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Review Article

CRITICAL CARE

Remote ischaemic preconditioning and survival in noncardiac surgery: a meta-analysis of randomised trials

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Abstract

Background: Remote ischaemic preconditioning (RIPC) is an intervention involving brief periods of limb ischaemia to protect remote organs from subsequent ischaemic injury. Although evidence exists on the beneficial effects of RIPC on biomarkers, its effect on survival is unknown. We performed a meta-analysis of randomised controlled trials (RCTs) to evaluate whether RIPC improves survival in noncardiac surgery.

Methods: We searched several electronic databases for randomised trials comparing RIPC *vs* a control group in adult noncardiac surgical settings. The primary outcome was mortality at the longest follow-up available. We conducted a random-effects meta-analysis to calculate the risk ratio (RR) and 95% confidence intervals (CIs). Bayesian statistics were used to estimate the probability of mortality benefit (RR <1).

Results: We identified 72 RCTs, which included 7457 subjects. Mortality was reported in 28 RCTs and was lower in the RIPC group compared with the control group (88/2122 [4.1%] *vs* 102/1767 [5.8%]; RR 0.74, 95% CI 0.57–0.98, P=0.03; I^2=0%; moderate certainty; number needed to treat = 67), corresponding to a 97.0% probability of any reduction in mortality. RIPC was also associated with a reduced incidence of postoperative stroke (moderate certainty) and with a shorter duration of hospital stay (low certainty).

Conclusions: Remote ischaemic preconditioning was associated with improved survival and reduced postoperative stroke and hospital stay in noncardiac surgery. These findings warrant careful considerations of the benefits of RIPC and support the need for a large, multicentre RCT to confirm these promising results.

Systematic review protocol: CRD42024588358 (PROSPERO).

Keywords: acute kidney injury; anaesthesia; meta-analysis; mortality; noncardiac surgery; organ protection; remote ischaemic preconditioning (RIPC)

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Editor's key points

- Remote ischaemic preconditioning is a promising and cost-effective technique that may reduce postoperative complications after noncardiac surgery.
- The authors included a large number of subjects from randomised clinical trials examining the use of remote ischaemic preconditioning in noncardiac surgical procedures.
- Remote ischaemic preconditioning was found to be associated with improved survival and a decreased rate of major complications after noncardiac surgery. However, large, multicentre randomised controlled trials are required to validate these potential benefits.

More than 300 million noncardiac surgical procedures are conducted globally each year, and the numbers are expected to further increase.[1] In this context, the proportion of older or frail patients undergoing surgical procedures is also increasing, leading to a higher perioperative risk of adverse events and a corresponding possible negative impact on quality of life, length of hospitalisation, and healthcare costs.[2] Consequently, scalable interventions that show promise to reduce perioperative morbidity and mortality, particularly in this population, have the potential to significantly impact global healthcare.

Over the past 20 yr, remote ischaemic preconditioning (RIPC), has gained attention as a promising affordable technique to reduce postoperative complications. RIPC operates on the hypothesis that brief episodes of limb ischaemia can safeguard other organs. During ischaemia, the limb releases a series of molecular mediators into the bloodstream that are proposed to mediate a protective state against subsequent ischaemic insults in both the affected limb and distant organs.[3] Recent evidence has highlighted the complexity of this phenomenon, demonstrating the involvement of multiple mechanisms underlying RIPC, including changes in intercellular communications and activation of humoral, neuronal, and systemic pathways.[4,5] Exosomes seem to play a key role, acting as carriers of biomolecules.[4]

Literature on RIPC has primarily focused on its impact on surrogate biomarkers associated with renal and myocardial injury, with limited investigation on its potential effects on survival and other relevant clinical perioperative outcomes.[6] Indeed, most published studies are underpowered to identify the potential of a beneficial impact of RIPC on clinical outcomes. In the setting of cardiac surgery, positive results of RIPC in biomarkers and clinical outcomes observed in small trials were not confirmed in subsequent large multicentric randomised controlled trials (RCTs).[7,8]

Nonetheless, the potential role of RIPC in adult noncardiac surgery remains understudied. To address this gap in the evidence, we performed a meta-analysis of RCTs to evaluate the impact of RIPC on survival and relevant perioperative outcomes in this population.

Methods

This meta-analysis was registered in the PROSPERO International prospective registry of systematic reviews (CRD42024588358). The following PICO (Population, Intervention, Comparison, Outcome, Study design) criteria were used: adult patients undergoing elective noncardiac surgery (P); remote ischaemic preconditioning (I); standard care or sham intervention (C); mortality at the longest follow-up available (O); and randomised clinical trials (S). This manuscript adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[9] (PRISMA Checklist is available in Supplementary Table S1).

