



Review article

Association of intraoperative hypotension and severe postoperative complications during non-cardiac surgery in adult patients: A systematic review and meta-analysis

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ABSTRACT

Background: Intraoperative hypotension (IOH) is a common side effect of non-cardiac surgery that might induce poor postoperative outcomes. The relationship between the IOH and severe postoperative complications is still unclear. Thus, we summarized the existing literature to evaluate whether IOH contributes to developing severe postoperative complications during non-cardiac surgery.

Methods: We conducted a comprehensive search of PubMed, Embase, Cochrane Library, Web of Science, and the CBM from inception to 15 September 2022. The primary outcomes were 30-day mortality, acute kidney injury (AKI), major adverse cardiac events (myocardial injury or myocardial infarction), postoperative cognitive dysfunction (POCD), and postoperative delirium (POD). Secondary outcomes included surgical-site infection (SSI), stroke, and 1-year mortality.

Results: 72 studies (3 randomized; 69 non-randomized) were included in this study. Low-quality evidence showed IOH resulted in an increased risk of 30-day mortality (OR, 1.85; 95% CI, 1.30–2.64; $P < .001$), AKI (OR, 2.69; 95% CI, 2.15–3.37; $P < .001$), and stroke (OR, 1.33; 95% CI, 1.21–1.46; $P < .001$) after non-cardiac surgery than non-IOH. Very low-quality evidence showed IOH was associated with a higher risk of myocardial injury (OR, 2.00; 95% CI, 1.17–3.43; $P = .01$), myocardial infarction (OR, 2.11; 95% CI, 1.41–3.16; $P < .001$), and POD (OR, 2.27; 95% CI, 1.53–3.38; $P < .001$). Very low-quality evidence showed IOH have a similar incidence of POCD (OR, 2.82; 95% CI, 0.83–9.50; $P = .10$) and 1-year-mortality (OR, 1.66; 95% CI, 0.65–4.20; $P = .29$) compared with non-IOH in non-cardiac surgery.

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Conclusion: Our results suggest IOH was associated with an increased risk of severe postoperative complications after non-cardiac surgery than non-IOH. IOH is a potentially avoidable hazard that should be closely monitored during non-cardiac surgery.

1. Introduction

Intraoperative hypotension (IOH) is a common side-effect during non-cardiac surgery that has received much attention recently because of its frequent occurrence and presumed adverse consequences [1]. More than 90% of patients receiving anesthesia for the surgery are expected to experience one or more IOH [2]. Factors such as age, surgical type, anesthetic drugs, surgical manipulation, and existing comorbidities can contribute to developing IOH [3,4]. IOH reduces perfusion of organs and results in major kidney damage, neurological or cardiac events, and even death [5]. The rate of acute kidney injury, 30-day mortality, myocardial injury, and postoperative delirium can be up to 23.7%, 8.0%, 2.3%, and 14%, respectively. However, not all studies have reported an association between IOH and postoperative complications [6]. Clinical studies on the association between IOH during non-cardiac surgery and postoperative adverse outcomes remain unclear and controversial [6–8].

Until now, no widely accepted definition of IOH has been available [9]. The incidence of IOH varies in the literature depending on its definition used [9]. Several reviews [10,11] have focused on the association of IOH with postoperative morbidity and mortality. However, the duration of IOH was not reported, and the selected outcomes are not comprehensive in these reviews, meaning this important topic has yet to be fully explored. Furthermore, several large cohort studies [20,24,43,44] focusing on this issue have been published recently.

Therefore, the authors decided to conduct an updated meta-analysis to evaluate the effects of IOH on postoperative organ dysfunction and severe postoperative complications in non-cardiac surgery.

2. Methods

Our study aim to appraise the association of IOH with severe postoperative complications in patients undergoing non-cardiac surgery. We wrote the review based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (registration number: CRD42021278672) [12].

2.1. Data sources, search strategy, and eligibility criteria

We conducted a comprehensive literature search of PubMed, Embase, Cochrane Library, Web of Science, and the Chinese Biomedical Literature database (CBM) from inception to 10 July 2022. Weekly e-mail alert was received on the basis of a previously developed search strategy saved in PubMed (i.e., 'MyNCBI') and Embase for any new potential studies. The literature search was rerun for all relevant databases on 15 September 2022. No limits or filters on the searches were applied. We also hand-searched the references of selected studies for potentially relevant articles. Combinations of the following Medical Subject Headings (MeSH) terms and keywords were used: hypotension, hypotensive, blood pressure, artery pressure, arterial pressure, systolic pressure, diastolic pressure, vascular hypotension, low blood pressure, intraoperative period, intraoperative periods, low mean arterial pressure, intraoperative, intra-operative, complication, complications, mortality, fatal outcome, organ damage, organ failure, postoperative cognitive dysfunction, kidney injury, AKI, heart failure, myocardial damage, renal failure, cerebrovascular accident, non-cardiac surgery, postoperative. **Appendix S1** shows the detailed search strategy.

Studies were eligible if they met the predefined inclusion and exclusion criteria described in **Appendix S2**.

2.2. Study selection

Two reviewers (JY and HW) independently screened titles and abstracts for potential inclusion. A full-text assessment was made to determine the final inclusion of the potentially relevant articles. Between each assessment, we discussed the results to reach a consensus on interpreting the inclusion criteria. We resolved any disagreements regarding study eligibility by consensus, and a third reviewer (XDD) was consulted if necessary. The relevant study authors were contacted for clarification if the information required to assess eligibility was unavailable or unclear. We used EndNote software version X8 (Clarivate Analytics) to identify duplicate publications. When a hospital or institution published their cases more than once, if the recruitment periods overlapped, we included the paper with a bigger sample to minimize the possibility of double counting [13].

2.3. Data extraction

All data were collected using a predefined standardized form. Two authors (HL and SSX) extracted the data independently and in duplicate. We resolved discrepancies through discussion to achieve a consensus. A pilot test was performed to ensure consistency in the data extraction process before the formal data collection. Severe postoperative complications were defined according to the Clavien-Dindo classification (grade III, IV, or V) [14].

The primary outcomes were 30-day mortality, acute kidney injury (AKI), major adverse cardiac events (myocardial injury or

myocardial infarction), postoperative cognitive dysfunction (POCD), and postoperative delirium (POD). Secondary outcomes included surgical-site infection (SSI), stroke, and 1-year mortality. The following data were extracted as follows: general characteristics of included studies (author names, title, publication date), type of the study, sample size, the definition of IOH, study subject characteristics (demographic characteristics, age, sex, comorbidities, type of surgery), outcome measures and analyses (number of events, types of postoperative patient outcomes). Study authors were contacted to obtain missing information or clarify the available information. However, we have yet to receive a response at the time of submission.

