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**Critical Appraisal of Gastric Conduit Ischaemic Conditioning (GIC) prior to
Oesophagectomy: A Systematic Review and Meta-Analysis**

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Critical Appraisal of Gastric Conduit Ischaemic Conditioning (GIC) prior to Oesophagectomy: A Systematic Review and Meta-Analysis

Abstract

Introduction

Anastomotic leaks remain a major complication following oesophagectomy, accounting for high morbidity and mortality. Recently, gastric ischaemic conditioning (GIC) has been proposed to improve anastomotic integrity through neovascularisation of the gastric conduit. This systematic review and meta-analysis aim to determine the impact of GIC on postoperative outcomes following oesophagectomy.

Methods

A systematic literature search was performed to identify studies reporting GIC for any indication of oesophageal resection up to 25th April 2019. The primary outcome was anastomotic leak. Secondary outcomes were conduit necrosis, anastomotic strictures, overall and major complications or in-hospital mortality. Meta-analyses were conducted using random-effects modelling.

Results

Nineteen studies reported on GIC, of which 13 were comparative studies. GIC was performed through ligation in 13 studies and embolisation in six studies. GIC did not appear to reduce anastomotic leakages (OR 0.80, CI₉₅: 0.51 - 1.24, p=0.3), anastomotic strictures (OR 0.75, CI₉₅: 0.35 - 1.60, p=0.5), overall complications (OR 1.02, CI₉₅: 0.48 - 2.16, p=0.9), major complications (OR 1.06, CI₉₅: 0.53 - 2.11, p=0.9), or in-hospital mortality (OR 0.70, CI₉₅: 0.32 - 1.53, p=0.4). However, GIC was

1 associated with reduced rates of conduit necrosis (OR 0.30, CI₉₅: 0.11 - 0.77,
2 p=0.013).

3

4 **Conclusion**

5 GIC does not appear to reduce overall rates of anastomotic leakage

6 after oesophagectomy but seems to reduce severity of leakages. More in depth

7 studies are recommended.

8

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1 **Introduction**

2 Oesophageal cancers remain the sixth most common cause of cancer-related
3 deaths worldwide.(1) Whilst multimodality treatment has improved long-term survival
4 of patients with oesophageal cancers, oesophagectomy remains the mainstay of
5 curative treatment.(2) Anastomotic leaks remain a major complication following
6 oesophagectomy (3) with mortality rates ranging between 5% - 9%.(4-8) They are
7 also associated with longer hospital stays, increased hospital costs,(3, 9) and have
8 been demonstrated to adversely impact both overall (median: 36 vs 55 months) and
9 disease-free survival (median: 34 vs 48 months).(3) While there is growing literature
10 on the burden of anastomotic leaks, the factors associated with anastomotic leaks
11 are poorly understood.(10, 11) Several factors have been thought to impact on
12 anastomotic leaks such as location of the anastomosis and reconstruction technique
13 of performing the oesophagogastric anastomosis.(12)

14
15 Over the last few years, there has been increasing interest in the role of gastric
16 ischaemic conditioning (GIC) prior to oesophagectomy. Early evidence from animal
17 experiments appear to demonstrate that partial devascularisation of the proximal
18 stomach prior to oesophagectomies improves the perfusion of the proximal stomach.
19 This therefore enhances the oesophagogastric anastomosis following surgery.(13)
20 Several randomised controlled trials (RCTs) have evaluated the impact of ischaemic
21 conditioning of the gastric tube, either by embolisation of the left gastric artery(14) or
22 by laparoscopic ligation of the left gastric artery and/or short gastric arteries(15) prior
23 to oesophagectomy. Although some of the RCTs performed an early
24 oesophagectomy after GIC within a few days,(14, 16) others performed an

1 oesophagectomy more than 2 weeks after GIC.(17, 18) As a result, there remains no
2 consensus on the timing of surgery following GIC to date.

3

4 Given uncertainty on the current evidence on the benefits of GIC prior to
5 oesophagectomy, this systematic review aims to summarise the evidence on the
6 methods of GIC, the time period from GIC to oesophagectomy, and assess the
7 impact of GIC on postoperative morbidity (i.e. anastomotic leaks and conduit
8 necrosis) and mortality.