Search strategy and selection criteria

Two researchers independently searched PubMed, Embase, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and proceedings from major congresses to identify relevant published and unpublished studies from inception to June 2024. The complete PubMed search strategy is detailed in the Supplementary material—Search String. All RCTs comparing RIPC with a control group in adult noncardiac surgery setting were eligible. Exclusion criteria were non-parallel design trials (i.e. cross-over), overlapping populations, neurosurgical studies, cardiac surgery studies, studies where RIPC was applied in nonsurgical procedures, and nonhuman studies. Identified articles were merged into a single excel file and deduplicated. Two investigators then independently assessed eligibility at the title/abstract level, followed by full-text reviews of potentially relevant articles. Disagreements were resolved through discussion with one senior investigator. All randomised trials comparing RIPC were included in the qualitative analysis, whereas only studies reporting at least one clinical outcome of interest were included in the quantitative analysis. The corresponding authors of the articles not reporting the primary outcome were contacted twice via e-mail to retrieve the missing data.

Data collection and risk-of-bias assessment

Data were extracted by two investigators using a standardised data collection form. Extracted variables included study identification (journal, first author, and year of publication), patient details (number of patients receiving RIPC *vs* control and surgical specialty), type of control intervention, anaesthetic agents, and primary and secondary outcome data. The primary outcome was all-cause mortality at the longest follow-up available. Secondary outcomes were as follows: kidney function (peak postoperative serum creatinine, peak postoperative serum neutrophil gelatinase-associated lipocalin, glomerular filtration rate, acute kidney injury, and renal replacement therapy), cardiac function (peak postoperative troponin levels, myocardial injury, myocardial infarction, arrhythmias, and congestive cardiac failure), stroke;, and hospital length of stay. All secondary outcomes were extracted as per the author's definitions. We also extracted data on harm or serious adverse events related to RIPC as reported in each study.

The risk of bias for each included RCT was assessed using the Cochrane risk-of-bias tool for randomised trials version 2 (RoB 2).[10] Publication bias was evaluated through visual inspection of the funnel plot. The overall quality of evidence for the primary outcome was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[11]

Data analysis and synthesis

Data analysis was performed using IBM SPSS Statistics for Macintosh (version 28.0, IBM, Armonk, NY, USA). We used a random-effects Mantel–Haenszel model to calculate the risk

ratio (RR) and 95% confidence intervals (CIs) and a fixed-effects Mantel–Haenszel model as sensitivity analysis, using Review Manager (version 5.4.1, Cochrane Collaboration, Oxford, UK). Heterogeneity was quantified using I^2 and Tau^2 statistics. The number needed to treat (NNT) was calculated for mortality using the following formula: NNT = absolute value of (1/[(1 − weighted risk ratio) * absolute risk of control group]), reported whole numbers with decimals rounded up. Statistical significance was defined as $P<0.05$ for all tests and varying RIPC protocols. A Bayesian meta-analysis was conducted using R (version 2019, R Foundation for Statistical Computing 2019, Vienna, Austria) and the bayesmeta package.[12] We used a non-informative normal prior [N~(0, 10^2)] for the effect (μ) and an informative prior for the heterogeneity parameter (τ) based on the work of Turner and colleagues.[13] We then estimated the probability of any benefit (μ<0 on the log scale) and illustrated this by plotting the probability density function on the RR scale. A trial sequential analysis (TSA) was also performed to assess the required information size, using a diversity-adjusted approach with a two-sided alpha of 0.05 and a power of 80%, assuming a relative risk reduction of 10%. TSA was conducted using TSA Viewer software (version 0.9.5.10 Beta, Copenhagen Trial Unit, Copenhagen, Denmark).

We performed subgroup analyses on the effect of RIPC in different surgical interventions, in studies using or avoiding propofol, and in studies having upper or lower limbs as RIPC target. A sensitivity analysis of low *vs* intermediate/high risk-of-bias studies for the primary outcome was also performed. No imputation of missing data and no worst/best-case scenario sensitivity analyses were performed.

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Protocol deviations

During the peer-review process, we made a number of changes. We added fixed-effects sensitivity analyses to the planned random-effects analyses. We also added a subgroup analysis with studies using or avoiding propofol. Finally, we included trials performing RIPC in districts different from upper or lower limbs (e.g. direct vascular clamp of the peripheral vessel) as performed in previous meta-analyses on this topic.

Results

From 3973 records identified through the literature search, we included 72 RCTs,[6,14–84] all but one published in peer-review journals,[29] comprising a total of 7457 patients (Fig. 1 and Table 1). Studies were published between September 2007 and May 2024. Twenty-two studies were performed in abdominal surgery, 20 in vascular surgery, 14 in orthopaedics, six in kidney transplant, four in lung, two in liver transplant, two in plastic surgery, one in lung transplant, and one in head and neck surgery. Four studies were multicentric. Thirty-five studies were conducted in Europe, 28 in Asia, four in North America, two in South America, two in Australia, and one in

