Effects of Sodium-Glucose Cotransporter 2 on Amputation Events: A Systematic Review and Meta-Analysis of Randomized-Controlled Trials

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Key Points

What is new?

- Across 15 randomized-controlled trials with a combined cohort of 63,716 patients, there was no significant difference in amputation events across different types of sodium-glucose cotransporter 2 (SGLT2) inhibitors, different baseline populations, and different duration of SGLT2 inhibitor use.

What are the clinical implications?

- This study will aid physicians in assessing the risk of amputations when initiating treatment with SGLT2 inhibitors.

Keywords

Sodium-glucose cotransporter 2 inhibitors · Amputations

Abstract

Introduction: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are increasingly utilized in the treatment of diabetes mellitus as well as therapeutic extra-glycemic effects. However, there are still concerns over complications such as amputation events, given the results from the Canagliflozin Cardiovascular Assessment Study (CANVAS) trial. Hence, we

conducted a systematic review and meta-analysis of randomized-controlled trials to investigate the effect of SGLT2 inhibitors on amputation events. **Methods:** Four electronic databases (PubMed, Embase, Cochrane, and SCOPUS) were searched on November 21, 2020, for articles published from January 1, 2000, up to November 21, 2020, for studies that examined the effect of SGLT2 inhibitors on amputation events. Random-effect pair-wise meta-analysis for hazard ratios and fixed-effect Peto odds ratio meta-analysis were utilized to summarize the studies. **Results:** A total of 15 randomized-controlled trials were included with a combined

cohort of 63,716 patients. We demonstrated that there was no significant difference in amputation events across different types of SGLT2 inhibitors, different baseline populations, and different duration of SGLT2 inhibitor use. **Discussion/Conclusions:** In this meta-analysis, SGLT2 inhibitors were not associated with a significant difference in amputation events.

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Introduction

The sodium-glucose cotransporter 2 (SGLT2) inhibitor is an increasingly utilized treatment option for diabetic and heart failure patients [1]. It reduces glucose reabsorption via inhibiting SGLT2 receptors in the proximal convoluted tubules of the kidneys, improving glycemic control in patients [2]. This provides another pharmacotherapeutic option to tackling diabetes [3].

In addition, many studies have demonstrated the extra-glycemic benefits of SGLT2 inhibitors, including weight loss [4], blood pressure reduction [5], reduction in cardiovascular events [6–8], and improvement in renal function [9]. A previous meta-analysis of randomized-controlled trials also showed similar metabolic and cardiovascular benefits extending to nondiabetic patients [1].

Although SGLT2 inhibitors have been included in cardiovascular guidelines [10], some clinicians are still concerned about the risk of amputation with the use of these drugs. Notably, in the 2017 Canagliflozin Cardiovascular Assessment Study (CANVAS) trial [11], patients in the study group who were administered canagliflozin had more amputation events than patients receiving placebo (6.3 vs. 3.4 participants affected per 1,000 person-years). However, the amputation events reported among other SGLT2 inhibitor trials were variable, with other trials showing no difference when compared to placebo or even a decrease in amputation events [7, 12–14].

In a previous meta-analysis of 3 studies published in 2019, the odds ratio for amputation was insignificant with SGLT2 inhibitor use [15]. With the recent publication of more SGLT2 inhibitor clinical trials [7, 14, 16–21], we believe that it is timely to conduct an updated meta-analysis examining the hazard ratio (HR) and Peto odds ratio (POR) for amputation events with SGLT2 inhibitors as compared to placebo, given that the concerns of risk of amputation still exist. Hence, we conducted an updated systematic review and meta-analysis to determine the risk of amputation events of different SGLT2 inhibitors in

both diabetic and nondiabetic patients. We hypothesized that the risk of amputation events was not associated with SGLT2 inhibitor use, irrespective of SGLT2 inhibitor type and the diabetic status of patients.

Methodology

The data that support the findings of this study are available from the corresponding author upon reasonable request. The meta-analysis was reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. Searches of 4 databases (PubMed, Embase, Cochrane, and SCOPUS) were conducted on November 21, 2020, for articles published from January 1, 2000, up to November 21, 2020.

