline or criteria used to diagnose diabetes, diagnostic techniques used to ascertain COVID-19 infection, the average age of the study population, and the study design. These details are presented in. a tabular form. Pre-piloted data abstraction sheets were used to abstract the data.

Risk of bias evaluation

The reviewed studies' risk of bias assessment transpired via the National Heart, Lung, and Blood Institute's tool.[13] The 'yes' or 'no' categorization followed for each study's respective risk of bias components, based on if a study did or did not address this, respectively. If such judgment was not possible, 'cannot determine' or 'not applicable' labeling ensued based on whichever was the best applicable categorization.

Review authors' role

The review authors conducted the study selection, data abstraction, and critical appraisal independently, and resolved any conflict in an opinion by discussion, and did not require a third-party consultation.

Meta-analysis

From published manuscripts, estimation of the pooled weighted prevalence of missing treatment outcome data of hospitalized COVID-19 infected diabetes patients ensued by random effect (DerSimonian and Laird) meta-analysis. The 95% confidence interval (CI) and variance stabilization transpired using the exact binomial method and Freeman-Tukey double arcsine transformation, respectively. Heterogeneity estimation happened by I^2 statistics (at values 25, 50, and 75% heterogeneity were categorized as low, moderate, and high, respectively) [14] and p-value of Chi^2 statistics (statistically significant at $p<0.1$). The meta-analysis findings are presented using a forest plot and table.

Subgroup analysis

The subgroup-wise weighted prevalence estimation of missing prognosis data transpired for continents, countries, diabetes types, and sample size (≤100 versus >100).

Publication bias

Small study effects got evaluated using visually and statistically by funnel plots and Egger's test, respectively.

Heterogeneity assessment

A univariate meta-regression analysis (random-effect) ensued for each of the above-stated subgrouping variables to explain heterogeneity, and its statistical significance was determined at $p<0.1$. As none of these models produced a statistically significant outcome, we did not include these variables in an adjusted meta-regression model.

Sensitivity analysis

We repeated the overall pooled prevalence meta-analysis by dropping a study each time to see how each study contributed to the meta-analysis model. Stata statistical software (version 16) of StataCorp, College Station, Texas, USA, and MetaProp [15] package was used for the analysis.

Results

Scope of this review

The database search and additional searches retrieved altogether 996 citations, of which 779 records got skimmed following the elimination of duplicates. Out of the 54 articles requiring full-text reading, ten publications published in 2020 got included in this review (Figure 1) [16–25]. The primary reason for excluding papers read in full-text was non-reporting the outcome data of interest (61.0%; n=27). The last date of the search was 19-Nov-2020. Majority of the recruited studies were case series (70.0%) [16–22], followed by cross-sectional studies (20.0%) [23, 24] and retrospective cohort study (10.0%) [25].

The data of the recruited studies came from 6687 COVID-19 infected inpatient diabetes patients from four continents (Asia, Australia, Europe, and North America). Most of these patients belonged to the US (76.8%; n=5137). About 20.7% (n=1386) of the hospitalized COVID-19 patients with diabetes had either type 1 or 2 diabetes, another 1.3% (n=87) had type 2 diabetes, and for the remaining study participants, the exact diabetes type remains unknown. The salient features of the reviewed studies got presented in Table 1.