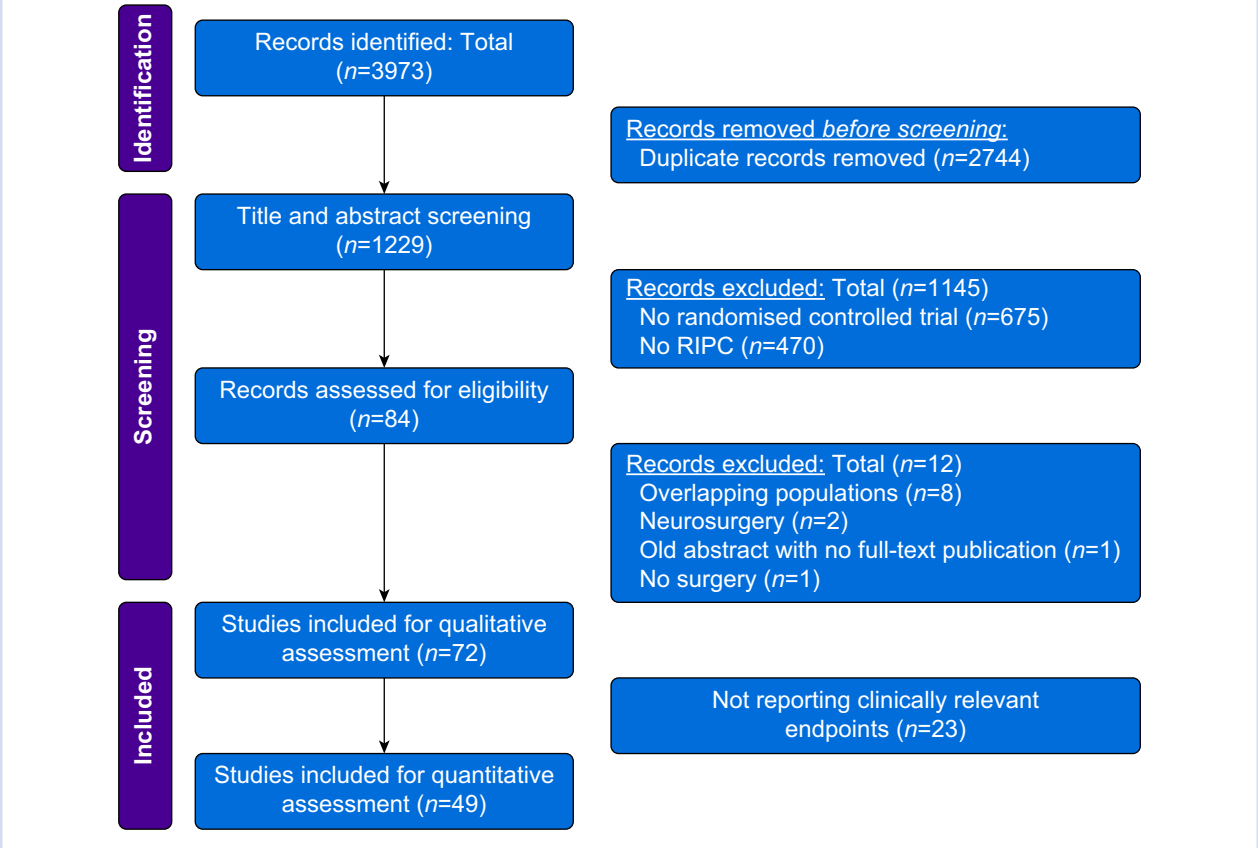

Fig 1. Study selection flowchart. RIPC, remote ischaemic preconditioning.

Table 1 Characteristics, timing, and location of remote ischaemic preconditioning in included studies. RIPC, remote ischaemic preconditioning. *Only qualitative assessment performed. †Cycles performed in different limbs.

