Esophageal Atresia and Associated Duodenal Atresia: A Cohort Study and Review of the Literature

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Abstract

Introduction Esophageal atresia (EA) is associated with duodenal atresia (DA) in 3 to 6% of cases. The management of this association is controversial and literature is scarce on the topic.

Materials and Methods We aimed to (1) review the patients with EA + DA treated at our institution and (2) systematically review the English literature, including case series of three or more patients.

Results Cohort study: Five of seventy-four patients with EA had an associated DA (6.8%). Four of five cases (80%) underwent primary repair of both atresia, one of them with gastrostomy placement (25%). One of five cases (20%) had a delayed diagnosis of DA. No mortality has occurred. Systematic Review: Six of six-hundred forty-five abstract screened were included (78 patients). Twenty-four of sixty-eight (35.3%) underwent primary correction of EA + DA, and 36/68 (52.9%) underwent staged correction. Nine of thirty-six (25%) had a missed diagnosis of DA. Thirty-six of sixty-eight underwent gastrostomy placement. Complications were observed in 14/36 patients (38.9 ± 8.2%). Overall mortality reported was 41.0 ± 30.1% (32/78 patients), in particular its incidence was 41.7 ± 27.0% after a primary treatment and 37.0 ± 44.1% following a staged approach.

Conclusion The management of associated EA and DA remains controversial. It seems that the staged or primary correction does not affect the mortality. Surgeons should not overlook DA when correcting an EA.

Keywords
- duodenal atresia
- esophageal atresia
- gastrostomy
- systematic review

Introduction

The incidence of esophageal atresia (EA) is ~1:3,000 live births, while the incidence of duodenal atresia (DA) is ranged between 1:5,000 and 1:10,000 live births.[1,2] Both EA and DA could be associated with further congenital anomalies. The presence of DA has been reported to be detected in ~3 to 6% of babies with EA (with or without tracheoesophageal fistula, TEF)[1,3–5] with a survival rate ranging from 3 to 75%.[4,6]

The management of the association of EA and DA is still controversial, to the best of our knowledge.[4,7] Even if several management strategies have been reported to treat the

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single atresia, the treatment of both anomalies together is not well established, up to now.[4,7] Only a few retrospective studies looking specifically to this association have been published up to date and the management differs in each of these papers.[1–7] Some authors have suggested a staged repair of EA and DA,[1,7] while others have reported that a combined approach seemed safe and effective.[4,5]

Further controversies concerned the necessity of a gastrostomy placement to decompress the stomach and to protect the duodenal anastomosis, both after the combined and the staged repair.

With the present study, we aimed (1) to review all the cases of combined EA and DA treated in a single center and (2) to systematically review the literature with regard to this associated congenital anomaly, trying to determine which surgical approach seems to emerge as the gold standard.

Materials and Methods

Cohort Study

A retrospective review of the medical charts of all the patients with a diagnosis of EA treated at our department in a 20-year period (2000–2019) was completed. Afterward, we focused on those cases with an association of EA and DA. Data collected included gender, gestational age (GA), birth weight (BW), prenatal diagnosis, associated anomalies, age at surgery, operative technique, intraoperative findings, gastrostomy placement, delayed/missed diagnosis of DA, length of hospital stay, and mortality. The type of EA was classified according to the gross classification,[8] whereas DA was classified according to the Gray and Skandalakis classification.[9]

Systematic Review and Meta-Analysis

The systematic review was drafted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[10] and was registered on PROSPERO (National Institute for Health Research, registration number CRD42020182627).[11]

A systematic review of the literature was made using a defined search strategy. Two investigators (*MEM* and *DDR*) independently searched scientific databases (PubMed/MEDLINE, Scopus, Cochrane Collaboration, and Web of Science) using a combination of keywords (►Table 1). MeSH headings and terms used were "esophageal atresia," "esophageal atresia AND duodenal atresia," and "esophageal atresia AND associated duodenal atresia" (Supplementary File 1, available in the online version). Studies published up to April 27, 2020 were included. Case reports, opinion articles, experimental studies, and case series with less than 3 patients were excluded. All gray literature publications (i.e., reports, theses, conference proceedings, bibliographies, commercial documentations, and official documents not published commercially) were excluded. The full text of the potentially eligible studies was retrieved and independently assessed for eligibility by the same two investigators. Any disagreement between them over the eligibility of particular studies was resolved through discussion with a third author (*GLi*).