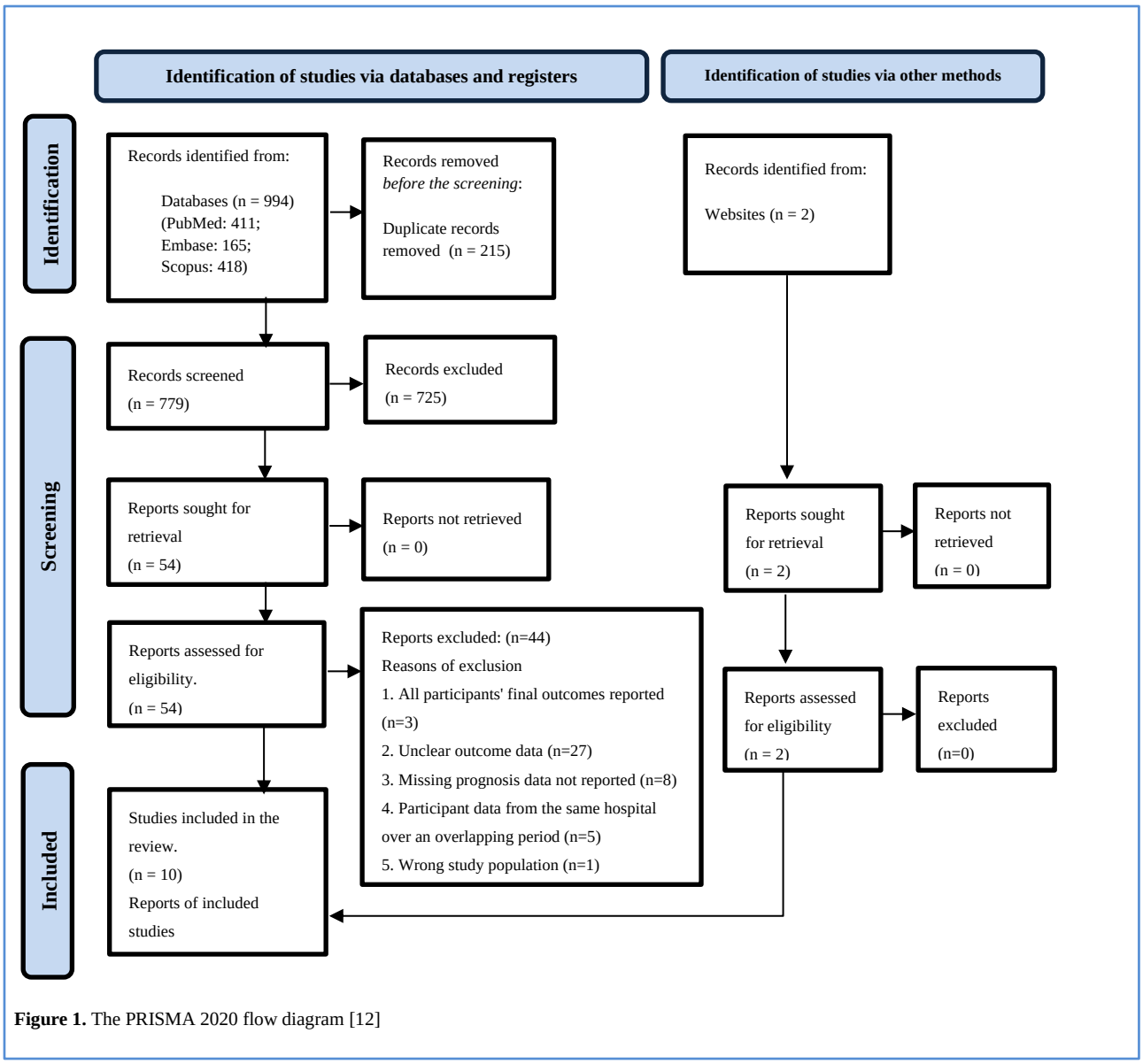

Figure 1. The PRISMA 2020 flow diagram [12]

Risk of bias evaluation

Upon critical appraisal, the case series were of fair quality [16–22], whereas the remaining study types were of good quality [23–25]. Table 2 depicts the study design-specific risk of bias assessment for the respective studies.

Meta-analysis findings

The overall pooled weighted prevalence of inpatient COVID-19 infected diabetes patients whose outcome data did not get reported in COVID-19 literature was 33.0% (95% CI: 15.0-53.0%; I^2: 99.53%; P of Chi^2: <0.001) (Figure 2). Subgroup-wise, among the four continents, it was highest in studies conducted in Europe (63%; 95% CI: 61.0-66.0%). The latter was about three times higher than North America (24%; 95% CI: 3.0-55.0%; I^2: 99.75%; P of Chi^2 <0.001). The proportion of missing treatment outcome data reporting among hospitalized COVID-19 infected diabetes patients was marginally higher (5%) in studies with a larger sample size (i.e., n >100) (Table 2).