First author	Year	RIPC/control	Specialty	Ischaemia minutes	Reperfusion minutes	Cycles	Clamp location
Abdallah MYY[14]	2023	38/38	Vascular surgery	10	10	2†	Upper limb
Ali ZA[15]	2007	41/41	Vascular surgery	10	10	2	Iliac artery
Antonowicz SS[16]	2018	41/43	Abdominal surgery	5	5	3	Upper limb
Arikan MN[17]*	2023	30/30	Orthopaedic surgery	5	5	3	Upper limb
Asadi M[18]*	2022	15/19	Vascular surgery	5	5	3	Upper limb
Bang JY[19]	2019	168/170	Kidney transplantation	5	5	3	Upper limb
Castillo DG[6]	2023	60/60	Vascular surgery	5	5	4	Upper limb
Chen Y[20]	2013	40/40	Kidney transplantation	5	5	3	Lower limb
Choi ES[21]	2019	54/54	Vascular surgery	5	5	4	Lower limb
Chung J[22]	2021	41/40	Kidney surgery	5	5	4	Upper limb
Coverdale NS[23]	2018	71/68	Vascular surgery	5	5	3	Upper limb
Eerik K[24]*	2022	45/47	Vascular surgery	5	5	4	Upper limb
Ekeloef S[25]	2021	316/309	Orthopaedic surgery	5	5	4	Upper limb
Fudickar A[26]	2014	20/20	Plastic surgery	6	6	1	Femoral artery
Garcia S[27]	2016	100/101	Vascular surgery	5	5	3	Upper limb
García-de-la-Asunción J[28]*	2017	27/27	Lung surgery	5	5	3	Lower limb
García-de-la-Asunción J[29]*	2011	20/20	Lung surgery	5	5	3	Upper limb
Han M[30]*	2023	44/44	Abdominal surgery	5	5	3	Upper limb
Hardt JLS (hepatectomy)[31]	2024	51/51	Liver surgery	10	10	3	Upper limb
Hardt JLS (rectal cancer)[32]*	2024	27/27	Abdominal surgery	10	10	3	Upper limb
He Z[33]	2017	45/45	Abdominal surgery	5	5	3	Upper limb
Healy DA[34]	2015	99/99	Vascular surgery	5	5	4	Upper limb
Hou YY[35]	2017	43/22	Kidney surgery	5	5	3	Upper limb
Hu S[36]*	2010	20/20	Orthopaedic surgery	5	5	3	Upper limb
Huang J[37]	2013	41/41	Kidney surgery	5	5	3	Lower limb
Jamshidi F[38]*	2016	20/20	Orthopaedic surgery	5	5	3	Lower limb
Jung KW[39]	2020	149/145	Liver transplantation	5	5	3	Upper limb
Kanoria S[40]	2017	8/8	Liver surgery	10	10	3	Lower limb
Karabayirli S[41]*	2017	50/50	Abdominal surgery	10	10	1	Pneumoperitoneum
Kepler T[42]	2020	49/49	Vascular surgery	5	5	4	Upper limb
Kil HK[43]	2018	8/8	Kidney surgery	5	10	3	Upper limb
Koca K[44]*	2011	15/15	Orthopaedic surgery	5	5	3	Lower limb
Kong E[45]	2023	30/30	Liver surgery	5	5	3	Upper limb
Krag AE[46]	2020	30/30	Head and neck surgery	5	5	4	Upper limb
Kuusik K[47]*	2021	54/57	Vascular surgery	5	5	4	Upper limb
Li C[48]	2013	31/31	Vascular surgery	5	5	3	Upper limb
Li C[49]	2014	108/108	Lung surgery	5	5	3	Upper limb
Lin E[50]	2014	30/30	Lung transplantation	5	5	3	Lower limb
Lin L[51]*	2010	15/15	Orthopaedic surgery	5	5	3	Lower limb
Liu X[52]	2019	70/70	Liver surgery	5	5	3	Upper limb
Memtsoudis SG[53]	2014	17/17	Orthopaedic surgery	5	5	1	Lower limb
Memtsoudis SG[54]	2010	30/30	Orthopaedic surgery	5	5	1	Lower limb
Min SH[55]	2022	23/23	Plastic surgery	5	5	4	Upper or lower
Mouton R[56]	2015	34/35	Vascular surgery	5	5	3	Upper limb
Murphy N[57]	2014	31/31	Vascular surgery	5	5	3	Upper limb
Murphy T[58]	2010	10/10	Orthopaedic surgery	5	5	3	Lower limb
Nicholson ML[59]	2015	40/40	Kidney transplantation	5	5	4	Lower limb
Nielsen MB[60]	2019	110/115	Kidney transplantation	5	5	4	Lower limb
Oh CS[61]	2020	29/34	Orthopaedic surgery	5	5	3	Lower limb
Oh CS[62]*	2017	36/36	Orthopaedic surgery	5	5	3	Upper limb
Park SK[63]	2018	30/30	Orthopaedic surgery	5	5	3	Upper limb
Pedersen TF[64]	2018	72/70	Vascular surgery	5	5	3	Upper limb
Pereira FEC[65]*	2016	10/10	Abdominal surgery	5	5	1	Lower limb
Rakić M[66]*	2018	20/20	Liver surgery	5	5	3	Upper limb
Robertson FP[67]	2017	20/20	Liver transplantation	5	5	3	Lower limb
Salazar Islas TL[68]	2023	25/25	Abdominal surgery	5	10	3	Lower limb
Sullivan PJ[69]*	2009	12/13	Orthopaedic surgery	5	5	3	Lower limb
Teo JY[70]	2020	24/26	Liver surgery	5	5	4	Upper limb
Thomas KN[71]	2016	42/43	Vascular surgery	5	5	3	Upper limb
Van Zeggeren L[72]	2021	46/46	Abdominal surgery	5	5	3	Upper limb
Veighey KV[73]	2019	614/198	Kidney transplantation	5	5	4	Upper limb
Wahlstrom KL[74]*	2023	30/30	Abdominal surgery	5	5	4	Upper limb

