

# Meta-analysis of interleukin 6, 8, and 10 between off-pump and on-pump coronary artery bypass groups

Fanbo Meng<sup>1</sup>, Jianghong Ma<sup>2</sup>, Wei Wang<sup>2</sup>, Baisong Lin<sup>2\*</sup>

<sup>1</sup>Department of Cardiology, China Japan Union Hospital of Jilin University, Changchun, China, <sup>2</sup>Department of Cardiac Surgery, China Japan Union Hospital of Jilin University, Changchun, China

## ABSTRACT

This study aimed to evaluate the role of off-pump coronary artery bypass (CAB) surgery on the decrease of postoperative inflammatory responses in patients. We systematically searched databases of PubMed and Embase to select the related studies. Interleukin (IL) 6, 8, and 10 were used as outcomes and pooled analysis was performed using R 3.12 software. Standardized mean differences (SMDs) and their 95% confidence intervals (95% CIs) were considered as effect estimates. A total of 27 studies, including 1340 participants, were recruited in this meta-analysis. The pooled analyses showed that postoperative concentration of IL-10 at 12 hours was significantly lower in off-pump CAB group compared to on-pump CAB group (SMD = -1.3640, 95% CI = -2.0086--0.7193). However, no significant differences were found in pre and postoperative concentrations of IL-6 and 8 between off-pump and on-pump CAB groups. These results suggest that there is no advantage of off-pump CAB surgery in the reduction of inflammation compared to on-pump CAB surgery.

**KEY WORDS:** Coronary artery bypass; interleukins; meta-analysis; IL-6; IL-8; IL-10; off-pump coronary artery bypass surgery; on-pump coronary artery bypass surgery

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## INTRODUCTION

Inflammation is a major complication after coronary artery bypass (CAB) surgery. On-pump CAB is the standard surgery for transmyocardial laser revascularization due to its merits of safety, good effect, and low mortality. However, on-pump CAB surgery can generate some unavoidable adverse reactions such as inflammation.

To reduce the inflammation induced by operation and to improve the clinical outcome, off-pump CAB surgery is proposed, where a surgeon sutures blood vessels while the heart is beating. The benefits of off-pump CAB surgery are reduced operative time, cost, and complications compared with on-pump CAB surgery [1]. A previous meta-analysis showed that off-pump CAB surgery can reduce the risk of postoperative stroke [2]. However, off-pump CAB surgery is more difficult to perform, and advanced operative skills are required.

Although a number of benefits of off-pump CAB surgery have been reported, the effect of off-pump CAB surgery on the reduction of inflammation remains unclear. Some studies have shown that off-pump CAB surgery can significantly reduce the postoperative inflammation [3,4], while others reported contrasting results [5,6].

Interleukins (ILs) are a class of cytokines that are produced by leukocytes [7]. ILs have been shown to play important roles in a series of immunological and inflammatory responses [8,9]. For example, IL-6, 8, and 10 are common cytokines involved in inflammation. IL-6 is an anti-inflammatory cytokine which plays important roles in inducing acute phase reactions and controlling local or systemic acute inflammatory responses [10]. IL-8 is a major neutrophil chemotactic factor involved in the acute inflammation [11]. IL-10 is essential for regulating macrophage and neutrophil infiltration as well as cytokine production during the inflammatory response of cutaneous wound healing [12].

To evaluate the effect of off-pump CAB surgery on the reduction of postoperative inflammation, we systematically meta-analyzed the levels of IL-6, 8, and 10 in patients who underwent CAB surgery and compared the results between off-pump and on-pump CAB groups.

\*Corresponding author: Baisong Lin, Department of Cardiac Surgery, China Japan Union Hospital of Jilin University, No. 126, Xiantai Street, Changchun, Jilin 130033, China.  
E-mail: [baisonglins7@126.com](mailto:baisonglins7@126.com)

## MATERIALS AND METHODS

### Source of data

Up to April 2016, PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) and Embase (<http://www.embase.com>) databases were searched systematically using the predesigned search strategy. The search terms included (“coronary artery bypass” OR “coronary artery bypass grafting” OR “CABG”) AND (“non-pump” OR “on-bypass”) AND (“off-pump” OR “off-bypass” OR “OPCAB”) AND (“interleukin” OR “IL”).