Table 1 Inclusion criteria of the systematic review

Publication	
Language	English
Time period	1950–2019
Subject	Human studies
Study type	Retrospective Prospective Case–control Cohort
Excluded	Case-report Editorials Letters Gray literature
Keywords	Esophageal atresia Duodenal atresia Associated duodenal atresia

Data were compared using Student's *t*-test or Fisher's exact test and are expressed as mean ± standard deviation [SD]. When median and range were reported, mean ± SD were estimated, as reported.[12]

Quality Assessment

The risk of bias for each study was evaluated in duplicate (*GLa* and *AR*) using the methodological index for nonrandomized studies (MINORS).[13] Differences between the two reviewers were resolved through consensus and discussion with a third author (*GLi*). The total score for this 12-item instrument ranges between 0 and 24 points with a validated "gold standard" cutoff of 19.8. Moreover, the present study was assessed in duplicate by two investigators (*GLi* and *PLC*) using a measurement tool to assess systematic reviews, AMSTAR 2.[14] A PRISMA figure following PRISMA checklist criteria was created.[10]

Results

Cohort Study

During the study period (2000–2019), we identified 74 babies with a diagnosis of EA (38 males, 36 females). Mean GA was 37.1 ± 3.2 weeks, while mean BW was 2,550 ± 683 g. Only 1/74 babies (1.3%) had a prenatal diagnosis of double bubble, while in 17/74 (22.9%) a polyhydramnios was identified. The EA was type I in 5 cases, type III in 68 patients, and type IV in 1 newborn. The VACTERL association (i.e., vertebral defects, anal atresia, cardiac defects, TEF, renal anomalies, and limb abnormalities) was detected in 4/74 patients (5.4%), while 3/74 babies (4.0%) had an associated Trisomy 21.

In 5/74 patients (6.8%) with EA (1 type I and 4 type III), an associated DA had been detected. Demographic data and associated anomalies of these five patients with associated EA and DA are shown in ►Table 2. There were two males and three females, with a mean GA of 34.75 ± 1.5 weeks and a mean BW of 1.911 ± 448.2 g. Prenatal diagnosis of DA was made in ⅕ patient, while in ⅗ a polyhydramnios was detected. Only ⅕ newborn had a diagnosis of VACTERL

Table 2 Patients with esophageal atresia and duodenal atresia: associated anomalies and screening for VACTERL association

No. of patients	Sex	Prenatal diagnosis	GA (wk)	BW (g)	Type of EA	Type of intervention	Delayed diagnosis	VACTERL association	Associated anomalies	Trisomy 21
1	F	Polyhydramnios	n.a.	n.a.	III	TEF repair, primary esophageal anastomosis Duodeno-duodenostomy + gastrostomy	No	No	None	No
2	M	n.a.	33	1,350	I	Primary esophageal anastomosis Duodeno-jejunostomy	No	No	Bronchial hypoplasia	No
3	F	Polyhydramnios	36	2,365	III	TEF repair, primary esophageal anastomosis Duodenal web resection (10 d later)	Yes	No	Clubfoot	No
4	F	Polyhydramnios	36^{+5}	2,160	III	TEF repair, primary esophageal anastomosis Duodenal web resection	No	Yes	Interatrial defect; pyelectasis	No
5	M	Duodenal atresia	34^{+5}	1,770	III	TEF repair, primary esophageal anastomosis Duodeno-duodenostomy	No	No	Anorectal malformation	No

Abbreviations: EA, esophageal atresia; GA, gestational age; n.a., not available; TEF, tracheoesophageal fistula; VACTERL, Vertebral, Anorectal, Cardiac, Tracheo-Esophageal fistula, Renal, Limbs anomalies.

association. None of these five patients with EA + DA had an associated Trisomy 21. The group of five patients with an associated EA and DA was comparable to those 69 newborns with an isolated EA with regard to BW, GA, and sex distribution (►**Table 3**).