Continued

Table 1 Continued

First author	Year	RIPC/control	Specialty	Ischaemia minutes	Reperfusion minutes	Cycles	Clamp location
Wahlstrom KL[75]*	2022	65/72	Orthopaedic surgery	5	5	4	Upper limb
Walsh SR (aortic)[76]	2010	22/18	Vascular surgery	10	10	2†	Iliac artery
Walsh SR (carotid)[77]	2010	34/36	Vascular surgery	10	10	2†	Lower limb
Walsh SR (endovascular aneurysm repair)[78]	2009	18/22	Vascular surgery	10	10	2†	Lower limb
Wu G[79]	2020	40/40	Liver surgery	5	5	3	Upper limb
Wu J[80]*	2014	24/24	Kidney transplantation	5	5	3	Iliac artery
Yang X[81]*	2023	40/40	Abdominal surgery	5	5	3	Upper limb
Yang Y[82]*	2024	80/80	Lung surgery	5	5	3	Lower limb
Yi M[83]*	2023	50/50	Abdominal surgery	5	5	3	Upper limb
Zhao W[84]	2017	63/126	Vascular surgery	5	5	twice daily for 2 weeks	Upper limb

Africa. Major exclusions are detailed in Supplementary Table S2. In 44 studies, RIPC was obtained by inflating and deflating a cuff on the upper limbs. In 22 studies, the cuff was positioned on the lower limbs. In one study, the cuff was applied to either the upper or lower limbs. Other methods were adopted in the remaining five studies. Most studies used an RIPC strategy of 5 min of inflation followed by 5 min of deflation, for a total of three to four cycles (Table 1). Eighteen trials did not report the anaesthetic plan. Although 44 studies used propofol for infusion, maintenance, or sedation, only 10 trials avoided propofol.

Of the 72 included studies, 49 reported at least one clinical outcome of interest and were therefore included in the quantitative analysis.

Primary outcome

RIPC was associated with a significant reduction in overall mortality compared with control (88/2122 [4.1%] *vs* 102/1767 [5.8%]; RR 0.74, 95% CI 0.57–0.98, P=0.03; I^2=0%; moderate certainty; NNT= 67, with 28 studies and 3889 patients included) (Fig. 2 and Supplementary Table S3). Bayesian

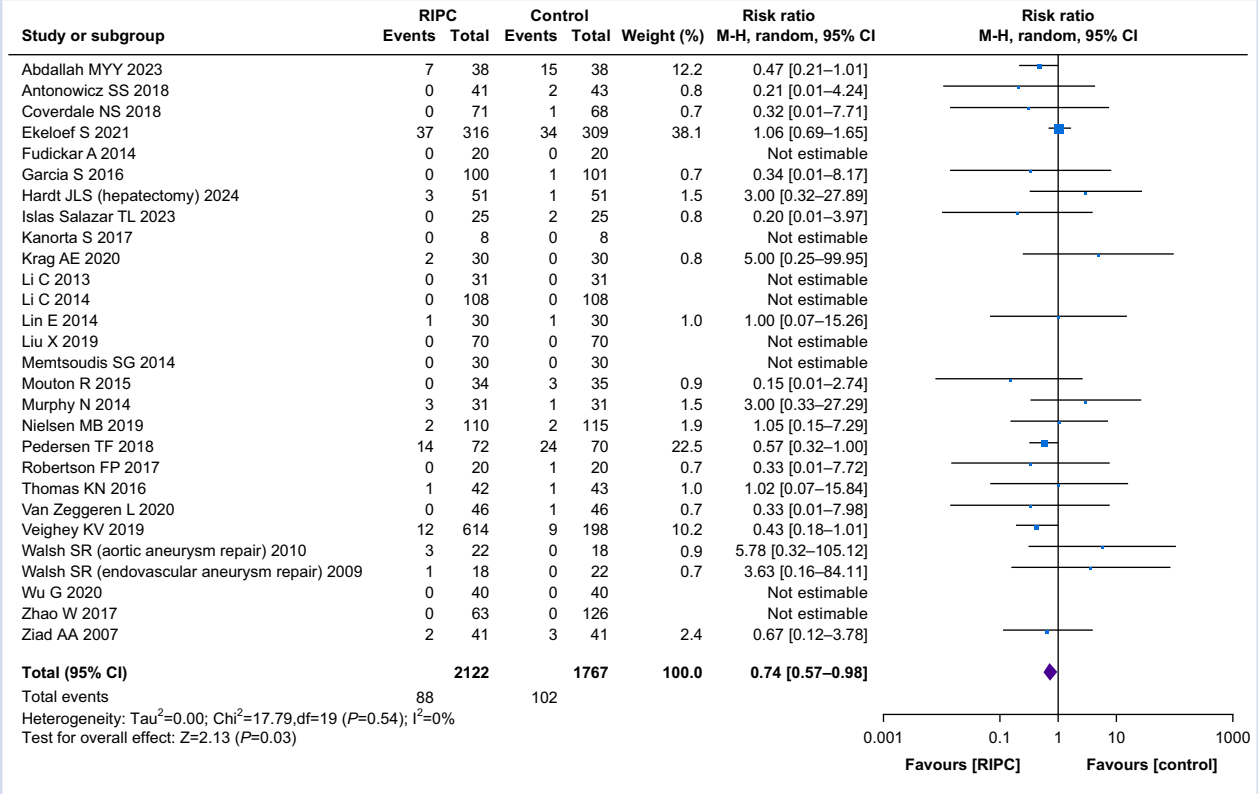

Fig 2. Forest plot for postoperative mortality. RIPC, remote ischaemic preconditioning.