Publication bias and heterogeneity assessment

On visual inspection, the funnel plots appeared somewhat symmetrical (Figure 3). The statistical evaluation of the small study effect did not suggest any publication bias (p = 0.617). The univariate meta-regression analysis was not statistically significant for any of the predictors (Table 3).

Sensitivity analysis

On iterating the meta-analysis while dropping a study each time, the prevalence varied between 29-37%.

Discussion

Altogether, this review included ten articles published in 2020 reporting of 6687 COVID-19 infected diabetes patients sourcing from Asia, Australia, Europe, and North America. Meta-analysis suggested a considerable underreporting of the treatment outcome data of hospitalized COVID-19 infected diabetes patients. This non-reporting was highest in Europe. Juxtaposing this review's findings with other review articles on COVID-19 was beyond the scope due to conceptual novelty and the non-availability of identical review articles.

Implications

While the number of COVID-19-diabetes-related publications soars at an unprecedented rate during the ongoing SARS-CoV-2 pandemic, it is vital to evaluate the completeness and rigor of this novel evidence. In this regard, the findings of this paper may serve as an identifier and reminder of the bulk of crucial prognosis data lost from the contemporary COVID-19-diabetes literature due to underreporting and may encourage researchers to take initiatives to ensure completeness of prognosis data reporting among COVID-19 infected hospitalized diabetes patients. It emphasizes the plausible constraints of COVID-19 research in the context, like limitations in funding or available time to ensure complete reporting of studies. Given the substantial burden of underreported prognostic data, policymakers may consider fetching regular updates from the researchers to calibrate the existing policies accordingly.

Strengths and weaknesses

The key strength of this study is its uniqueness in exploring an unexplored area of COVID-19-diabetes literature. Besides, this review is likely to be comprehensive as its literature search did not get restricted to any date range or geographic boundary. Despite these strengths, our systematic review has a few weaknesses. This review could not include potential studies published in the non-English language since the authors are not adept in any other language. Besides, our estimates are based on observational study designs, considered to be a weaker source of evidence than randomized clinical trials.

Conclusion

Globally, the under-reporting of hospitalized COVID-19 infected diabetes patients' treatment outcomes is substantial. It increases the threat of biasing the expanding COVID-19 literature. The researchers may consider releasing such initially non-published prognostic data as adjunct reports in the post-publication period to decrease the risk of such bias. Journals might also take the initiatives to permanently identify such updated supplementary reports by providing digital object identifiers and electronically linking these to the parent publication. Alternatively, when feasible, the researchers may defer their manuscript drafting until the treatment outcomes of all admitted patients are known.

Abbreviation

CI: Confidence interval; COVID-19: coronavirus disease; PRISMA: The Preferred Reporting Items for Systematic Review and Meta-Analysis

Declaration

acknowledgment

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Availability of data and materials

Data will be available by emailing sumanta.saha@uq.net.au on receiving a legitimate request

Authors' contributions

Sumanta Saha designed and conceptualized this study analyzed and drafted this manuscript's first and final draft. Both authors participated in study selection, data abstraction, and critical appraisal. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

We conducted the research following the Declaration of Helsinki. However, Review Articles need no ethics committee approval.

Consent for publication

Not applicable

Competing interest

The authors declare that they have no competing interest.

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Table 1. Salient findings of the reviewed studies