9

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1 **Methods**

2 *Search Strategy*

3 A systematic search of PubMed, EMBASE and the Cochrane Library databases
4 were conducted on the 25th April 2019 by two independent investigators (SKK, CB).
5 The search terms used were 'gastric ischaemic conditioning' or 'laparoscopic
6 conditioning' and 'oesophagectomy' or 'esophagectomy' individually or in
7 combination and they are presented as shown in Supplementary Table 1. A manual
8 search of reference lists in recent reviews or from eligible studies were also
9 performed to ensure that no pertinent studies were missed.(19) This paper was
10 reported according to the with Preferred Reporting Items for Systematic Reviews and
11 Meta-Analyses (PRISMA) (20, 21) and Assessing the methodological quality of
12 systematic reviews (AMSTAR)(22) guidelines and prospectively registered on the
13 PROSPERO database (Registration CRD42019137432) as previously reported.(19)

15 *Inclusion and Exclusion Criteria*

16 Inclusion criteria for this review were: (1) studies reporting GIC (through any method)
17 in human subjects undergoing oesophagectomy for any indication; (2) studies
18 published in English language. Exclusion criteria were: (1) Conference abstracts,
19 review articles, and case reports (<5 patients). Following exclusion of duplicates, two
20 researchers (SKK, CB) independently evaluated titles and abstracts of studies
21 identified from the literature search. In the event where a study was considered to be
22 potentially relevant to the research question, a full copy of the publication was
23 obtained for a full text review.(21) Any areas of disagreement in study inclusion or
24 exclusion between the two primary researchers (SKK, CB) were resolved through
25 discussion and discussion with the senior author (BT).

1 *Study Outcomes*

2 The primary outcome measure was anastomotic leaks. The secondary outcome
3 measures were anastomotic strictures, conduit necrosis, overall complications
4 (Grade I-V) and major complications (\geq Grade III) reported according to Clavien-
5 Dindo Classification,(23) pulmonary complications and in-hospital mortality.

6

7 *Data Extraction*

8 Two primary researchers (SKK, CB) independently extracted data on study
9 characteristics (author, year of publication, country of origin, study design
10 (retrospective/prospective cohort study, RCTs), patient number with and without
11 GIC), patient demographics (age, sex), method and details of GIC and reported
12 clinical outcomes of interest as described above.

13

14 *Assessment of methodological quality*

15 Methodological quality and standard of outcome reporting within included studies
16 were assessed by two independent researchers (SKK, JB). Methodological quality
17 was formally assessed using the Newcastle-Ottawa score for cohort studies (SKK,
18 JB).

19

20 *Statistical analysis*

21 This systematic review and meta-analysis was conducted in accordance with the
22 recommendations of the Cochrane Library and PRISMA guidelines as described
23 above.(24) Statistical significance was considered when $p < 0.05$ and all analyses
24 were performed using the R Foundation Statistical software (R 3.2.1) and Stata 15
25 (Version 15.1, StataCorp, College Station, Texas) as previously reported.(21, 25)

1 Analysis was performed by calculating the odds ratio (OR) for categorical variables.
2 The random effects (DerSimonian-Laird) method was used for the meta-analysis of
3 all outcomes. The I_2 value was to assess the degree of heterogeneity between
4 studies and I_2 values were considered to represent low, moderate, and high degrees
5 of heterogeneity where values were <25%, 25–75%, and >75%, respectively.
6 Assessment of small study bias was carried out through visual assessment of funnel
7 plots and egger regressions as previously reported.(21, 26, 27)

8

9

1 **Results**

2 *Study Characteristics*

3 This literature review identified 19 studies as reported according to the PRISMA
4 guidelines (21, 26) (Figure 1). Baseline characteristics of included studies are
5 presented in Table 1 and 2. This study included 1,596 patients undergoing
6 oesophagectomy, of which 56% (n=890) received gastric ischaemic conditioning. Of
7 the included 19 studies, 13 studies reported ligation technique and five studies
8 reported embolisation techniques. A summary of quality assessment of included
9 studies are presented in Supplementary Table 2.