2.4. Risk of bias and certainty of evidence

Two reviewers (HL and XY) assessed the risk of bias in included studies using the Cochrane Risk of Bias tool 2.0 (RoB 2) for randomized trials and the Newcastle-Ottawa scale (NOS) for observational cohort and case-control studies [15,16]. There are five domains of bias included in RoB 2: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. Three levels can be assigned to each domain: low risk of bias, some concerns, or high risk of bias. For cohort and case-control studies, there were three grouping items of the NOS scale as follows: selection (maximum 4 points), comparability (maximum 2 points), and exposure/outcomes (maximum 3 points). An observational study can have a maximum of nine stars. We categorized the observational study as poor (0–3 points), fair (4–6 points), or high (≥ 7 points) quality. Any disagreements that arose between the reviewers were resolved through discussion. A third reviewer (XDD) was to settle unresolved disputes. We used the GRADEpro guideline development tool (GDT) app to rate evidence and present it in a summary of findings table [17].

2.5. Data analysis

Characteristics of each study and results were described and tabulated. Heterogeneity between studies was calculated using the I^2 statistic, which describes the percentage of total variation across studies attributable to heterogeneity rather than chance. The degree of heterogeneity was classified into four categories: low ($I^2 \leq 25\%$), moderate ($25\% < I^2 \leq 50\%$), large ($50\% < I^2 \leq 75\%$), or very large ($I^2 > 75\%$). $I^2 > 75\%$ is considered to indicate substantial heterogeneity. We used the an inverse variance, a fixed-effects method if I^2 was less than 50%. For I^2 was 50% or greater, a random-effects method was used. Publication bias was assessed by visually inspecting a funnel plot and also evaluated by using the Egger test. A two-sided p-value less than 0.05 will be considered statistically significant. All analyses will be performed using Stata statistical software version 13.0 (StataCorp, College Station, Texas).

We planned a sensitivity analysis, excluding studies at high risk of bias (e.g., NOS score less than four stars) to assess the robustness of our findings. Considering transplant surgery had distinctly different patient populations and surgical manipulation from non-cardiac surgery, we planned subgroup analyses by the type of surgery (transplant surgery vs. non-transplant surgery).

3. Results

3.1. Search results and study selection

The initial search in PubMed ($n = 284$), Embase ($n = 2877$), Cochrane Library ($n = 459$), Web of Science ($n = 128$), and the CBM ($n = 89$) resulted in 3837 articles. Twelve articles were identified through hand-searching. A total of 269 potentially eligible records were identified after screening ($n = 214$) and removing duplicates ($n = 3365$). 197 articles were excluded after full-text assessment (reasons for exclusion are described in **Appendix S3**). Two articles focused on similar outcomes were reported by the same hospital, and the study period overlapped [18,19]. Thus, we only included the study with a bigger sample to minimize the possibility of double counting [19]. The flowchart of the study selection process is presented in **Fig. 1**.

3.2. Study characteristics

A total of 72 studies published between 1998 and 2022 were included in the systematic review and meta-analysis [7,19–89]. These articles were published in English, Portuguese, and Chinese (with sample sizes ranging from 28 to 358,391). Sixty-nine (95.83%) were observational studies, and three (4.17%) were randomized controlled trials (RCTs). The included studies showed heterogeneity in the participant characteristics, the definition of IOH, and the duration of IOH. Twenty-eight studies investigated the effect of IOH on AKI, 4 studied myocardial injury, 10 studied myocardial infarction, 4 reported stroke, 17 reported postoperative delirium (POD), 7 reported postoperative cognitive decline (POCD), 7 studies reported 30-day mortality, 2 reported 1-year mortality, and 3 reported surgical-site infection (SSI). The main characteristics of the included studies are presented in **Table 1**. **Appendix S4** shows the definition of the outcomes used in the included studies.

3.3. Assessments of risk of bias for each included study

The risk of bias was mostly low-to-moderate for observational studies, and only three cohort [36,83,89] studies were graded as poor quality, indicating that most of the studies were of fair-to-high quality (**Appendix S5**). Two randomized studies [29,45] were at low risk of bias, and one [38] was at medium risk (**Appendix S6**).

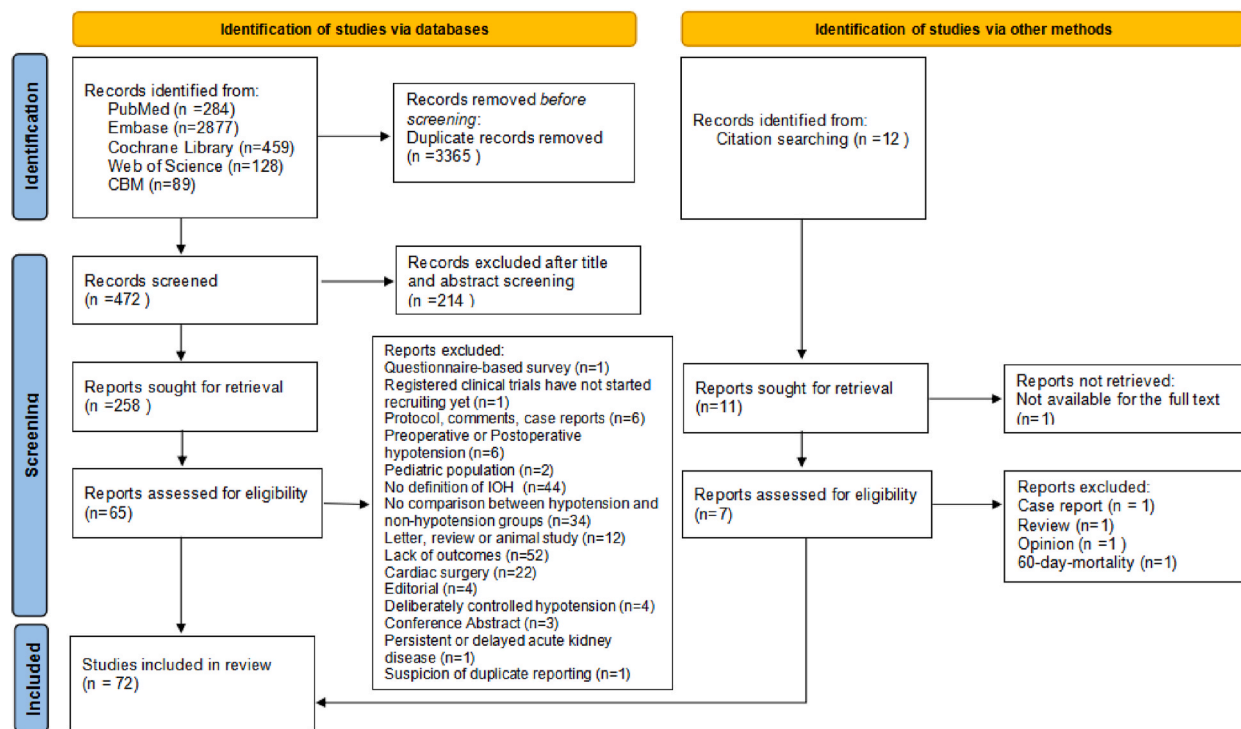


Fig. 1. PRISMA Flow Diagram.