One out of five patient (20%) with the combined anomaly had a delayed diagnosis of duodenal web and underwent a second surgical procedure on day 10 of life. The remaining four patients underwent primary esophageal anastomosis and duodeno-duodenostomy or duodeno-jejunostomy, with only one gastrostomy required (20%).

We observed an early anastomotic esophageal leak (2nd postoperative day) not responsive to conservative treatment in the only patient who had a delayed diagnosis of duodenal web. The duodenal anomaly was suspected on the basis of a postoperative biliary drainage from the nasogastric probe and evidenced at the contrast study performed to confirm the esophageal dehiscence. Both conditions were surgically corrected on the same procedure on day 10 of life.

Mean length of stay was 34.7 ± 7.8 days (range: 26–41 days).

In mid- and long-term outcomes, one patient was lost to follow up, and the remaining four patients are alive at a mean ± SD follow-up of 9.4 ± 7.1 years (range: 1.5–20 years). Mean ± SD BMI-for-age is 15.625 ± 3.57 (range: 10.8–19.3), mean ± SD weight-for-age z-score is -0.45 ± 0.93 (range: −1.18 to −0.87), mean ± SD height-for-age z-score is $+0.45 \pm 0.60$ (range: 0.40 to −1).

Systematic Review

Of 645 titles and abstract screened, 20 full-text articles were analyzed and 6 met the inclusion criteria (78 patients; ►**Fig. 1**).[1,3–7] Thirteen patients presented a type I EA, and 65 cases had a type III EA (►**Table 4**). Twenty-four out of sixty-eight patients (35.3%) underwent primary correction of both the anomalies. A staged approach has been reported in 36/68 cases (52.9%). However, in 9/36 of them (25%) the staged approach was caused by a delayed diagnosis of DA. Eight out of sixty-eight patients (11.8%) died before surgery. Thirty-six out of sixty-eight babies (52.9%) underwent a gastrostomy placement. Duodenal atresia was approached first in 16/36 (44.4%) patients who underwent a staged correction, with a reported mortality rate of 31% (5/16 patients). In the staged approach, the mortality rate was 20% (4/20 patients) when EA was corrected at first. The reported incidence of missed DA was 13.2 ± 14.4% (9/68 patients; range 0–33.3%) and the missed DA was detected between the 3rd and 22nd day of life. When mentioned, all missed DA where associated with

Table 3 Demographics of the cohort groups: isolated esophageal atresia (EA) versus EA associated with duodenal atresia (EA + DA)

	Group isolated EA ($n = 69$ patients)	Group EA + DA ($n = 5$ patients)	*p*-Value
Birth weight (g, mean ± SD)	2.576 ± 676	1.911 ± 448	0.08[a]
Gestational age (wk, mean ± SD)	37.1 ± 2.9	34.7 ± 1.5	0.26[a]
M: F	36: 33	2: 3	0.67[b]

Abbreviation: SD, standard deviation.
[a]Student's *t*-test.
[b]Fisher's exact test.