Studies evaluating the number of amputation events from the use of SGLT2 inhibitors were included. Comparisons were done against the placebo group, and the HRs/PORs for the relevant studies were analyzed. We included all randomized-controlled trials, according to the Population, Intervention, Comparison, Outcome, and Study design (PICOS) inclusion and exclusion criteria (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000520903). We excluded all studies which did not report amputation events.

Four reviewers independently conducted the literature search and data extraction, and all conflicts were resolved by mutual consensus. During the title and abstract review stage, an “inclusive” approach was utilized, where only studies that clearly fit the exclusion criteria such as the study being a nonclinical trial or not involving SGLT2 inhibitor use were excluded; the rest of the studies were included. Clinical trials involving SGLT2 inhibitors were selected for full-text review to identify if subgroup analysis of amputation events was performed.

Apart from amputation events, baseline information in all studies were collected for age, sex, body weight, body mass index, systolic blood pressure, diastolic blood pressure, glycated hemoglobin, low-density lipoprotein cholesterol, and comorbidities. For studies involving diabetic patients, information on proportion of type 1 diabetes mellitus, type 2 diabetes mellitus, and duration of diabetes mellitus was collected. For the SGLT2 inhibitor regimes, we collected data of the drug name, drug dosage, drug frequency, control group, length of intervention, and mean length of follow-up. Data relating to blinding and withdrawals were extracted to assess the risk of bias. Quality control was performed by 2 independent reviewers using the Cochrane Risk of Bias tool, which assesses 7 domains (random sequence generation, allocation concealment, masking of participants and personnel, blinding of outcome assessment; incomplete outcome data, selective outcome reporting, and other sources of bias) (online suppl. Fig. 1). The quality of pooled evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [23], which accounts for statistical heterogeneity, publication bias, risk of bias, indirectness, and statistical imprecision, as shown in Table 1. Publication bias was assessed via visual inspection of funnel plot with no data points lying outside of pseudo-confidence intervals [24, 25] (online suppl. Fig. 2, 3). A PRISMA checklist [26] is included in online supplementary Figure 4.

Table 1. GRADES assessment

Outcomes	Pooled outcomes (95% CI)	Patients (included studies, <i>n</i> , <i>n</i>)	Statistical heterogeneity	Quality of evidence (GRADE)
HR				
Amputation events	HR 1.33 (0.92–1.92)	31,703 (3 trials)	$I^2 = 77\%$ ($p = 0.01$)	⊕⊕⊕⊕ ^a
Amputation events by canagliflozin	HR 1.48 (0.84–2.60)	14,543 (2 trials)	$I^2 = 82\%$ ($p = 0.02$)	⊕⊕⊕⊕ ^{a, b}
POR				
Amputation events	POR 1.12 (0.91–1.38)	36,070 (17 trials)	$I^2 = 0\%$ ($p = 0.72$)	⊕⊕⊕⊕
Amputation events in heart failure patients	POR 1.08 (0.49–2.38)	5,104 (3 trials)	$I^2 =$ not applicable	⊕⊕⊕⊕ ^a
Amputation events in chronic kidney disease patients	POR 0.94 (0.68–1.32)	15,168 (3 trials)	$I^2 = 0\%$ ($p = 0.57$)	⊕⊕⊕⊕
Amputation events in type 1 diabetes patients	POR 7.42 (0.77–71.31)	4,531 (7 trials)	$I^2 = 0\%$ ($p = 1.00$)	⊕⊕⊕⊕
Amputation events in type 2 diabetes patients	POR 1.17 (0.92–1.49)	22,137 (6 trials)	$I^2 = 0\%$ ($p = 0.65$)	⊕⊕⊕⊕
Amputation events by dapagliflozin	POR 0.96 (0.65–1.43)	9,590 (4 trials)	$I^2 = 0\%$ ($p = 0.54$)	⊕⊕⊕⊕
Amputation events by empagliflozin	POR 7.39 (0.15–372.38)	2,535 (4 trials)	$I^2 =$ not applicable	⊕⊕⊕⊕ ^a
Amputation events by sotagliflozin	POR 1.03 (0.64–1.66)	12,678 (5 trials)	$I^2 = 1\%$ ($p = 0.37$)	⊕⊕⊕⊕
Amputation events for trials with <1 year of intervention	POR 7.47 (0.47–119.37)	1,143 (4 trials)	$I^2 = 0\%$ ($p = 0.99$)	⊕⊕⊕⊕ ^b
Amputation events for trials with 1 year of intervention	POR 7.43 (0.46–118.82)	4,333 (8 trials)	$I^2 = 0\%$ ($p = 0.99$)	⊕⊕⊕⊕
Amputation events for trials with >1 year of intervention	POR 1.10 (0.89–1.35)	30,594 (5 trials)	$I^2 = 0\%$ ($p = 0.78$)	⊕⊕⊕⊕
Sensitivity analysis with exclusion of Yale et al. [34]	POR 1.12 (0.91–1.38)	35,786 (15 trials)	$I^2 = 0\%$ ($p = 0.72$)	⊕⊕⊕⊕