3.4. Primary outcomes

3.4.1. 30-Day mortality

Seven studies [7,21,34,47,53,72,89] reported the association between IOH and risk of 30-day mortality and included 68,881 participants and 1377 deaths (2.00%). Low-quality evidence showed that, compared with non-IOH, IOH was associated with increased 30-day mortality (OR, 1.85; 95% CI, 1.30–2.64; $P < .001$; $I^2 = 83\%$) after non-cardiac surgery (Fig. 2).

3.4.2. AKI

Twenty-eight studies [19,20,22–26,28,30,33,41,51,54,59,63,67,68,70,73–80,85,88] investigated the effect of IOH on AKI and included 160,836 participants and 10,497 AKI (6.52%). Low-quality evidence showed that IOH was associated with a higher risk of postoperative AKI (OR, 2.69; 95% CI, 2.15–3.37; $P < .001$; $I^2 = 88\%$) within 7 days after non-cardiac surgery than non-IOH (Fig. 3).

Major adverse cardiac events (myocardial injury or myocardial infarction)

Four studies [19,21,42,47] reported myocardial injury, and 10 studies [21,29,32,33,42,45,48,52,61,65] addressed myocardial infarction. Very low-quality evidence showed that adult patients with hypotension during non-cardiac surgery were more likely to have a postoperative myocardial injury (OR, 2.00; 95% CI, 1.17–3.43; $P = .01$; $I^2 = 96\%$) (Fig. 4). The association between IOH and myocardial infarction was similar, with IOH associated with an increased risk of myocardial infarction (OR, 2.11; 95% CI, 1.41–3.16; $P < .001$; $I^2 = 84\%$; very low certainly) after non-cardiac surgery (Fig. 5).

3.4.3. POCD and POD

Only six non-randomized studies [46,55,64,69,81,83] and one randomized trial [38] with a sample size of 643 participants reported the outcomes of POCD (49 of 150 vs. 78 of 493 [19.75%]). Very low-quality evidence showed that adult patients with or without IOH during non-cardiac surgery had a similar likelihood of POCD (OR, 2.82; 95% CI, 0.83–9.50; $P = .10$; $I^2 = 77\%$) (Appendix S7). In the analysis of POD [27,31,35–38,43,45,49,56–58,62,66,82–84], results with very low-quality evidence showed that a higher risk of POD was associated with IOH (OR, 2.27; 95% CI, 1.53–3.38; $P < .001$; $I^2 = 81\%$) compared with non-IOH (Appendix S8).

3.5. Secondary outcomes

3.5.1. SSI

Three studies reported SSI (178 of 1031 vs. 354 of 2594 [14.68%]). One [39] of these studies reported no difference between the IOH and non-IOH groups regarding the development of SSI (OR, 1.10; 95% CI, 0.87–1.38). However, the other two studies [60,71] provided evidence that IOH was associated with a higher risk of SSI than non-IOH. Overall, low-quality evidence showed no significant

Table 1
Characteristics of the included studies.

First author, yr	Study design	Study period	Country	Setting	Age (yr)	Sex (male, %)	Comorbidity (%)	Type of surgery	Type of anesthesia	Outcomes	sample size	No. of IOH	Definition and duration of IOH	Main findings
Park 2020	Cohort	2004–2015	South Korea	Seoul National University Hospital; Seoul National University Bundang Hospital	58 (44–70)	47.4	Not reported	General, Neurosurgery, Orthopedics, Urologic, Thoracic surgery	GA; LA	AKI	75,224	53,180	MAP<65 mmHg; Not reported	IOH is associated with higher risks of postoperative AKI after noncardiac surgery
Van Waes2016	Cohort	2010/01/01–2011/12/31	Canada	University Health Network Hospital Toronto; University Medical Center Utrecht	73.7 (7.8)	69.1	61.6	Vascular surgery	GA; LA	Myocardial injury; myocardial infarction; 30-day mortality	890	450	MAP<60 mmHg; >1 min	IOH was associated with postoperative myocardial injury
Liao 2020	Cohort	2017/11–2019/11	China	Affiliated Hospital of Qingdao University	59 (52–65)	60.8	40.0	Liver resection	GA	AKI	796	164	MAP<65 mmHg; >10 min	IOH was associated with AKI in age ≥65 years patients following liver resection
Sun 2015	Cohort	2009/11–2012/12	Canada	Toronto General Hospital	61 (14)	47.0	Not available	Noncardiac	GA	AKI	5127	3337	MAP<65 mmHg; >5 min	IOH is associated with postoperative AKI
Tang 2019	Cohort	2011/12/01–2016/07/01	China	Third Xiangya Hospital	18–60	55.6	Not available	Noncardiac	GA	AKI	4952	144	MAP<55 mmHg; >10 min	There was a considerably increased risk of postoperative AKI when IOH last for more than 10 min
Braüner2020	Cohort	2018/01/01–2018/12/31	Denmark	Copenhagen University Hospital	82.4 (8.8)	73.2	46.2	Hip fracture	GA	AKI	299	114	MAP≤55 mmHg; >5 min	AKI was common following hip fracture surgery and associated with increased mortality
Davison 2022	Cohort	2015/01–2019/12	USA	Providence Sacred Heart Medical Center	62.3 (16.6)	54.0	57.0	Noncardiac	GA	AKI	3507	1732	MAP<55 mmHg; >10 min	IOH was an independent risk factor for AKI
Tobar2018	Cohort	2010/01–2013/03	Chile	Hospital Clínico Universidad de Chile	73 (7)	39.3	Not reported	elective open colon surgery	GA	POD	28	17	MAP↓>20%; Not reported	Post-operative lactate and rSO2 variables were not associated with delirium
Jang 2019	Cohort	2011/01–2015/01	South Korea	Anam Hospital	77.6 (65–97)	26.6	56.8	Femoral neck fracture	GA	AKI	248	44	MAP<55 mmHg; >5 min	AKI was found to occur frequently after surgery for femur neck fracture

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Table 1 (continued)