Author, year	Country	Continent	Dates	Total diabetes admissions	Missing prognosis data	Diabetes type	Diabetes diagnosis method	COVID-19 diagnosis method	Mean age of the study population*	Study design
Agarwal, 2020[23]	US	North America	March 11 to May 07, 2020	1279	87	Unclear	Clinical Modification code or HbA1c ≥6.5%	RT-PCR	Mean±SD:18 6 20 (n=1,279)	Cross-sectional
Cariou, 2020[16]	France	Europe	March 10 to April 10, 2020	1317	877	Type 1 and 2 diabetes	Personal history or HbA1c ≥6.5%	RT-PCR	Mean±SD:169.8 ± 13.0 (n=1,317)	Case series
Ciceri, 2020[17]	Italy	Europe	February 25 to March 24, 2020	69	5	Type 1 and 2 diabetes	Unclear	RT-PCR	Median (IQR): 65 (56–75) (n= 410)	Case series
Croft, 2020[18]	US	North America	Unclear	5	1	Type 2 diabetes	Unclear	RT-PCR	Mean: 49 years; (n=5)	Case series
Liu, 2020[24]	China	Asia	January 16, 2020, to March 16, 2020	19	13	Unclear	Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2017 edition)	seventh Trial Version of the Novel Coronavirus Pneumonia Diagnosis and Treatment Guidance	DM patients (mean ±SD): non-critical (61.57 ± 12.01), critical (59.36 ± 12.31)	Cross-sectional
Marcello, 2020[19]	US	North America	March 05 to April 16	2045	420	Unclear	Unclear	RT-PCR	Median (IQR): 50.2 (36.6-61.9); (n=22176)	Case series
Richardson, 2020[20]	US	North America	March 01 to April 04	1808	1051	Unclear	Unclear	RT-PCR	Median (IQR): 63 (52-75) (n=5700)	Case series
Wu, 2020[21]	Australia	Australia	March 20 and May 01, 2020	8	2	Type 2 diabetes	Unclear	Unclear	Mean±SD: 55±11.9 years (n=8)	Case series
Zhang, 2020a[22]	China	Asia	January 03 to April 14, 2020	74	10	Type 2 diabetes	Unclear	Chinese National Health Committee (version 5).	Median (IQR): 62(56–72) (n=74)	Case series
Zhang, 2020b[25]	China	Asia	January 29 to February 12	63	40	Unclear	medical history and guidelines for the prevention and control of T2DM in China	World Health Organization interim guidance	Median (IQR): 65 (57–71) (n of diabetes patients=63)	Retrospective cohort study

*n is the total sample size for which demographic data are presented in the respective studies

Abbreviations: IQR: interquartile range; RT-PCR: Reverse transcription-polymerase chain reaction; SD: standard deviation

Table 2. Overall and subgroup weighted prevalence of missing prognosis data among inpatient COVID-19 patients with diabetes

Subgroup	Category	Number of Studies	Number of admitted COVID-19 patients with diabetes	Number of admitted COVID-19 patients with diabetes with missing prognosis data	Mean prevalence of missing prognosis data in COVID-19 infected patients with diabetes		Heterogeneity measures	
					%	95% CI	I^2 (%)	Chi^2 (p-value)
Continent	Asia	3	156	63	46	11.0-84.0	-	-
	Australia	1	8	2	25	3.0-65.0	-	-
	Europe	2	1386	882	63	61.0-66.0	-	-
	North America	4	5137	1559	24	3.0-55.0	99.75	<0.001
Country	Australia	1	8	2	25	3.0-65.0	-	-
	China	3	156	63	46	11.0, 84.0	-	-
	France	1	1317	877	67	64.0-69.0	-	-
	Italy	1	69	5	7	2.0-16.0	-	-
	US	4	5137	1559	24	3.0-55.0	99.75	<0.001
Diabetes type	Both type 1 and 2	2	1386	882	63	61.0-66.0	-	-
	Type 2	3	87	13	12	5.0-21.0	-	-
	Unclear	5	5214	1611	40	16.0, 67.0	99.68	<0.001
Sample size	≤100	6	238	71	31	8.0-59.0	93.43	<0.001
	>100	4	6449	2435	36	11.0-66.0	99.84	<0.001
Overall		10	6687	2506	33	15.0-53.0	99.53	<0.001

Abbreviation: CI: confidence interval

Table 3. Univariate meta-regression analysis for the prevalence studies on missing prognosis data of COVID-19 patients with diabetes.