HR, hazard ratio; POR, Peto odds ratio; GRADE, Grading of Recommendations Assessment, Development, and Evaluation. ^a Downgraded by 2 levels for substantial statistical heterogeneity. ^b Downgraded by 1 level for statistical imprecision.

Statistical Analysis

The results were quantitatively pooled and analyzed using Review Manager version 5.4, using general approaches laid out by the Cochrane Handbook. For studies with results that factored in the length of intervention, HRs were reported and analyzed using the inverse variance method. For studies with results that did not factor in the length of intervention, PORs were reported and analyzed [27]. As amputation events are rare adverse events, some studies have zero reported events and the POR analysis has been observed to be the least biased and most powerful method for event rates below 1% [28]. This provides the best confidence interval coverage which was consistently observed across 3 different meta-analytical scenarios [29]. Corrections for results with zero counts are not necessary when using the POR method, allowing analysis when events are very rare [30]. Random-effect models were performed to account for between-study variance in scenarios where the POR fixed-effect model was not preferred. In our study, the random-effect model was performed for “HR for amputations outcome” and “subgroup analysis for Canagliflozin,” and the POR fixed-effects model was utilized in all other analyses. Between-study heterogeneity was presented using I^2 and τ^2 statistics. We considered I^2 of <30% to indicate low heterogeneity between studies, 30–60% to indicate moderate heterogeneity, and >60% to indicate substantial heterogeneity. Two-sided p values of <0.05 were regarded to indicate nominal statistical significance. Subgroup analyses were performed for different types of SGLT2 inhibitors, different baseline populations, and duration of SGLT2 inhibitor intervention.

Results

The PRISMA flowchart is presented in online supplementary Figure 5. Literature search of the 4 databases (PubMed, Embase, Cochrane, and SCOPUS) retrieved 6,755 results, and hand search did not uncover any additional studies. Two thousand four hundred thirty-seven duplicates were removed. Title and abstract screening excluded a further 4,004 studies. Full-text screening excluded 329 studies. Fifteen studies were included for the meta-analysis. In addition, some studies reported different doses of SGLT2 inhibitor, and these doses were analyzed separately [16, 31–34].

Baseline Characteristics

The 15 studies comprised a combined cohort of 63,716 patients. The participant baseline characteristics of the included studies are shown in Table 2. Across the 15 studies, the SGLT2 inhibitor drug name, dosage, frequency, length of intervention, and length of follow-up was summarized and is attached in online supplementary Table 2.

Pooled HR for Amputation

The pooled amputation outcomes reported in HRs were analyzed in Figure 1. Comparing the 3 studies [11, 13, 19], the random-effects model did not show any sig-