First author, yr	Study design	Study period	Country	Setting	Age (yr)	Sex (male, %)	Comorbidity (%)	Type of surgery	Type of anesthesia	Outcomes	sample size	No. of IOH	Definition and duration of IOH	Main findings
Sessler 2018	RCT	2011/01–2013/12	22 countries	88 centers in 22 countries	69 (10)	53.0	86.0	Noncardiac	GA; LA	Myocardial infarction	9765	3404	SBP<90 mmHg require treatment; >10 min	IOH associated with a composite of myocardial infarction and death
Hallqvist2017	Cohort	2012/10–2013/05; 2015/10–2016/04	Sweden	Karolinska University Hospital	67 (58–74)	53.0	44.0	Noncardiac	GA; LA	AKI	470	286	SBP↓>40%; >5 min	There was a high incidence of perioperative AKI in noncardiac surgery
Wang 2019	Cohort	2018/04/04–2018/12/28	China	Shanghai Eye, Ear, Nose, and Throat Hospital	65.5 (6.4)	99.1	34.6	Laryngectomy	LA	POD	323	28	SBP↓>30%; >30 min	IOH lasting at least 30 min is a risk factor associated with POD
Xu2015	Cohort	2008/03/01–2010/02/28	China	Five university hospitals located in different regions of China	69.7 (6.4)	52.0	56.6	Noncardiac	GA; LA	Myocardial infarction	1422	455	SBP↓>30%; >10 min	IOH is an independent risk factor of major adverse cardiac events in Chinese elderly patients who underwent non-cardiac surgery
Alghanem2020	Cohort	2010/01–2015/01	Jordan	The University of Jordan	71.7 (14.2)	52.8	77.3	traumatic hip surgery	GA; Spinal anesthesia	AKI; myocardial infarction	502	91	SBP↓≥30%; >10 min	There was an association between IOH and post-operative complications in patients undergoing traumatic hip surgery
Monk 2015	Cohort	2001–2008	USA	Six Veterans Affairs medical centers	59.5 (12.8)	92.8	Not reported	Noncardiac	GA; LA	30-day mortality	18,756	3407	MAP<55 mmHg; >5 min	IOH is associated with increased 30-day operative mortality
Hirsch 2015	Cohort	2001/06–2006/04	USA	University of California	73.6 (6.2)	49.4	Not reported	Noncardiac	GA; LA	POD	540	32	MAP<50 mmHg; Not reported	IOH had predictive value in postoperative delirium
Robinson 2009	Cohort	2006/10–2007/07	USA	Denver Veterans Affairs Medical Center	64 (9)	97.0	Not reported	Noncardiac	GA; LA	POD	144	78	SBP<90 mmHg; Not reported	Delirium is common in elderly patients after a major operation
Tognoni2011	Cohort	Not reported	Italy	University-Hospital San Martino	74.3 (0.4)	90.0	55.6	Urological	GA; LA	POD	90	25	SBP<90 mmHg; Not reported	Age, cognitive and functional status, previous history of

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Table 1 (continued)

First author, yr	Study design	Study period	Country	Setting	Age (yr)	Sex (male, %)	Comorbidity (%)	Type of surgery	Type of anesthesia	Outcomes	sample size	No. of IOH	Definition and duration of IOH	Main findings
Langer 2019	RCT	2014/11–2016/04	Italy	Policlinico Ca' Granda Hospital	80 (4)	47.5	Not reported	Noncardiac	GA	POD; POCD	101	50	MAP↓>10%; Not reported	delirium and IOH are the best predictor of POD IOH did not correlate with POD or POCD in elderly patients undergoing general anesthesia for non-cardiac surgery
Kobayashi 2021	Cohort	2009/04/01–2018/03/31	Japan	Jichi Medical University Saitama Medical Center	≥50	64.3	56.8	Noncardiac	GA	AKI	6296	5800	SBP<90 mmHg; >5 min	IOH is associated with AKI
Salmasi2017	Cohort	2005/01/06–2014/03/01	USA	Cleveland Clinic	59 (15)	44.3	Not reported	Noncardiac	GA; LA	Myocardial injury; AKI	57,315	41,085	MAP<65 mmHg; Not reported	IOH is progressively related to both myocardial injury and AKI
Babazade2016	Cohort	2009–2013	USA	Cleveland Clinic	Not reported	57.0	41.0	Noncardiac	GA	SSI	2521	801	MAP<55 mmHg; >1 min	There is no association between IOH and SSI after colorectal surgery
Sessler 2012	Cohort	2005/01–2012/12	USA	Cleveland Clinic	>40	Not reported	Not reported	Noncardiac	GA	30-day mortality	24,120	7695	MAP<70 mmHg; Not reported	Hospital stay and mortality are increased in patients having a low blood pressure
Hsieh 2016	Case-control	2005/01–2011/12	USA	Cleveland Clinic	72 (11)	37	80	Noncardiac	GA	Stroke	502	387	MAP<75 mmHg; Not reported	There is no association between IOH and postoperative stroke
Yu2018	Cohort	2005/01–2015/12	South Korea	Asan Medical Center	54.8 (12.5)	61.8	42.0	Percutaneous nephrolithotomy	LA	AKI	662	176	MAP<70 mmHg; >1 min	IOH is an important risk factor for AKI
Hallqvist2016	Cohort	2012/10–2013/05	Sweden	Karolinska University Hospital	67 (57–74)	47.0	43.0	Noncardiac	GA; LA	Myocardial injury; myocardial infarction	300	34	SBP↓>50%; >1 min	There was an association between IOH and myocardial damage
Wachtendorf2022	Cohort	2005–2017	USA	Massachusetts General Hospital; Beth Israel Deaconess Medical Center	52.8 (16)	48.5	38.2	Noncardiac	GA	POD	316,717	140,047	MAP<55 mmHg; >15 min	IOH is associated with POD

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Table 1 (continued)

First author, yr	Study design	Study period	Country	Setting	Age (yr)	Sex (male, %)	Comorbidity (%)	Type of surgery	Type of anesthesia	Outcomes	sample size	No. of IOH	Definition and duration of IOH	Main findings
Wongtangman2021	Cohort	2005/11–2017/09	USA	Massachusetts General Hospital; Beth Israel Deaconess Medical Center	53.0 (16.1)	49.0	40.4	Noncardiac	GA	Stroke	358,391	160,109	MAP<55 mmHg; >15 min	IOH is not associated with stroke
Williams-Russo 1999	RCT	1993/03–1995/08	USA	Hospital for Special Surgery	55–65	55.0	Not reported	Total hip replacement	Epidural anesthesia	POD, myocardial infarction	235	117	MAP<55 mmHg; Not reported	Elderly patients can safely receive controlled hypotensive epidural anesthesia
Boos 2005	Case-control	2001/09/24–2001/12/07	Brazil	Hospital Governador Celso Ramos	53.9 (20.9)	61.8	Not reported	Noncardiac	GA; LA	POCD	55	23	SBP↓>30%; >5 min	Mini-Mental State Examination is an independent predictor of POCD
Roshanov2017	Cohort	2007/08–2011/01	/	12 centers in eight regions (Brazil, Spain, Canada, Australia, USA, Hong Kong, Colombia, Malaysia)	64.8 (11.8)	48.5	Not reported	Noncardiac	GA; LA	Myocardial injury; stroke; 30-d-mortality	14,687	4162	MAP<90 mmHg; >1 min	Withholding angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers before major noncardiac surgery was associated with a lower risk of death
Sabaté2011	Cohort	2007/10–2008/06	Spain	Twenty-three hospitals in Catalonia	67 (47–81)	48.3	Not reported	Noncardiac	GA; LA	Combined cardiac events, including myocardial infarction, stroke.	3387	313	MAP↓>20%; Not reported	IOH is an independent risk factors for adverse cardiac events
Patti 2011	Cohort	2007/02–2009/02	Italy	V. Cervello Hospital	69.0 (2.8)	40.0	Not reported	Colorectal surgery	GA; LA	POD	100	18	MAP<60 mmHg; Not reported	POD is common after colorectal surgery
Vasivej2016	Case-control	2009/01–2013/12	Thailand	Songklanagarind Hospital; hospital of Prince of Songkla University	58.6 (14.7)	51.9	42.9	Noncardiac	GA	Stroke	210	22	MAP<65 mmHg; Not reported	IOH is a predictors for stroke
Thakar2007	Cohort	2003/01–2005/01	USA	University of Cincinnati Medical Center	43 (10)	16.5	57.0	Gastric bypass	GA	AKI	491	100	MAP<60 mmHg; Not reported	Postoperative AKI is not infrequent after gastric bypass surgery
Barone 2002	Case-control	1996–1999	USA	Stamford Hospital	74 (11)	55.0	40.0	Noncardiac	GA; LA	Myocardial infarction	60	25	SBP<100 mmHg; >10 min	IOH associated with perioperative