10

11 *Anastomotic Leaks*

12 Anastomotic leaks were reported in 11 studies, of which seven reported ligation and
13 three reported utilising the embolization technique for GIC. There were no significant
14 differences in anastomotic leaks in patients with and without GIC (OR: 0.80, p=0.3)
15 (Table 3). However, in patients undergoing embolisation, rates of anastomotic leaks
16 were significantly lower in those undergoing GIC (OR: 0.25, p=0.005).

17

18 *Conduit Necrosis*

19 Conduit necrosis was reported in four studies, all of which used the ligation
20 technique for GIC. There were significantly lower rates of conduit necrosis in patients
21 undergoing GIC (OR: 0.30, p=0.013).

22

23 *Anastomotic Strictures*

24 Anastomotic strictures were reported in five studies of which three reported ligation
25 and two reported the embolization technique. There was no significant difference in

1 stricture rates in the entire cohort (OR: 0.75, $p=0.5$) in patients with and without
2 ischaemic preconditioning (Table 3).

3

4 *Overall and Major Complications*

5 Overall and major complications were reported in five and three studies respectively.

6 There was no significant differences in rates of overall (OR: 1.02, $p=0.9$) and major

7 (OR: 1.06, $p=0.9$) complications in the entire cohort in patients with and without

8 ischaemic preconditioning (Table 3)

9

10 *Pulmonary Complications*

11 Pulmonary complications were reported in five studies, of which one did not report

12 the technique used. There was no significant difference in rates of pulmonary

13 complications (OR: 0.90, $p=0.6$) in patients with and without ischaemic

14 preconditioning (Table 3)

15

16 *In-hospital Mortality*

17 In-hospital mortality was reported in seven studies, of which four reported ligation

18 and two reported the embolisation technique. One study did not report the technique

19 used. There was no significant difference in rates of in-hospital mortality (OR: 0.70,

20 $p=0.4$) in patients with and without ischaemic preconditioning (Table 3)

21

1 **Discussion**

2 Oesophagectomy is recognised as one of the most morbidity-prone surgical
3 procedures, associated with anastomotic leak rates as high as 40%. (3, 12) Although
4 mortality rates following oesophagectomy have reduced significantly to below 5% in
5 tertiary specialist centres over the last decade from 30% in the 1970s, (12) with
6 studies demonstrating improvement in mortality rates in high-volume units compared
7 to low-volume units, (28, 29) the morbidity rates following oesophagectomy remain
8 high and range between 30% - 50%. (30, 31) Anastomotic leaks remain a major
9 complication occurring in up to 40% of cases, requiring immediate
10 treatment. (32) Whilst cervical anastomoses are recognised to be associated with
11 higher risk of developing anastomotic leaks; (33, 34) thoracic anastomotic leaks are
12 more likely to develop serious complications and consequently require surgical re-
13 exploration. (30, 33) To improve anastomotic leak rates following oesophagectomy,
14 preoperative ischaemic conditioning of the stomach conduit has been proposed by
15 several groups as a new strategy to tackle this.

16
17 This systematic review and meta-analysis demonstrate that GIC prior to
18 oesophagectomy is feasible and safe either by surgical ligation or by embolisation. In
19 addition, this study has highlighted that GIC by embolization and not ligation was
20 associated with significantly lower rates of anastomotic leaks and conduit necrosis.
21 However, this systematic review did not demonstrate any differences for other
22 endpoints studied such as anastomotic stricture rate, overall and major
23 complications, pulmonary complications and in-hospital mortality.

24

1 This study also highlights that GIC is a safe procedure. It is associated with lower
2 anastomotic complications after oesophagectomy, with comparable overall morbidity
3 and mortality profile. This may be explained by several factors. Firstly, selective
4 ligation of the gastric blood supply may result in neovascularisation of the remaining
5 vessels, hence improving blood flow to the site of conduit anastomosis and an
6 associated increase in tissue oxygenation.(35-39) These findings highlight a
7 protective impact on the anastomosis during critical initial healing, leading to reduced
8 risk of anastomotic complications. Secondly, during the oesophagectomy, the
9 stomach does not need to be manipulated to the same extent that a non-GIC
10 stomach does, which is less traumatic to the future conduit.