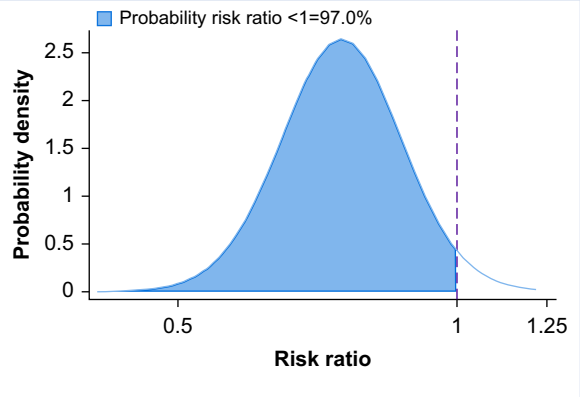

Fig 3. Probability density function for the combined posterior distribution of mortality difference.

analysis revealed a 97.0% probability of mortality reduction from RIPC (Fig. 3). The funnel plot showed no major asymmetry (Supplementary Fig. S1). The Z-curve of the TSA did not cross the O'Brien–Fleming alpha-spending boundary with a required information size of 5,705 (Supplementary Fig. S2).

According to the RoB 2 assessment, the majority of studies were considered to be at low (54%) risk of bias or with some concerns (39%) (Supplementary Fig. S3). When considering mortality, the risk of bias was deemed low, as the reporting of mortality outcomes was not affected by selective outcome reporting. Consequently, the overall GRADE assessment resulted in a moderate level of evidence supporting a reduction in mortality with RIPC. Accordingly, the overall grading resulted in a moderate level of evidence in favour of a reduction in mortality with RIPC, as reported in Supplementary Table S3. The confidence interval remains wide, preventing a precise estimation of the magnitude of this effect based on the available data.

The sensitivity analysis using the fixed effect confirmed the results of the primary analysis (Table 2 and Supplementary Fig. S4), and we found no difference in the direction and magnitude of the effect between low and intermediate/high risk-of-bias studies (P for interaction = 0.43; Supplementary Fig. S5). Similarly, we found no interaction between patients undergoing vascular surgery *vs* other surgeries (P for interaction = 0.18; Supplementary Fig. S6), between studies using or avoiding propofol (P for interaction = 0.23; Supplementary Fig. S7), and between studies having upper or lower limbs as RIPC target (P for interaction = 0.78; Supplementary Fig. S8).

Secondary outcomes

We observed a reduction in postoperative biomarkers of renal dysfunction such as peak postoperative serum creatinine (15 studies, 1292 patients; mean difference = −5.45, 95% CI −8.09 to −2.81, P=0.05; low certainty) (Supplementary Figs. S9–S11 and Supplementary Table S3) in RIPC patients with no statistically significant difference in the rate of clinical acute kidney injury or in the need for renal replacement therapy (Supplementary Figs. S12 and S13).

We found no statistically significant differences in peak postoperative cardiac troponin value, myocardial injury, myocardial infarction, arrhythmias, and heart failure (Supplementary Figs. S14–S18).

Notably, we observed a reduction in stroke rate (10 studies, 1642 patients; RR 0.46, 95% CI 0.24–0.87, P=0.02; moderate certainty) (Fig. 4, Supplementary Fig. S19, and Supplementary Table S3) and in length of hospital stay (30 studies, 3560 patients; mean difference = −0.8 days, 95% CI −0.26 to −0.34,

Table 2 Outcome results using the random-effects method and sensitivity analyses using the fixed-effects method. MD, mean difference; NGAL, neutrophil gelatinase-associated lipocalin; RR, risk ratio; SMD, standardised mean difference. *Used only for serum troponin comparison.