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Table 1 (continued)

First author, yr	Study design	Study period	Country	Setting	Age (yr)	Sex (male, %)	Comorbidity (%)	Type of surgery	Type of anesthesia	Outcomes	sample size	No. of IOH	Definition and duration of IOH	Main findings
Nakamura 2009	Case-control	1980–2007	Japan	University of Miyazaki	70.8 (9.4)	70.9	87.5	Thoracic aortic operation	GA; LA	30-day mortality	72	3	SBP<70 mmHg; Not reported	myocardial infarction stent graft repair had low mortality
Sharma 2006	Case-control	1997/07–2003/08	USA	University of Pittsburgh Medical Center	42.3 (9.2)	19.0	56.0	Laparoscopic gastric surgery	GA; LA	AKI	1800	1114	SBP<100 mmHg; >5 min	AKI is not common after laparoscopic gastric bypass
Kim 2016	Cohort	2012/11–2013/12	South Korea	Severance Hospital	72 (5)	37.9	63.2	Lumbar spinal surgery	GA; LA	POCD	87	9	MAP↓>60%; Not reported	IOH is associated with POCD
Nakatani 2022	Cohort	2016/04–2020/12	Japan	Nara Medical University	75 (69–80)	80.6	88.6	Transurethral resection	GA; LA	POD	324	53	MAP<60 mmHg; Not reported	Older age is associated with POD
Xue 2016	Cohort	2010/06–2015/02	China	First People's Hospital of Lianyungang	74.8 (6.4)	/	Not reported	Transurethral resection of prostate	GA; Spinal anesthesia	POD	358	78	MAP<65 mmHg; Not reported	Older age is associated with POD
Ansaloni2010	Cohort	2005/05/16–2006/03/25	Italy	St Orsola-Malpighi University Hospital	75.8 (7.4)	40.9	51.5	Noncardiac	GA; LA	POD	357	39	MAP<65 mmHg; >5 min	POD is common in elderly patients after elective surgery
Shen 2022	Cohort	2016/01–2020/12	China	Xuanwu Hospital	81.3 (4.4)	51.8	62.7	Aabdominal surgery	GA	AKI	573	116	MAP<65 mmHg; Not reported	IOH is a risk factor of AKI
Zhang 2021	Cohort	2015/04/01–2018/06/30	China	Peking University Cancer Hospital	58.9 (10.7)	73.4	27.4	Resection for gastric cancer	GA	SSI	880	92	SBP<90 mmHg; >10 min	IOH increase the incidence of SSI
Kheterpal2009	Cohort	2002–2006	USA	University of Michigan Medical School	>18	51.2	Not reported	Noncardiac	GA; LA	Myocardial infarction	7740	2854	MAP<60 mmHg; Not reported	IOH can predict cardiac adverse events
White 2016	Cohort	2013/05/01–2013/07/31	UK	The National Hip Fracture Database	>18	/	Not reported	Hip fracture	GA; Spinal anesthesia	30-day mortality	10,302	8163	MAP<75 mmHg; Not reported	IOH increased mortality
Marcantonio1998	Cohort	Not reported	USA	Brigham and Women's Hospital	67 (9)	45.0	Not reported	Noncardiac	GA; LA	POD	1341	352	MAP↓>33%; Not reported	IOH associated with POD
Tallgren2007	Cohort	2002/04–2003/12	Finland	Helsinki University Hospital	66 (58–73)	86.9	66.7	Infrarenal aortic repair	GA	AKI	69	11	MAP<60 mmHg; >15 min	IOH is a risk factor of AKI
Zhang 2012	Cohort	Not reported	China	Beijing Tiantan Hospital	67.9 (5.6)	33.8	Not reported	Arthroplasty surgeries	GA	POCD	68	3	MAP↓>30%; Not reported	Arthroplastic surgery under isoflurane inhalation anesthesia causes differential serum protein expression in elderly patients

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Table 1 (continued)

First author, yr	Study design	Study period	Country	Setting	Age (yr)	Sex (male, %)	Comorbidity (%)	Type of surgery	Type of anesthesia	Outcomes	sample size	No. of IOH	Definition and duration of IOH	Main findings
House 2016	Cohort	2007/01/01–2012/08/07	USA	Vanderbilt University Medical Center	54 (13)	52.9	42.4	Noncardiac	GA	Myocardial infarction	46,799	38,213	MAP<60 mmHg; Not reported	Surgical Apgar score is associated with myocardial injury
Yang 2016	Cohort	2012/01–2014/03	China	First Affiliated Hospital of Dalian Medical University	81 (6)	48.5	43.6	Noncardiac	GA	POD	480	29	SBP↓>30%; Not reported	IOH associated with POD
Yue 2013	Cohort	2007/04–2012/03	China	Zhongshan Hospital	Not reported	78.8	Not reported	Abdominal aortic aneurysm repair	GA	AKI	71	16	MAP<65 mmHg; Not reported	AKI is common after abdominal aortic aneurysm repair
Ellis 2018	Cohort	2013/06–2017/04	Australia	University of Queensland	18–70	61.4	54.4	Nephrectomy	GA	AKI	184	44	MAP<60 mmHg; ≥5 min	Preoperative dehydration may be associated with postoperative acute kidney injury
Deiner2015	Cohort	Not reported	USA	Mount Sinai Hospital	74 .0 (5.4)	51.9	23.4	Noncardiac	GA	POCD	77	21	MAP<55 mmHg; >5 min	Burst suppression may be protective for POCD
Brinkman 2015	Cohort	2011/09–2013/01	Canada	University of Manitoba	67.9 (9.1)	65.0	67.5	Open repair of abdominal aortic aneurysms	GA	AKI	40	35	MAP<65 mmHg; Not reported	AKI is common after abdominal aortic aneurysm repair
Ishikawa 2014	Cohort	2009/01/01–2009/12/31	Japan	Keiyukai Sapporo Hospital	67 (60–75)	55.0	16.7	Elective open surgery for colorectal cancer	GA	SSI	224	33	SBP<80 mmHg; >5 min	SSI is common for elective open surgery
Yeheyis2021	Cohort	2017/08/01–2020/03/30	Ethiopia	School of Medicine, Addis Ababa University	54 (12.08)	39.0	11.0	Esophagectomy	GA	30-day mortality	54	28	SBP<90 mmHg; >5 min	IOH is not associate with mortality
Jing 2021	Cohort	2017/03–2019/12	China	China-Japan Friendship Hospital	59 (51–62)	83.0	73.0	Lung transplantation	GA	AKI	191	41	MAP<65 mmHg; Not reported	AKI is common after lung transplantation
Knight 2022	Cohort	2013/06–2017/06	USA	University of Pittsburgh Medical Center	51 (14)	57.0	59.0	Lung transplantation	GA	AKI	245	244	MAP≤65 mmHg; >15 min	IOH is associate with AKI after lung transplant
Balci 2017	Cohort	2014/03–2015/08	Turkey	Kartal Kosuyolu Training Hospital	46.1 (15.4)	63.3	42.9	Lung transplantation	GA	AKI	30	15	MAP<70 mmHg; Not reported	AKI is common after lung transplantation
Joosten2021	Cohort	2014–2019	Belgium	Erasmus Hospital	57 (48–64)	70.0	62.0	Liver transplantation	GA	AKI	205	203	MAP<65 mmHg; Not reported	AKI is common after liver transplant
Xu2010	Cohort	2004/01–2005/09	China	First Affiliated Hospital, Zhejiang University School of Medicine	45 (9)	86.3	Not reported	Liver transplantation	GA	AKI	102	28	SBP<90 mmHg; >15 min	IOH is associate with AKI after lung transplant