11

12 There are several limitations to this study. Firstly, included studies exhibit a high risk
13 of bias, as these were single-centre, retrospective studies,(15, 17, 40) and reported
14 unclear outcome definitions, specifically for anastomotic leaks or follow-up.

15 Secondly, no randomised controlled trials (RCTs) that adequately adjusts for all
16 confounding factors exist. However, this is largely a reflection on the lack of adoption
17 of GIC in wider centres to allow a high-powered RCT to be conducted. Thirdly,
18 variation in the GIC protocols exist due to the different waiting times and techniques
19 (i.e. ligation or embolisation of the left gastric artery). Only one study(41) evaluated
20 the efficacy of additional ligation of other arterial branches (i.e., short gastric vessels)
21 which enhanced the effect of ischaemic preconditioning, but total patient numbers
22 are too small to draw a meaningful conclusion. As a result, further evaluation of this
23 aspect is required. As current guidelines recommend neoadjuvant therapy regimes
24 in locally advanced oesophageal cancer,(42-44) the benefits of GIC in these settings
25 cannot be answered. This is because if GIC were to be carried out during staging

1 laparoscopy prior to neoadjuvant treatment, the waiting time between GIC and
2 oesophageal resection may be longer (>5 weeks) than in all of the current studies
3 identified in this systematic review.

4

5 **Conclusion**

6 This systematic review and meta-analysis demonstrate that GIC before
7 oesophagectomy appears to be feasible and safe but does not significantly reduce
8 the rate of postoperative anastomotic leakage or stricture, major complications, or in-
9 hospital mortality. Based on these results, preconditioning cannot generally be
10 recommended for patients undergoing oesophagectomy. However, evaluation of GIC
11 in the context of high-quality RCTs should explore various technical modifications
12 (e.g. ligation of additional vessels to the left gastric artery), unstudied clinical settings
13 (neoadjuvant therapy), and in high-risk groups (patients with visceral
14 atherosclerosis).

15

16

17 **Provenance and peer review**

18 Not Commissioned, internally reviewed

19

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Table 1 Characteristics of Included Studies

Study Name	Study Design	Study Country	Study Duration	Comparative	Number, n	GIC, n	No GIC, n	Method of GIC	GIC Waiting Times, days
Bludau 2010(37)	PCS	Germany	August 2006 - June 2008	None	19	19		Ligation: LGA, Short gastric arteries	4-5 days
Kohler 2019(45)	PCS	Germany	NR	GIC vs No GIC	22	14	8	Ligation: LGA, LGV	3 - 7 days
Prudius 2018(46)	PCS	Czech Republic	NR	GIC vs No GIC	15	8	7	Ligation: LGA	NR
Veeramootoo 2009(47)	PCS	United Kingdom	April 2004 - August 2008	GIC vs No GIC	97	42	55	Ligation: LGA	5 or 14
Akiyama 1998(35)	RCS	Japan	NR	GIC vs No GIC	79	54	25	Embolisation: RGA, LGA, Splenic artery	NR
Berrisford 2009(15)	RCS	United Kingdom	April 2004 - June 2007	GIC vs No GIC	77	22	55	Ligation: LGA, LGV	16
Diana 2011(48)	RCS	Switzerland	2000 - 2009	GIC vs No GIC	57	19	38	Embolisation: LGA, Splenic artery	17
Farran 2010(49)	RCS	Spain	January 2001 - December 2007	None	39	39		Embolisation: LGA, Splenic artery	14 - 21
Ghelfi 2016(50)	RCS	Germany	March 2008 - January 2015	GIC vs No GIC	59	46	13	Embolisation: LGA, RGA, Splenic artery	30
Holscher 2007(51)	RCS	Germany	December 2003 - September 2005	None	83	83		Ligation: LGA, LGV	4
Isomura 1999(52)	RCS	Japan	January 1993 - December 1995	None	37	34		Embolisation: RGA, LGA, Splenic artery	14
Nguyen 2011(53)	RCS	USA	NR	GIC vs No GIC	152	81	71	Ligation: LGA, Short gastric arteries	6
Pham 2017(36)	RCS	USA	July 2008 - January 2014	GIC vs No GIC	30	21	9	Ligation: LGA, Short gastric arteries	121
Prochazka 2018(54)	RCS	Czech Republic	January 2012 - June 2014	None	33	33		Ligation: LGA	20 or 49
Schroder 2010(16)	RCS	Germany	June 1996 - April 2008	GIC vs No GIC	419	238	181	NR	4-5 days
Siegal 2019(55)	RCS	USA	January 2010 - December 2015	GIC vs No GIC	207	38	169	Ligation: LGA, Short gastric arteries	98 days
Wajed 2012(40)	RCS	United Kingdom	April 2004 - January 2010	GIC vs No GIC	131	67	64	Ligation: LGA	14
Yetasook 2013(56)	RCS	USA	October 2008 - July 2011	None	24	24		Ligation: LGA, Short gastric arteries	NR
Veeramootoo 2012(57)	RCT	United Kingdom	NR	GIC vs No GIC	16	8	8	Ligation: LGA	NR