Subgroup	Category	Univariate model		
		OR	P-value	95% CI
Continent	North America	1		
	Asia	2.95	0.389	0.17, 50.72
	Australia	1.17	0.929	0.02, 75.60
	Europe	1.386	0.812	0.06, 34.95
Country	US	1		
	Australia	1.17	0.919	0.03, 51.58
	China	2.95	0.332	0.22, 39.06
	France	7.00	0.243	0.16, 307.79
	Italy	0.27	0.420	0.01, 12.06
Diabetes type	Unclear	1		
	Both type 1 and 2	0.63	0.707	0.04, 10.47
	Type 2	0.37	0.376	0.03, 4.37
Sample size	≤100	1		
	>100	1.21	0.841	0.15, 9.86

Abbreviations: CI: confidence interval; OR: odds ratio

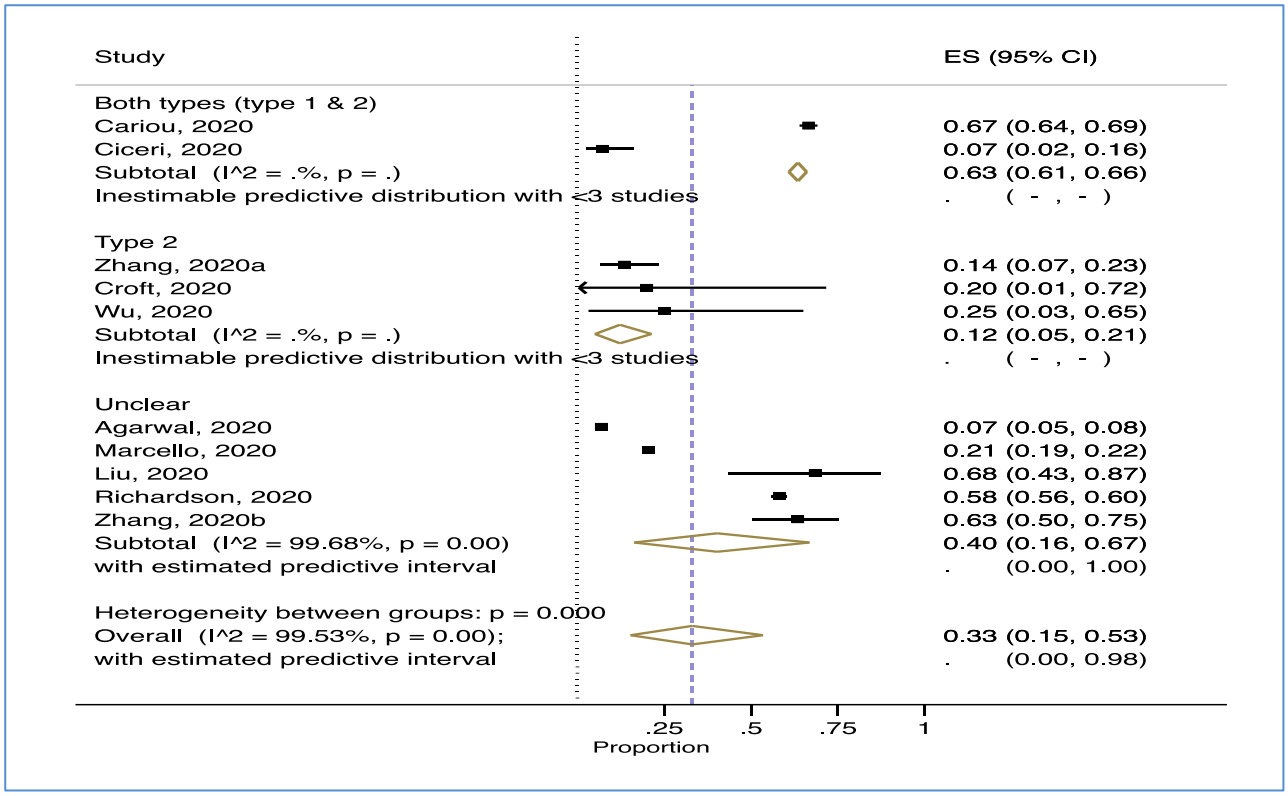

Figure 2. Forest plot depicting the overall pooled prevalence of missing prognosis data of COVID-19 infected diabetes patients; Zhang, 2020a[22], Zhang, 2020b[25] The diamonds are centered on the summary of the overall and subgroup-wise prevalence estimates, and their widths indicate the corresponding 95% CI.