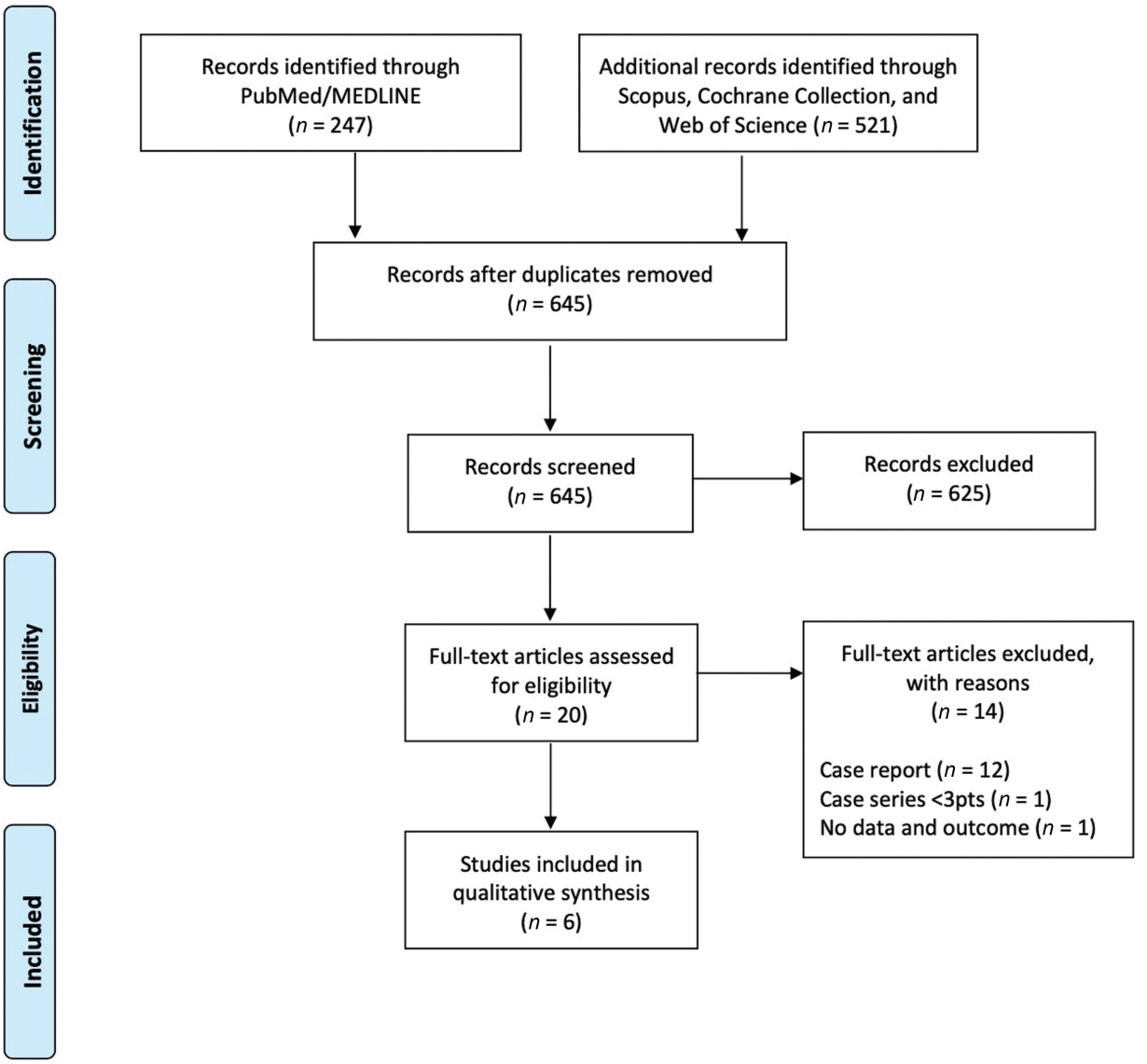

Fig. 1 Diagram of workflow in the systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

type III EA, as in our cohort study (►**Table 4**). When reported, the missed DA web was found in one patient and a duodenal stenosis in one further infant.

Complications were observed in 38.9 ± 8.2% of the patients (14/36 patients, range 33–50%), when mentioned (►**Table 4**). The most common complications reported were esophageal strictures requiring dilatation (in 8 patients) and severe gastroesophageal reflux requiring fundoplication (in 7 patients).

The overall mortality reported was 41.0 ± 30.1% (32/78 patients), ranging between 0 and 72% (►**Table 4**). When further analyzed, the mortality rate was 41.7 ± 27.0% (5/12 cases, range: 0–50%) after a primary treatment and 37.0 ± 44.1% (10/27 patients, range 12.5–100%) following a staged approach.

Quality Assessment

None of the included studies reached the gold standard cutoff on MINORS of 19.8 out of 24 (►**Table 5**). All papers included were retrospective, with lack of data with regard to the follow-up. Moreover, as most of these papers have reported data in small case series (►**Table 4**), no statistical analysis has commonly been done. However, when independently assessed by two senior authors (*GLi* and *PLC*) using AMSTAR 2,[14] the present systematic review and meta-analysis received a high score (Supplementary File 2, available in the online version). A list of excluded articles is provided (Supplemental File 3, available in the online version). The PRISMA checklist was then completed (Supplementary File 4, available in the online version).