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Table 1 (continued)

First author, yr	Study design	Study period	Country	Setting	Age (yr)	Sex (male, %)	Comorbidity (%)	Type of surgery	Type of anesthesia	Outcomes	sample size	No. of IOH	Definition and duration of IOH	Main findings
Mizota2017	Cohort	2008/03–2015/04	Japan	Kyoto University Hospital	55 (44–61)	48.9	Not reported	Liver transplantation	GA	AKI	231	198	MAP<50 mmHg; >1 min	AKI is common after liver transplant
Chen 2017	Cohort	2003/01–2011/02	China	Zhongshan Hospital	50.4 (9.6)	89.2	92.9	Liver transplantation	GA	AKI	566	54	SBP<90 mmHg; >15 min	Post-liver transplantation AKI is common
Wysusek2015	Cohort	2009/01–2012/08	Queensland	Princess Alexandra hospital	49 (12)	69.1	48.5	Liver transplantation	GA	AKI	97	33	SBP<90 mmHg; >15 min	AKI is common after liver transplant
Cai 2006	Cohort	2004/08–2004/11	China	Zhongshan Hospital	69.7 (5.23)	82.3	46.7	Noncardiac	GA	POCD	79	31	MAP<60 mmHg; >5 min	IOH is a risk factor of POCD
Wang 2015	Cohort	2011/01–2012/12	China	Yongchuan hospital	>18	49.5	24.4	Lumbar spinal	GA; Spinal anesthesia	POD	200	95	MAP<65 mmHg; Not reported	IOH is a risk factor of POD after spinal operation
Wang 2013	Cohort	2010/05–2012/08	China	Qingdao municipal hospital	74.0 (8)	53.5	62.5	Hip replacement	Epidural anesthesia	POD; POCD	200	33	MAP<65 mmHg; Not reported	IOH is a risk factor of POD after hip joint replacement
Ji2016	Cohort	2012/06–2015/08	China	Yangpu hospital	73 (6)	Not reported	Not reported	Laparoseopic	GA	POD	213	108	MAP↓>20%; MAP<65 mmHg	IOH associate with POD
Xie 2021	Cohort	2019/11–2020/11	China	Beijing cancer hospital	63 (13)	63.7	Not reported	Radical resection for colorectal cancer	GA	AKI	543	359	SBP<60 mmHg; Not reported	IOH associate with AKI after radical resection of malignant colorectal cancer
Monk 2005	Cohort	Not reported	USA	Shands Hospital	51 (37–65)	36.5	33.1	Noncardiac	GA	1-year-mortality	1064	203	SBP<80 mmHg; Not reported	Death during the first year after surgery is primarily associated with the natural history of preexisting conditions
Bijker2009	Cohort	2002/02–2003/08	Netherlands	University Medical Center Utrecht	52 (15.8)	51.6	22.3	Noncardiac	GA; LA	1-year-mortality	1705	88	SBP<80 mmHg; >1 min	IOH is not associate with 1-year mortality

IOH = intraoperative hypotension; GA = general anesthesia; LA = local anesthesia; POCD = postoperative cognitive dysfunction; POD = post operative delirium; SSI = surgical-site infection; AKI = acute kidney injury; MAP = mean arterial pressure; SBP = systolic blood pressure.

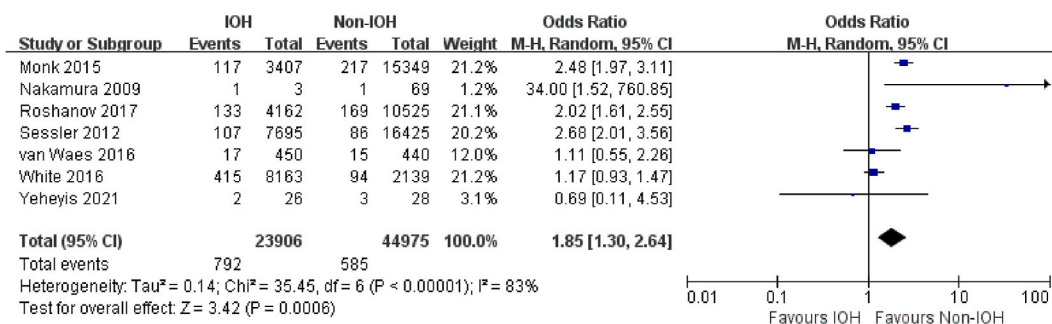


Fig. 2. Forest Plot of odds ratio (OR) for 30-day mortality for IOH VS Non-IOH during non-cardiac surgery.