Table 2. Baseline characteristics of studies

Author	Sample size	Sample size (diabetes)	T1 diabetes	T2 diabetes	Duration of diabetes, years	Age (mean)	Males	Current smoker	HTN	HLD	Obesity	Systolic blood pressure (mean)	Diastolic blood pressure (mean)	Body mass index/kg/m ² (mean)	HbA1c, %	LDL-C (mean)	History of heart disease (includes angina/MI, etc.)	History of stroke	History of kidney disease
Neal et al. [11]	10,142	10,142	0	10,142	13.5	63.3	6,509	1,806	9,125	NR	NR	136.6	77.7	32	8.2	2	6,656	NR	NR
Wiviott et al. [13]	17,160	17,160	0	17,160	10.5	63.95	10,738	NR	NR	NR	NR	134.95	NR	32.05	8.3	NR	5,658	NR	NR
Pertkovic et al. [19]	4,401	4,401	0	4,401	15.8	63	2,907	639	4,260	NR	NR	140	78.3	31.3	8.3	96.4	2,220	NR	4,401
Cannon et al. [16]	8,246	8,246	0	8,246	13	64.4	5,769	NR	NR	NR	NR	133.3	76.7	32	8.2	89.1	6,256	1,739	NR
Pollock et al. [21]	293	293	0	293	17.6	64.7	207	NR	NR	NR	NR	139.1	76.3	45.4	8.5	2.35	NR	NR	NR
Bhatt et al. [17]	10,584	10,584	0	10,584	NR	69	5,830	NR	NR	NR	NR	(median) 138.5	78	31.8	8.3	NR	NR	946	NR
Heerspink et al. [14]	4,304	2,906	0	2,906	NR	61.85	2,879	584	NR	NR	NR	137.05	77.5	29.5	NR	NR	NR	NR	4,304
Buse et al. [31]	793	793	793	0	24.4	46.1	383	NR	NR	NR	NR	120.1	76.1	29.66	7.57	NR	NR	NR	NR
McMurray et al. [7]	4,744	1,983	0	1,983	NR	66.35	3,635	NR	NR	NR	NR	NR	NR	28.2	NR	NR	4,744	NR	NR
Rosenstock et al. [33]	723	723	723	0	22.6	45.2	338	NR	NR	NR	NR	124.6	76.2	29.2	8.1	NR	NR	NR	NR
Ease-2																			
Rosenstock et al. [33]	961	961	961	0	21	43.1	469	NR	NR	NR	NR	123.5	75.6	28.2	8.18	NR	NR	NR	NR
Ease-3																			
Yale et al. [34]	215	215			9.9	64.8	120	NR	NR	NR	91	NR	NR	NR	8.4	NR	NR	NR	NR
Danne et al. [32]	782	782	782	0	18.4	41.2	406	NR	NR	NR	234	123.1	76.6	27.77	7.75	NR	Exclusion criteria	Exclusion criteria	NR
Nassif et al. [18]	263	166	0	166	NR	61.3	193	NR	NR	NR	NR	123.6	NR	30.7	7.15	NR	139	NR	NR
Lee et al. [20]	105	82	0	82	9.7	68.7	77	NR	NR	NR	NR	128	NR	30.7	7.2	NR	NR	NR	NR

HbA1c, glycated hemoglobin; hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; NR, not reported.

nificant difference in hazard rate (HR was 1.33 [95% CI: 0.92–1.92, $p = 0.13$]). Subgroup analysis for canagliflozin was done for 2 of the studies [11, 19], but there was no significant difference in hazard rate (HR was 1.48 [95% CI: 0.84–2.60, $p = 0.17$]) (online suppl. Fig. 6).

Pooled POR for Amputation

The pooled amputation outcomes reported in POR were analyzed in Figure 2. Comparing 12 studies, there was no significant difference in POR (POR was 1.12 [95% CI: 0.91–1.38], $p = 0.27$). Subgroup analysis of 3 studies with baseline population of heart failure patients [7, 18, 20] did not show any significant difference in POR (POR was 1.08 [95% CI: 0.49–2.38], $p = 0.84$) (online suppl. Fig. 7). Subgroup analysis of 3 studies with baseline population of chronic kidney disease patients [14, 17, 21] did not show any significant difference in POR (POR was 0.94 [95% CI: 0.68–1.32], $p = 0.73$) (online suppl. Fig. 8). Subgroup analysis of 4 studies with baseline population of solely type 1 diabetes mellitus patients [31–33] did not show any significant difference in POR (POR was 7.42 [95% CI: 0.77–71.31], $p = 0.08$) (online suppl. Fig. 9). Subgroup analysis of 4 studies with baseline population of solely type 2 diabetes mellitus patients [16, 17, 21, 34] did not show any significant difference in POR (POR was 1.17 [95% CI: 0.92–1.49], $p = 0.20$) (online suppl. Fig. 10).

Subgroup analysis was also done for different types of SGLT2 inhibitors. For dapagliflozin, 4 of the studies [7, 14, 18, 21] were analyzed and there was no significant difference in POR (POR was 0.96 [95% CI: 0.65–1.43], $p = 0.84$) (online suppl. Fig. 11). For empagliflozin, 3 of the studies [20, 33] were analyzed and there was no significant difference in POR (POR was 7.39 [95% CI: 0.15–372.38], $p = 0.32$) (online suppl. Fig. 12). For sotagliflozin, 3 of the studies [17, 31, 32] were analyzed and there was no significant difference in POR (POR was 1.03 [95% CI: 0.64–1.66], $p = 0.90$) (online suppl. Fig. 13).