Discussion

Duodenal atresia is often associated with other gastrointestinal anomalies alone or as part of a VACTERL syndrome.[2] In particular, DA can be found in 3 to 6% of babies with EA.[1,3–5] It is postulated that an early damage during organogenesis could explain this association.[4]

Table 4 Studies included in the systematic review, with the main characteristics of the missed diagnosis of duodenal atresia

	EA + DA (*n*)	Type EA	Missed DA, *n* (%)	Type of missed DA	Symptoms in missed DA	Type EA in missed DA	Complication, *n* (%)	Mortality, *n* (%)
Spitz et al, 1981[3]	18	2 type I 16 type III	n.r.	n.r.	n.r.	n.r.	n.r.	13 (72%)
Dave and Shi, 2004[4]	10	1 type I 9 type III	3 (30%)	n.r.	n.r.	n.r.	5 (50%)	1 (10%)
Ein et al, 2006[7]	24	7 type I 17 type III	4 (17%)	1 DS 3 n.r.	1 respiratory infection 3 n.r.	n.r.	n.r.	6 (25%)
Stark et al, 2007[6]	3	3 type III	1 (33%)	n.r.	Feeding intolerance	1 type III	1 (33%)	2 (67%)
Nabzdyk et al, 2014[1]	3	3 type III	0 (0%)	–	–	–	1 (33%)	0 (0%)
Fragoso et al, 2015[5]	20	2 type I 18 type III	1 (5%)	1 web	n.r.	1 type III	7 (35%)	10 (50%)
Present cohort study	5	1 type I 4 type III	1 (20%)	1 web	Anastomotic leakage, respiratory difficulties, gastric distension, delayed gastric emptying	1 type III	1 (20%)	0 (0%)

Abbreviations: DA, duodenal atresia; DS, duodenal stenosis; EA, esophageal atresia; n.r., not reported.

The protocol treatment of babies with the association of EA and DA is not well established, as poor literature is available about the topic.[4]

The challenging problems related to the association of EA (mainly type III) and DA rely on the risk of aspiration if the TEF is not ligated promptly. Nonetheless, the fistula fills the stomach of air that cannot pass through the intestine because of the presence of a DA and in addition the presence of an EA makes the drainage of the stomach through a nasogastric tube impossible to perform.[4,7]

The first study concerning the approach and the outcomes of the association between EA and DA comes from Spitz et al in 1981. Authors published a series of 18 cases of EA (16 of which type III) associated with DA.[3] They reported a mortality rate of 66.7%, mainly related to the associated anomalies and they conclude that if the patient has not life-threatening anomalies, the two atresia can be approached during the same surgery. Differently, a staged approach, with or without gastrostomy, should be the first choice.

Since those infants with a combined DA and EA malformation are often premature, some authors prefer a staged correction.[1,7] Hence, they suggested to approach the DA first, to better allow the baby to grow up and the esophageal segments to elongate enough, thus making the postponed esophageal anastomosis easier.[7]

Dave and Shi in 2004 published a series of 10 cases of associated EA and DA. They suggested a primary combined approach without gastrostomy, since a nasogastric tube should suffice to decompress the stomach.[4]

In our study, we did not find any statistically significant difference in terms of mortality after a staged or a primary correction of EA and DA, thus corroborating the primary correction as safe and feasible.

Another issue associated with the correction of the anomalies is the need for a gastrostomy placement. To the best of our knowledge, it is not clear in literature whether or not it could protect the duodenal anastomosis. In our series, we performed a gastrostomy only in one of five patients and we did not find any major complications in the other four patients.

The choice of a staged approach is sometimes the result of a missed diagnosis of DA. As a matter of fact, the only prenatal finding is in most cases a polyhydramnios. Thus, the incidence of missed DA has been reported to be up to 33%.[4,6] Moreover, the presence of a DA may be overlooked especially when associated with an EA without TEF, even if it could occur also in combination with type III EA, thus, implying the need for a further surgical procedure in fragile babies.