Abbreviations: GIC - Gastric ischaemic conditioning; LGA - left gastric artery; LGV - left gastric vein; NR - Not reported; PCS - prospective cohort study; RCS - retrospective cohort study; RCT - randomised controlled trial; RGA - right gastric artery; USA - United States of America

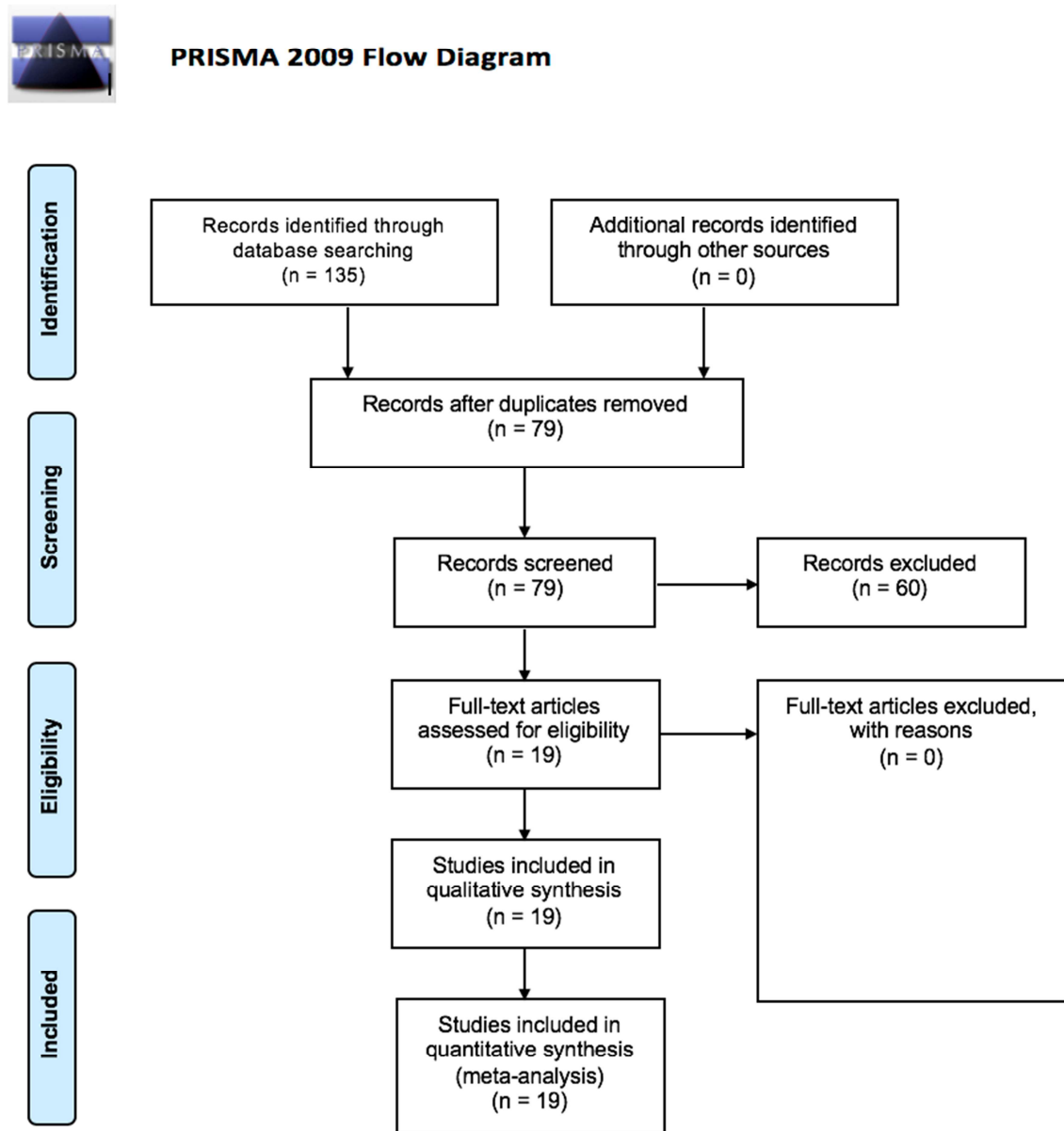
Study Name	Age, years	Male, n	Indication		Neoadjuvant Therapy		T Stage 3/4, n	Overall Stage 3/4, n	MIO, n
			Cancer, n	Benign, n	GIC, n	No GIC, n			
Bludau 2010(37)	61	17	19	0	13	-	NR	NR	NR
Kohler 2019(58)	NR	20	21	1	14	6	NR	NR	0
Prudius 2018(46)	NR	NR	15	0	4	0	NR	NR	NR
Veeramootoo 2009(47)	68	78	97	0	NR	NR	NR	NR	97
Akiyama 1998(35)	62	68	NR	NR	22	6	NR	NR	0
Berrisford 2009(15)	69	67	NR	NR	NR	NR	NR	77	77
Diana 2011(48)	64	46	57	0	5	11	NR	NR	NR
Farran 2010(49)	59.8 (9.3)	32	20	19	NR	-	NR	NR	0
Ghelfi 2016(50)	63	43	59	0	31	5	NR	18	0
Holscher 2007(51)	62	68	83	0	42	-	NR	38	0
Isomura 1999(52)	59	28	37	0	NR	-	NR	NR	NR
Nguyen 2011(53)	65	118	134	18	23	36	NR	NR	152
Pham 2017(36)	64	27	30	0	20	5	NR	11	30
Prochazka 2018(54)	61	30	33	0	33	-	NR	12	33
Schroder 2010(16)	60 (18 - 81)	349	419	0	144	66	183	NR	0
Siegal 2019(55)	65	172	194	13	36	120	NR	96	196
Wajed 2012(40)	67	109	131	0	NR	NR	NR	NR	131
Yetasook 2013(56)	62 (8)	19	24	0	21	-	NR	21	0
Veeramootoo 2012(57)	NR	NR	16	0	NR	NR	NR	NR	16