Subgroup analysis was further done for length of intervention with SGLT2 inhibitor. For studies with <1 year of intervention, 4 studies [18, 20, 21, 33] were analyzed and there was no significant difference in POR (POR was 7.47 [95% CI: 0.47–119.37], $p = 0.16$) (online suppl. Fig. 14). For studies with 1 year of intervention, 4 studies [31–34] were analyzed and there was no significant difference in POR (POR was 7.43 [95% CI: 0.46–118.82], $p = 0.16$) (online suppl. Fig. 15). For studies with >1 year of intervention, 4 studies [7, 14, 16, 17] were analyzed and there was no significant difference in POR (POR was 1.10 [95% CI: 0.89–1.35], $p = 0.37$) (online suppl. Fig. 16).

Fig. 1. HR of amputation outcomes. HR, hazard ratio.

Fig. 2. POR of amputation outcomes. POR, Peto odds ratio.

Characteristics of Included Studies

The individual breakdown of the risk of bias and study characteristics are summarized in online supplementary Table 3. Most studies were assessed to have a low or unclear risk of selection bias (random sequence generation and allocation concealment), performance bias, detection bias, and other bias. One study experienced high dropout rates, contributing to a high potential risk of attrition bias; Yale et al. [34] reported that 17.7% study participants did not complete the study. Yale et al. [34] also did not account for other confounders in diabetic treatment, contributing to a high risk of selective reporting bias.

Discussion

In this meta-analysis of 15 randomized-controlled trials of SGLT2 inhibitors for diabetic and nondiabetic patients, we demonstrated that there was no significant difference in hazard rate or risk of amputations for the various SGLT2 inhibitors compared to placebo. In addition, subgroup analysis of different types of SGLT2 inhibitors, different baseline populations, and duration of SGLT2 inhibitor intervention did not show any significant difference in hazard rate or risk of amputations as well.

Amputations are one of the major complications of diabetes associated with high morbidity and mortality, and diabetic patients are 8 times more likely to suffer from amputations compared to nondiabetic patients [35]. Various studies have quantified the extent of disease

burden, such as a 2017 study showing that the financial burden was an average of US \$10,827 per diabetic foot admission, US \$13,580 for every minor amputation, and US \$73,813 for major amputations [36]. As such, while effective diabetic control through antihyperglycemic agents is crucial to reduce disease burden of diabetes, it is essential to validate the amputation risks of SGLT2 inhibitors to ensure it is not a counterproductive treatment option.

It is important to highlight that in the 2017 CANVAS program [11], while there was a significant increase in amputation events for the canagliflozin group compared to placebo, there were several comorbidities that could have confounded the outcomes. The trial mentioned that history of amputations, peripheral vascular disease, or major adverse cardiovascular events might have led to increased amputation events in some patients [37]. In addition, the data from the CANVAS program combined the CANVAS and CANVAS-Renal trials. The CANVAS trial had 100-mg canagliflozin and 300-mg canagliflozin intervention groups whereas CANVAS-Renal trial only had 100-mg canagliflozin with an optional increase to 300 mg. However, the reported HR for amputations derived from the program did not differentiate between the 100-mg and 300-mg canagliflozin intervention groups, so it is unclear if amputation events were dose-related.

The US Federal Drug Association investigated the safety profile of canagliflozin and concluded that there was no definite causative link between canagliflozin exposure and amputation events [38]. The European Medicines Agency also evaluated canagliflozin and concluded a potential amputation risk for diabetic foot disease patients, although the results were based largely from the CANVAS trial and no clear mechanism was identified [39]. Furthermore, the 2019 Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) was another major trial on canagliflozin [19], but there was no significant increase in amputation events for the canagliflozin group compared to placebo. There was no evidence to show the reason for difference in outcomes as well [40]. Similarly, the trials on empagliflozin [6] as well as dapagliflozin [13] did not show any significant increase in amputation events for the respective SGLT2 inhibitors compared to placebo. To the best of our knowledge, this is the largest meta-analysis to date comprising 15 randomized-controlled trials and the only meta-analysis examining the risk ratio and HR of amputations with SGLT2 inhibitor use, compared to placebo. We demonstrated that com-

pared to placebo, across different subgroups and different types of SGLT2 inhibitor use that there was no significant associated risk of amputations with SGLT2 inhibitor use. Given its cardiovascular, metabolic, and renal benefits, the risk-benefit ratio tips in heavily favor of prescribing SGLT2 inhibitors for patients in whom such treatment is indicated.