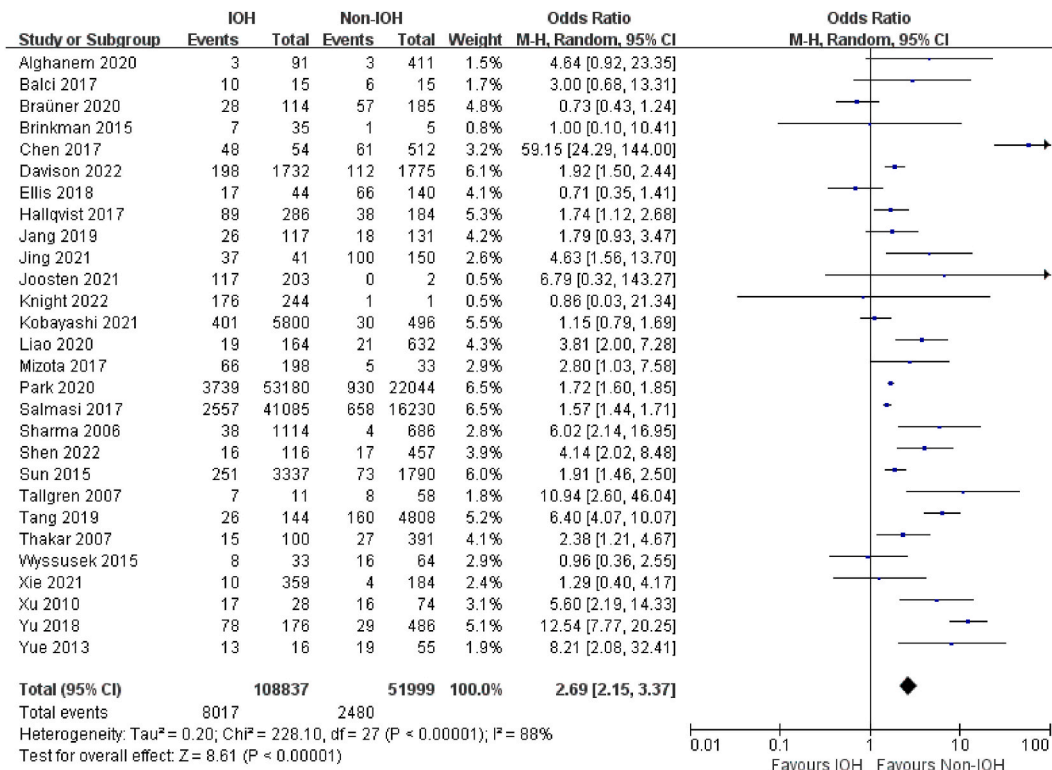


Fig. 3. Forest Plot of AKI for IOH VS Non-IOH during non-cardiac surgery.

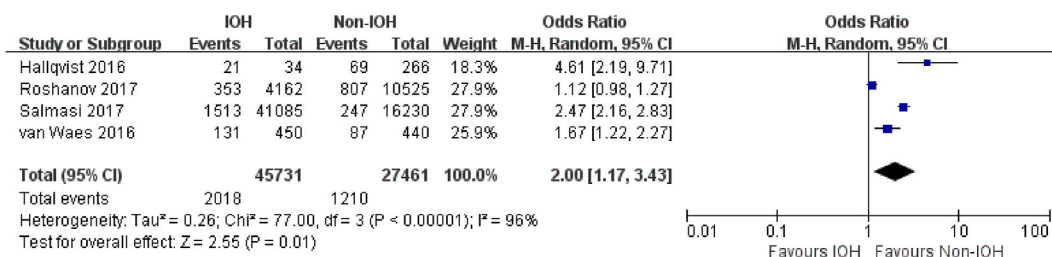


Fig. 4. Forest Plot of myocardial injury for IOH VS Non-IOH during non-cardiac surgery.

difference (OR, 1.83; 95% CI, 0.93–3.60; P = .08; I² = 80%) was found between IOH and non-IOH group (Appendix S9).

3.5.2. Stroke

Four studies [40,44,47,50] reported stroke (925 of 164,680 vs. 864 of 209,110[0.48%]). A slight difference was observed between

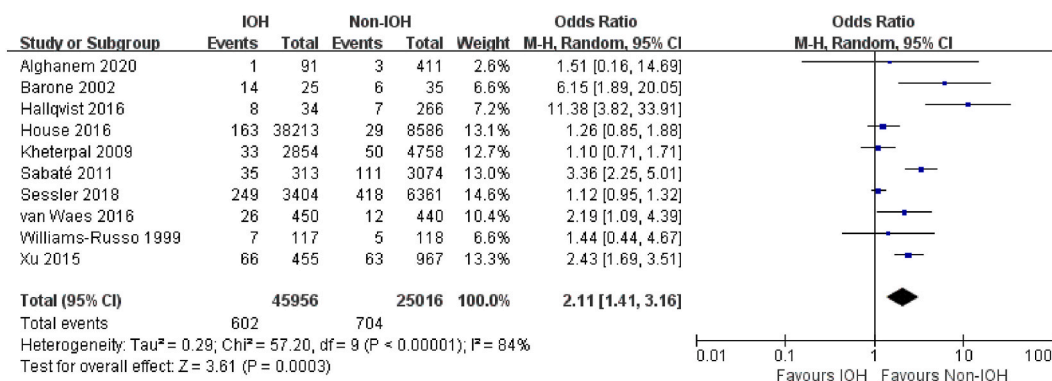


Fig. 5. Forest Plot of myocardial infarction for IOH VS Non-IOH during non-cardiac surgery.

the IOH and non-IOH groups regarding the development of postoperative stroke (OR, 1.33; 95% CI, 1.21–1.46; P < .001; I² = 26%). Low-quality evidence showed that adult patients with hypotension during non-cardiac surgery had higher odds of developing stroke than non-IOH (Appendix S10).

3.5.3. 1-Year mortality

Only two studies [86,87] reported very low rates of 1-year mortality after non-cardiac surgery (64 of 855 vs. 82 of 1914[5.27%]). Very low-quality evidence showed that compared with non-IOH, patients with IOH had a similar likelihood of 1-year mortality (OR, 1.66; 95% CI, 0.65–4.20; P = .29; I² = 81%) (Appendix S11).

3.5.4. Sensitivity and subgroup analysis

We conducted several sensitivity analyses to confirm the robustness of our findings. For sensitivity analysis, removing studies with a high risk of bias did not change the significance of the results. Moreover, the sensitivity analysis showed that studies with a high risk of bias contributed greatly to the overall heterogeneity. All three sensitivity analyses indicated that the results of the meta-analysis were robust (Appendix S12–S14). However, the sensitivity analyses showed patients who had hypotension during non-cardiac surgery had higher odds of postoperative SSI compared with non-IOH (OR, 2.50; 95% CI, 1.57–3.97; P < .001; I² = 0%) (Appendix S15). The test for subgroup differences (I² = 22.9%) indicates that surgery types (transplant surgery vs. non-transplant surgery) may have contributed to the heterogeneity of AKI (Appendix S16). We found differences between transplant surgery (OR, 4.46; 95% CI, 1.48–13.42; P = .008) and non-transplant surgery (OR, 2.32; 95% CI, 1.86–2.89; P < .001). The transplant surgery group had a broader confidence interval (95% CI, 1.48–13.42) than the non-transplant surgery (95% CI, 1.86–2.89).

3.5.5. Publication bias

There was no evidence of publication bias for outcomes with ten or more studies (Appendix S17–S19). The Egger test demonstrates no significant publication bias for AKI (P = .056), POD (P = .769), and myocardial infarction (P = .085).

3.5.6. Certainty of evidence

Six outcomes had a large effect (strong association, upgrade one level, OR > 2). Nevertheless, the certainty of evidence was mostly low-to-very low as most of the included studies were observational designs in nature (Appendix S20).