Outcomes	Number of studies	Number of patients	Random effect, RR (95% CI)	Random effect, P-value	Fixed effect, RR (95% CI)	Fixed effect, P-value	I^2 (%)
Mortality	28	3889	0.74 (0.57–0.98)	0.03	0.77 (0.59–0.99)	0.046	0
Stroke	10	1642	0.46 (0.24–0.87)	0.02	0.44 (0.24–0.83)	0.01	0
Acute kidney injury	18	1661	0.99 (0.74–1.32)	0.95	0.98 (0.82–1.17)	0.80	42
Renal replacement therapy	7	944	0.98 (0.71–1.36)	0.90	1.03 (0.78–1.37)	0.83	7
Myocardial injury	22	2540	0.88 (0.70–1.11)	0.28	0.81 (0.69–0.95)	0.01	31
Myocardial infarction	20	2260	0.81 (0.60–1.10)	0.17	0.76 (0.60–0.98)	0.03	12
Arrhythmia	8	639	1.32 (0.73–2.42)	0.36	1.38 (0.79–2.41)	0.26	0
Congestive cardiac failure	8	1334	0.64 (0.31–1.33)	0.24	0.69 (0.35–1.35)	0.28	0
Outcomes	**Number of studies**	**Number of patients**	**Random effect, MD/SMD* (95% CI)**	**Random effect, P-value**	**Fixed effect, MD/SMD* (95% CI)**	**Fixed effect, P-value**	**I^2 (%)**
Serum creatinine	15	1292	−6.20 (−12.40 to −0.01)	0.049	−5.45 (−8.09 to −2.81)	<0.01	65
Serum NGAL	5	504	−13.22 (−21.38 to −5.06)	<0.01	−13.16 (−19.13 to −7.19)	<0.01	5
Glomerular filtration rate	10	1566	2.49 (0.68–4.31)	<0.01	2.10 (1.28–2.92)	<0.01	55
Serum troponin	7	1280	−0.18 (-0.38 to 0.02)	0.07	−0.14 (−0.25 to −0.03)	0.01	65
Hospital length of stay	30	3560	−0.75 (−1.17 to −0.32)	<0.01	−0.34 (−0.47 to −0.20)	<0.01	78

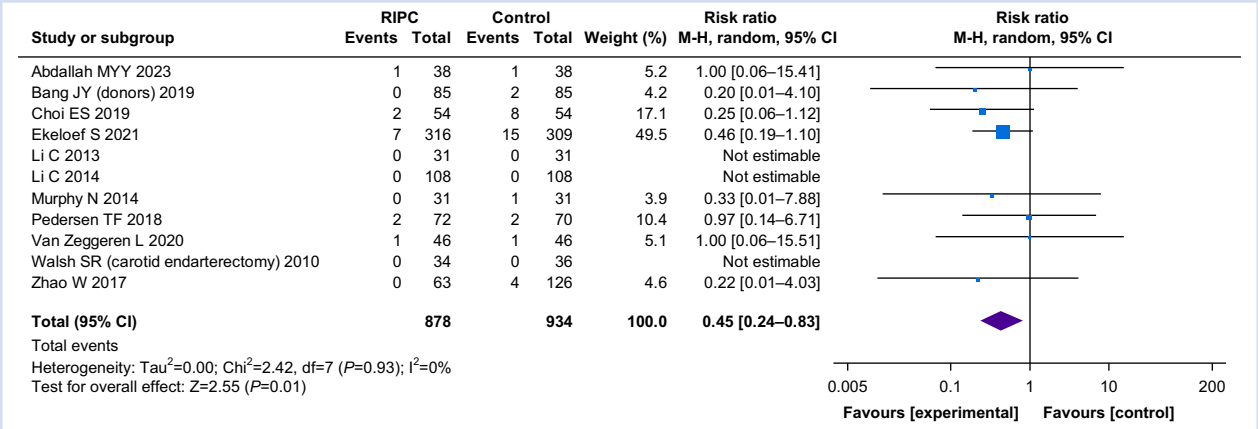

Fig 4. Forest plot for postoperative stroke rate. RIPC, remote ischaemic preconditioning.

P<0.001; low certainty) (Supplementary Fig. S20 and Table S3). The confidence interval for stroke rate remains wide, limiting the precision of the estimated stroke reduction.

The Rob2 and GRADE assessments for the secondary outcomes are reported in Supplementary Figures S21–S23 and Table S3.

Adverse events

Adverse events were reported in seven RCTs, with four studies reporting episodes of petechiae in 29/732 (4.0%) RIPC patients, three studies reporting limb ischaemia in 7/152 (4.6%) RIPC patients, and one study reporting one episode of deep vein thrombosis that occurred among the 99 patients (1%) receiving RIPC.

Discussion

General interpretation of the results

In this meta-analysis of RCTs, we found a 25% relative risk reduction in mortality in noncardiac surgery patients treated with RIPC as compared with standard care. This corresponded to an NNT <100 and a 97% probability of mortality reduction using a complementary Bayesian approach. We also found a reduction in perturbation of kidney biomarkers, in the rate of postoperative stroke, and in length of hospital stay in patients receiving RIPC.

Over the past two decades, the number of clinical trials on RIPC in clinical practice has steadily increased, driven by the positive results from animal studies.[85] Despite animal research suggesting possible beneficial effects, the existing RCTs have been underpowered to detect any effect of RIPC on mortality. Similarly, earlier meta-analyses could not identify a significant survival advantage in patients treated with RIPC for a variety of reasons. Zhang and colleagues[86] focused on specific surgical settings, whereas Papadopoulou and colleagues[87] and similar publications concluded their search before November 2021, missing more recently published RCTs. Characteristics and outcomes of the previous meta-analyses are provided in Supplementary Table S4.