Table 2 Baseline Demographics of Included studies

Table 3 Summary of postoperative outcomes of gastric ischaemic conditioning

Outcomes	Studies, n	OR (CI95%)	p-value	I ²
Anastomotic Leaks				
Overall	11	0.7973 [0.5115; 1.2428]	0.3	8
Ligation	7	1.2616 [0.6945; 2.2919]	0.4	0
Embolisation	3	0.2494 [0.0939; 0.6620]	0.005	0
Conduit Necrosis				
Overall	4	0.2977 [0.1149; 0.7710]	0.013	0
Ligation	4	0.2977 [0.1149; 0.7710]	0.013	0
Embolisation	0	-	-	-
Anastomotic Stricture				
Overall	5	0.7476 [0.3478; 1.6069]	0.5	20
Ligation	3	0.6496 [0.1834; 2.3007]	0.5	57
Embolisation	2	0.7320 [0.1466; 3.6541]	0.7	0
Overall Complications				
Overall	5	1.0168 [0.4785; 2.1610]	0.9	55
Ligation	4	0.8902 [0.3810; 2.0799]	0.8	62
Embolisation	1	-		
Major Complications				
Overall	3	1.0588 [0.5311; 2.1108]	0.9	0
Ligation	2	0.8976 [0.2471; 3.2604]	0.9	16
Embolisation	1	-		
Pulmonary Complications				
Overall	5	0.8960 [0.5684; 1.4126]	0.6	0
Ligation	2	0.9015 [0.4071; 1.9962]	0.8	24
Embolisation	2	1.3535 [0.5689; 3.2203]	0.5	0
In-hospital mortality				
Overall	7	0.6989 [0.3191; 1.5304]	0.4	21
Ligation	4	1.4411 [0.5313; 3.9088]	0.5	0
Embolisation	2	0.2656 [0.0207; 3.4119]	0.3	55

Figure 1 PRISMA Diagram of included studies



Supplementary Table 1 Summary of terms for literature search

1	Gastric ischemic conditioning.ti,ab.	29
2	ischemic conditioning.ti,ab.	1123
3	Gastric Ischemic Preconditioning.ti,ab.	27
4	Laparoscopic Conditioning.ti,ab.	4
5	Conditioning.ti,ab.	204966
6	1 or 2 or 3 or 4 or 5	204988
7	oesophagectomy.ti,ab.	4378
8	esophagectomy.ti,ab.	23837
9	exp Esophagectomy/	28826
10	7 or 8 or 9	38114
11	6 and 10	129

Supplementary Table 2 Summary of quality assessment of study quality

	Selection	Comparability	Outcome	Overall
Bludau 2010(37)	-	-	-	Non-Comparative
Kohler 2019(58)	2	0	3	5
Prudius 2018(46)	3	0	3	6
Veeramootoo 2009(47)	4	0	3	7
Akiyama 1998(35)	3	0	3	6
Berrisford 2009(15)	4	0	3	7
Diana 2011(48)	3	2	3	8
Farran 2010(49)	-	-	-	Non-Comparative
Ghelfi 2016(50)	3	2	3	8
Holscher 2007(59)	-	-	-	Non-Comparative
Isomura 1999(52)	-	-	-	Non-Comparative
Nguyen 2011(53)	4	0	3	7
Pham 2017(36)	4	0	3	7
Prochazka 2018(54)	-	-	-	Non-Comparative
Schroder 2010(16)	3	0	3	6
Siegal 2019(55)	2	0	3	5
Wajed 2012(40)	3	0	3	6
Yetasook 2013(56)	-	-	-	Non-Comparative

Critical Appraisal of Gastric Conduit Ischaemic Conditioning (GIC) prior to Oesophagectomy: A Systematic Review and Meta-Analysis

1. Nineteen studies reported on GIC, of which 13 were comparative studies.
2. GIC did not appear to reduce anastomotic leakages (OR 0.80, CI₉₅: 0.51 - 1.24, p=0.3) and anastomotic strictures (OR 0.75, CI₉₅: 0.35 - 1.60, p=0.5)
3. However, GIC was associated with reduced rates of conduit necrosis (OR 0.30, CI₉₅: 0.11 - 0.77, p=0.013)

The data has been extracted from all referenced studies for this meta-analysis.

Journal Pre-proof

International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

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None

Please state any sources of funding for your research

None

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

Not Applicable

Research Registration Unique Identifying Number (UIN)

Please enter the name of the registry and the unique identifying number of the study. You can register your research at <http://www.researchregistry.com> to obtain your UIN if you have not already registered your study. This is mandatory for human studies only.

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Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

Study design - SKK, BT
Data Collection - SKK, CB, JRB
Data Analysis - SKK, BT
Writing - SKK, BT

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Sivesh K Kamarajah