4. Discussion

In this systematic review and meta-analysis from 72 studies (69 cohort studies and 3 RCTs), IOH was independently associated with a higher risk of 30-day mortality, AKI, major adverse cardiac events (myocardial injury or myocardial infarction), POD, and stroke after non-cardiac surgery than non-IOH. Our review found very low-quality to low-quality evidence that IOH has a similar likelihood of POCD and 1-year-mortality compared with non-IOH in non-cardiac surgery. Available evidence suggests that IOH has a higher risk of severe postoperative complications after non-cardiac surgery than non-IOH.

The primary aim of this meta-analysis was to investigate the association of IOH with severe postoperative complications in patients undergoing non-cardiac surgery. Overall, our primary findings are supported by similar results from previous systematic reviews [10, 90] while adding to the evidence on the outcomes of SSI, stroke, and 1-year-mortality in adult patients who underwent non-cardiac surgery. However, previous systematic reviews only included studies published to June 2019, excluding recently published articles [26,43,56,74]. Furthermore, none of these studies rated the certainty of the evidence or included articles published in other languages.

More than 300 million non-cardiac surgeries are performed worldwide annually [91]. IOH is common during non-cardiac surgery and may be associated with organ ischemia and mortality [87]. Reducing postoperative mortality is a top priority for surgeons worldwide. However, evidence regarding the association between IOH and postoperative mortality conveyed inconsistent and conflicting results, with some studies finding an association between IOH and mortality and some not [92,93]. A multiple-center cohort

study used three methods to define the IOH (population thresholds, absolute thresholds, and percent change from baseline blood pressure) [34]. They found IOH was associated with 30-day mortality with any of these definitions. Their results stress the importance of the prevention of hypotension during surgery. Wickham et al. also urged improved management of IOH may be a simple intervention with real potential to reduce morbidity in elderly patients undergoing surgery [94]. Our study showed that IOH significantly increases the risk of 30-day mortality, which is in line with the results of the previous meta-analyses [10,11,95]. However, it is worth noting that the endpoints (30-d mortality, 60-d mortality, 90-day mortality, and 180-d mortality) selected by each study are different, although there have been an increasing number of studies on the correlation between IOH and postoperative mortality in non-cardiac surgery. What's more, it is difficult to weigh the role of IOH in these postoperative mortality rates considering most of it is all all-cause mortality.

Our study found that IOH was also associated with AKI, major adverse cardiac events (myocardial injury or myocardial infarction), and POD. Major adverse cardiovascular events and AKI are leading causes of morbidity and mortality following non-cardiac surgery, with up to one-third of 30-day mortality potentially attributable to myocardial injury [96]. A multicenter retrospective cohort [97] study including 368,222 non-cardiac surgical procedures revealed that IOH increased the occurrence of AKI, myocardial infarction, and stroke. Similarly, a retrospective cohort study of 33,330 non-cardiac surgeries showed mean arterial pressure (MAP) less than 55 mmHg is associated with AKI and myocardial injury even with a short duration of IOH [98]. A recent study by Wesselink and colleagues also confirmed IOH has a graded association with postoperative myocardial injury [99]. IOH was not associated with POCD in our study, consistent with two previous studies containing cardiac and non-cardiac surgeries [90,100]. Meanwhile, IOH was also associated with POD and stroke in this meta-analysis, which is inconsistent with previous systematic reviews or meta-analyses [10, 100]. Of note, these authors either included cardiac surgery [100], or only included articles published in English [10]. One explanation is that we included some articles [81–84] published in other languages to minimize the publication bias.

A secondary aim of our review was to determine the relationship between IOH and surgical-site infection, stroke, and 1-year mortality in non-cardiac surgery. The SSI and 1-year mortality were uncommon or rare after non-cardiac surgery. Our results showed that IOH has a similar likelihood of SSI and 1-year-mortality compared with non-IOH in non-cardiac surgery. Only two observational studies [60,71] with small sample sizes reported IOH was associated with a higher risk of SSI. But the largest retrospective cohort study [39] showed no association between IOH and SSI, probably because the outcomes are overwhelmingly determined by other baseline and surgical factors. All these three studies were abdominal surgery. Only two studies [86,87] contributed data for the analysis of 1-year mortality; No association was observed between IOH and 1-year mortality.

The heterogeneity of the included articles in this paper is high, which is affected by the variability of definitions used for IOH and the different thresholds examined. The lack of uniform criteria was a reason for the discrepancy among researchers. The baseline comparability of inclusion was inconsistent, with many studies targeted at high-risk groups and broad groups suffering from varying degrees of severe disease. The results of pre-specified sensitivity and subgroup analysis indicate that the surgical types may partly contribute to the heterogeneity. Various definitions of outcomes may also explain the high heterogeneity and make it difficult to appraise the occurrence of postoperative complications. The Perioperative Quality Initiative-3 workgroup has stated in its consensus statement that mean arterial pressure (MAP) should be maintained >60–70 mmHg during non-cardiac surgery to reduce postoperative complications [101]. A universally accepted standard definition of hypotension would facilitate further studies. Notably, most of the included studies were observational, resulting in the low certainty of evidence. Thus, further high-quality, including well-designed randomized trials of different surgery types in the general population, is urgently needed.

Collectively, our findings provide low to very low-quality evidence to support that IOH is a modifiable risk factor associated with severe postoperative complications. Thus, monitoring blood pressure during non-cardiac surgery could confer additional benefits.

4.1. Strengths and limitations

Our study had some strengths: First, we included several important clinical outcomes directly relevant to postoperative complications management after non-cardiac surgery. Second, articles with different languages were included to minimize publication bias. Third, this meta-analysis has provided an overview of the effect of IOH on multiple postoperative outcomes. We included various outcomes to address the review question comprehensively. Fourth, we rated the certainty of evidence using the GRADEpro approach.

A key limitation is that a high level of heterogeneity among studies was observed in most outcomes concerning the surgical types, definition and duration of IOH. Thus, the results of this review pertaining to outcomes with substantial heterogeneity should be interpreted accordingly. Furthermore, most of the included studies were observational, resulting in the low certainty of evidence. Only three randomized trials were identified for the relationship between IOH and postoperative complications. Thus, further high-quality research is urgently needed.

5. Conclusions

Our results suggest IOH was associated with an increased risk of severe postoperative complications after non-cardiac surgery than non-IOH. For patients undergoing non-cardiac surgery, IOH is a potentially avoidable hazard that should be closely monitored, and corresponding measures should be taken to reduce severe postoperative complications. There is also an urgent need for a universally accepted standard definition of IOH and further high-quality research.

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Author contributions

Dr. Duan had full access to all of the data in the study and takes responsibility for the integrity of the data. JHC, MT, JY, and HW drafted the manuscript. JC contributed to the design of the search strategy. JY and HW did the study selection. HL and SSX collected the data. HL and XY assessed the risk of bias. XW did the statistical analysis. All authors read, provided feedback and approved the final version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2023.e15997>.

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