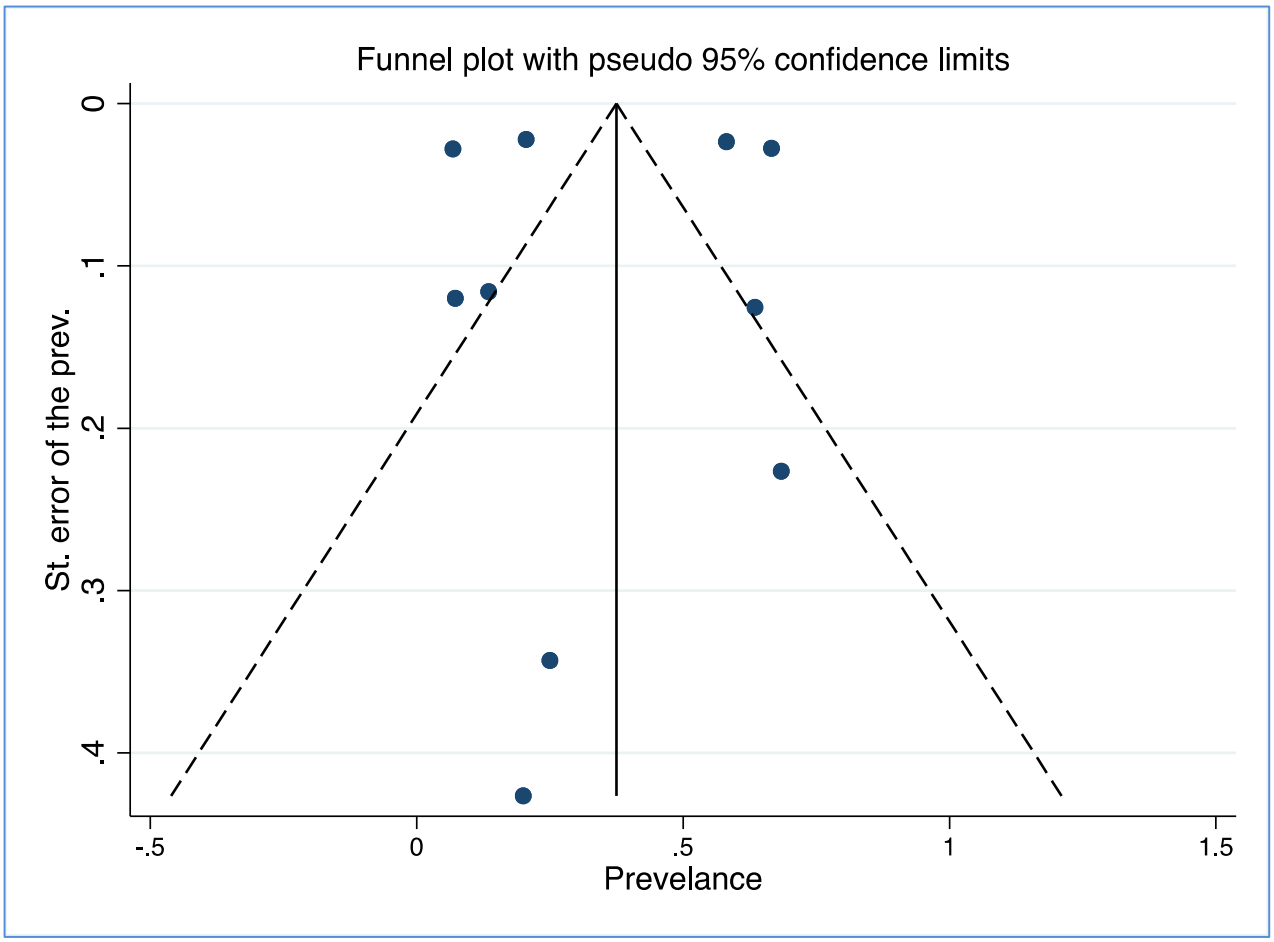

Figure 3. Funnel plot assessing small study effect on pooled prevalence among hospitalized COVID-19 patients with diabetes.

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