As suggested in the study by Nabzdyk et al in 2014, a careful observation of the preoperative abdominal X-ray could be essential in detecting those images suggestive of an associated DA.[1] However, as reported in the present systematic review as well as in our cohort study (►**Table 4**), the missed DA were usually those not complete atresia (i.e., duodenal web or duodenal stenosis). Therefore, the pathognomonic images at preoperative abdominal X-ray studies could have been not so indicative.

Conclusion

The management of the association of EA and DA remains controversial. From the analysis of the literature, it seems that the choice of a staged or a delayed approach does not influence the mortality. Moreover, the gastrostomy placement does not seem to be essential to protect the anastomosis. The presence of an associated DA when correcting an EA should not be overlooked.

Table 5 Risk of bias assessment for individual studies using methodological index for nonrandomized studies (MINORS)[13]

Item	Spitz et al, 1981[3]	Dave and Shi, 2004[4]	Ein et al, 2006[7]	Stark et al, 2007[6]	Nabzdyk et al, 2014[1]	Fragoso et al, 2015[5]
1. A clearly stated aim	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2
3. Prospective collection of data	0	0	0	0	0	0
4. Endpoints appropriate to the aim of the study	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	1	0	2	1	2	2
7. Loss to follow-up less than 5%	2	0	2	2	2	1
8. Prospective calculation of the study size	0	0	0	0	0	0
9. An adequate control group	2	1	2	1	1	1
10. Contemporary groups	2	2	2	2	2	2
11. Baseline equivalence of groups	2	2	2	1	2	2
12. Adequate statistical analysis	0	0	2	0	0	0
Total score	15	11	18	12	15	14

0 = not reported.
1 = reported but inadequate.
2 = reported and adequate.

Given the rarity of the combined congenital malformation, further multicentric studies would be needed to corroborate our results.

Ethical Approval

Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest

G.L. declares he received financial support for attending symposia from the Company Coloplast S.p.A. and from the Company AB Medica S.p.A. All others authors declared that they have no conflict of interest.

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Supplementary File 1: Search strategy

PubMed/MEDLINE

("Oesophageal atresia"[All Fields] OR "esophageal atresia"[MeSH Terms] OR ("esophageal"[All Fields] AND "atresia"[All Fields]) OR "esophageal atresia"[All Fields]) AND ("Familial duodenal atresia"[Supplementary Concept] OR "Familial duodenal atresia"[All Fields] OR "duodenal atresia"[All Fields])

Scopus

TITLE-ABS-KEY (esophageal AND atresia AND duodenal AND atresia)

Cochrane

- MeSH descriptor: Esophageal, Atresia, Duodenal, Atresia
- Explode all trees

Web of Science

TOPIC: (esophageal atresia AND duodenal atresia)
Timespan: All years. Databases: WOS, KJD, MEDLINE, RSCI, SCIELO.
Search language = Auto

Supplementary File 2 AMSTAR criteria for the present systematic reviews and meta-analysis assessed by two senior authors

Item	GLi	PLC
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review?	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Yes
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No meta-analysis conducted	No meta-analysis conducted
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No meta-analysis conducted	No meta-analysis conducted
13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	Yes	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No meta-analysis conducted	No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes
Total Yes, *n* (%)	**11/13(85)**	**12/13(92)**

Abbreviations: PICO, Population, Intervention, Control group, and Outcome; RoB, risk of bias.

Supplementary File 3 List of excluded studies with reasons for exclusion

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3, 4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5, S2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, 7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6, 7

(*Continued*)

Supplementary File 3 (*Continued*)

Section/topic	#	Checklist item	Reported on page #
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	S2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6, 7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6, 7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7, 8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	7, 8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

Abbreviations: N/A: not available; S: Supplementary file.

Supplementary File 4 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3, 4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4

Supplementary File 4 (*Continued*)

Section/topic	#	Checklist item	Reported on page #
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5, S2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, 7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6, 7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	S2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6, 7
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