Our study suggests that RIPC might reduce the rate of postoperative stroke. Perioperative stroke is a rare but potentially catastrophic complication after noncardiac surgery, characterised by high rates of mortality and long-term disability. A recent retrospective analysis of a large US database indicated that the incidence of overt stroke, defined as an acute event with neurological deficits lasting more than 24 h, ranged from 0.03% to 4%.[88] The number of patients experiencing this condition in the postoperative period could be even greater considering the incidence of covert stroke, a phenomenon diagnosed by radiological imaging but not easily recognised clinically. The international cohort study NEUROVISION reported an incidence of perioperative covert stroke of 7%.[89] Covert stroke is associated with postoperative delirium, cognitive decline, and long-term disability. More than 20% of patients with perioperative stroke will die within 30 days, and more than 50% will develop severe disability and diminished quality of life.[90] Although some preoperative risk factors can be optimised before surgical procedures, there is no clear scientific evidence supporting a preventive strategy to reduce the risk of perioperative stroke.

Limitations of included evidence

The possible beneficial effects of RIPC appear to be inhibited by several factors, including clinical conditions (e.g. prolonged hyperglycaemia[91]), drugs (e.g. beta-blockers, theophylline, and sulfonylureas[92]), and anaesthetic agents. According to Rossaint,[93] RIPC and propofol had an unfortunate relationship. Indeed, animal and human studies have indicated that this hypnotic drug could interfere with the neuronal and humoral pathways, diminishing RIPC organ protection.[94]

Limitations of the review process

Our study has limitations. We did not perform missing data imputation, introducing a potential bias by excluding studies with incomplete data. Moreover, despite strategies to address heterogeneity, some degree of variability among study results remains.

Despite a moderate level of certainty regarding the benefits for both mortality and stroke reduction, the broad confidence intervals constrain the precision and reliability of these estimates, preventing a definitive quantification of the effect. Moreover, the required information sizes were not reached in

the TSA, and the boundaries were not crossed, indicating that the evidence might be nonconclusive.

Our study also has strengths. This meta-analysis exclusively included RCTs, which constitute the highest level of medical evidence.[95] Methodological strengths include a complementary Bayesian and trial sequential analyses to help contextualise the findings. To the best of our knowledge, this meta-analysis is the first to demonstrate a significant mortality reduction from RIPC in patients undergoing noncardiac surgery.

Implications for practice and future research

An international prospective cohort study supported by the EUSOS group[2] reported that the incidence of in-hospital mortality after noncardiac surgery was ~4%. Because of the high number of surgical procedures performed annually, death after surgery is the second leading cause of mortality in the USA.[96] Therefore, any clinical strategy that can decrease postoperative mortality can save thousands of lives every year. With a 25% reduction in mortality, a simple learning curve, minimal costs, and limited side-effects, RIPC could serve as an effective and lifesaving intervention in both high-income and low- and medium-income countries.

Previous studies could not identify the best method for administering RIPC, whether through lower or upper limb ischaemia or regarding the number and duration of ischaemic cycles. Despite the lack of consensus, the majority of the RCTs conducted to date administered RIPC to the upper limb using 5-min cycles of ischaemia induced by a common blood pressure cuff or tourniquet. These interventions can be easily implemented at general anaesthesia induction, without patient discomfort, with minimal costs, and without prolonging surgical duration. With over three hundred million surgeries conducted globally each year, RIPC has the potential to significantly enhance perioperative survival. Compared with the previously reported reduction in biomarkers with RIPC, our findings also indicate improvements in patient-centred outcomes such as stroke and length of hospital stay. Notwithstanding our findings, the evidence from cardiac surgery should give us some measure of equipoise to conduct further study. Therefore, additional large multicentre RCTs in adults undergoing noncardiac surgery are necessary to confirm the positive results of this meta-analysis and provide a more precise estimate of the magnitude of the effect of RIPC overall and in specific subgroups (e.g. older adults and those at highest cardiovascular risk). The ongoing PRINCE trial[97] will randomise 1100 patients to receive RIPC or a sham procedure in the setting of noncardiac surgery. In addition to the huge sample size, other strengths of this trial will include its double-blind design and multinational participation.

Conclusions

This meta-analysis of RCTs demonstrated that remote ischaemic preconditioning is associated with improved survival and reduced postoperative stroke and hospital stay in noncardiac surgery. These findings warrant careful considerations of the benefits of remote ischaemic preconditioning and support the need for a large, multicentre RCT to confirm these promising results.

Authors' contributions

Conceptualisation: SF, GiL
Data collection: SF, GaL, RDC
Formal analysis: SF, RL, ST, VC, SV, TCL, GiL, MG
Methodology: SF, TCL, GiL
Writing—original draft preparation: SF, TCL, GiL, MG
Writing—review and editing: RL, ST, VC, SV, GaL, RDC
Validation: SF, RL, ST, VC, SV, GaL, RDC, GiL, MG
Supervision: GiL
Read and agreed to the published version of the manuscript: all authors

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Declaration of interest

The authors declare that they have no conflict of interest.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT 4o to assist with proofreading and language refinement. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Appendix

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Appendix A. Supplementary data

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