The pathophysiological mechanisms of how SGLT2 inhibitors lead to amputations are still largely unclear. It is hypothesized that canagliflozin has a higher diuretic effect compared to other SGLT2 inhibitors, leading to hemoconcentration and hyperviscosity which could increase the risk of peripheral tissue ischemia [41]. While the 2017 CANVAS trial has instigated more research into canagliflozin's amputation outcomes, there have been numerous other studies which have shown a small or no significant increase in amputation outcomes with the use of canagliflozin [42, 43].

Strengths

Our study is the largest meta-analysis of randomized-controlled trials to date, with a pooled cohort of >60,000 patients. In addition, our study comprises subgroup analyses for different types of SGLT2 inhibitors, different baseline populations, and duration of SGLT2 inhibitor intervention. This further confirms our findings that there was no significant association of amputation events with SGLT2 inhibitor use.

Limitations

Our study should be interpreted with some limitations taken into consideration. First, many studies did not report the baseline characteristics such as history of cardiovascular disease or history of peripheral vascular disease, which are important factors that might affect amputation outcomes as discussed above. This might lead to between-study differences and lead to difference in amputation outcomes.

Second, we were unable to conclude if SGLT2 inhibitors had dose-dependent effects on amputation risk. Meta-regression analysis could not be performed due to insufficient studies available.

Third, many studies did not report the site of amputation. For instance, the 2017 CANVAS trial investigated for toe and metatarsal amputation events while another canagliflozin trial [42] investigated for below-knee lower extremity amputation events. As such, it is difficult to comment on whether SGLT2 inhibitors have different risk of amputation at different anatomical sites. This will have a significant impact on patients' quality of life as a

toe amputation has less disease burden compared to a below-knee amputation in terms of ambulation and financial costs for prosthesis.

Fourth, the quantity and quality of randomized-controlled trials analyzed was limited and this might affect the quality of results derived from this meta-analysis. There were only 3 studies that reported HRs, with substantial heterogeneity ($I^2 = 77\%$) (Fig. 1). There were some subgroup analyses where the heterogeneity could not be reported as well.

Last, Yale et al. [34] had a high risk of attrition bias and selective reporting bias, which might affect the validity of results. Hence, a sensitivity analysis was done by excluding Yale et al. [34]. However, there was no significant difference in POR (POR was 1.12 [95% CI: 0.91–1.38], $p = 0.27$) (online suppl. Fig. 17).

Conclusion

We demonstrated that patients treated with SGLT2 inhibitors did not have any significant difference in amputation events compared to placebo across various subgroup analysis conducted. Although canagliflozin usage has led to higher amputation events in certain trials, there has been numerous trials showing insignificant results, and a clear association between SGLT2 inhibitors and amputation events has not been established. This study will aid physicians in assessing the risk of amputations when initiating treatment with SGLT2 inhibitors.

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Statement of Ethics

The meta-analysis was reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Ethics statement was not required since the research is a systemic review and meta-analysis of previously published studies. The completed PRISMA checklist was uploaded as supplementary material.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

C.S. was supported by the National University of Singapore Yong Loo Lin School of Medicine's Junior Academic Faculty Scheme.

Author Contributions

R.M.S., Y.N.T., Y.H.T., and C.S. designed the study and developed the study protocol and tools. R.M.S., Y.N.T., A.S.Y.Y., and S.L. were responsible for data collection. R.M.S., Y.N.T., Y.H.T., N.L.S., and C.S. analyzed data and wrote the manuscript. R.M.S., Y.N.T., Y.H.T., N.L.S., A.S.Y.Y., S.L., C.F.W., J.Y.A.C., C.H.L., M.Y.Y.C., T.C.Y., R.C.C.W., P.C., C.C.H., P.C., and C.S. contributed to the conceptualization of the research questions, interpretation of the results, and manuscript writing. All authors read and approved the final manuscript.

Data Availability Statement

All the data utilized are available on publicly available databases.

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