### Inclusion criteria

The following inclusion criteria were applied: (1) Off-pump and on-pump CAB surgeries were reported and (2) ILs were detected as an outcome. Reviews, reports, comments, and letters were excluded from our study.

### Data extraction

Two authors (FM and BL) independently extracted the following information from the included studies: the name of the first author, year of publication and study implementation, total number of the patients who had off-pump and on-pump CAB surgery, gender, age, body mass index (BMI), and length of stay in hospital and intensive care unit (ICU) for both, off-pump and on-pump CAB groups. The disagreements during data extraction were discussed with the third author and resolved by consensus.

### Statistical analysis

Statistical analyses were performed using R software version 3.12 (<http://cran.r-project.org/web/packages/Hmisc/index.html>). Standardized mean differences (SMDs) and their 95% confidence interval (95% CI) were used as effect estimates. Heterogeneity was assessed using Q statistic and  $I^2$  test [13]. If significant heterogeneity was found ( $p < 0.1$  or  $I^2 > 50\%$ ), random effects model was used for pooled analysis. Otherwise, the fixed effects model was used. Sensitivity analysis was carried out by removing each study, step by step, to evaluate the stability of the pooled results. Egger’s test was used for detecting publication bias and  $p < 0.05$  indicated a statistically significant publication bias.

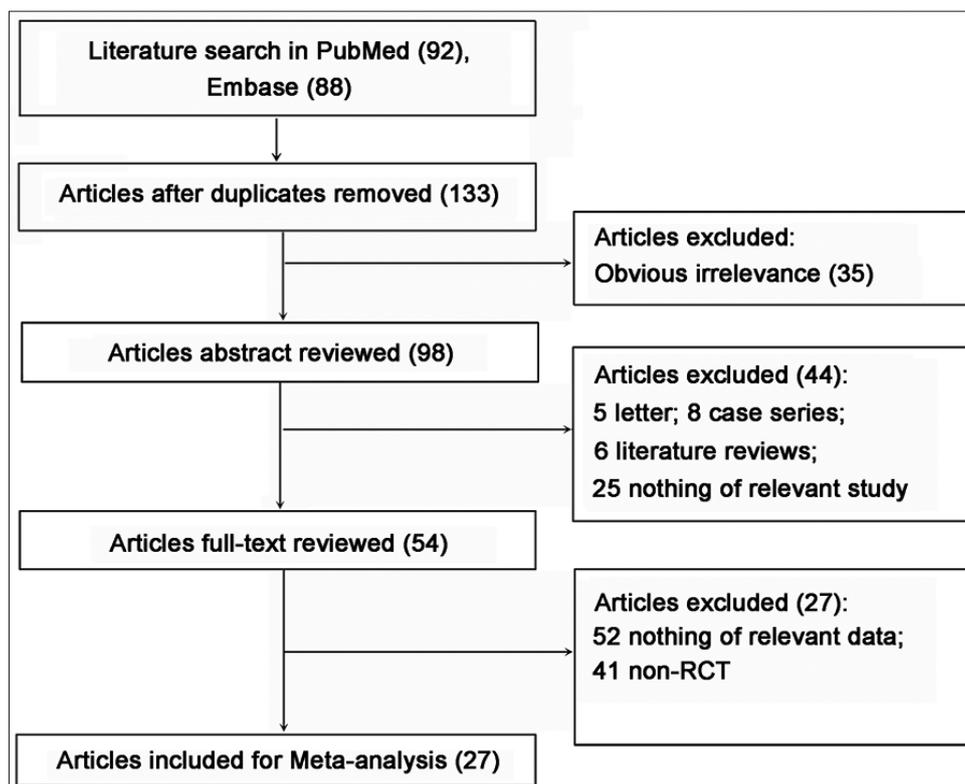
## RESULTS

### Study selection

The study selection process is shown in Figure 1. A total of 180 studies were identified by the primary search. First, 47 repeated studies were excluded. Second, 79 irrelevant studies were removed from the remaining 133 records by reading titles and abstracts. Third, 27 studies were removed by reading the full-texts. Finally, 27 studies were included in this meta-analysis [3-6,14-36].

### Characteristics of included studies

As shown in Table 1, the included studies were published from 2000 to 2014. The selected studies were conducted in



**FIGURE 1.** Literature search and study selection.

**TABLE 1.** The characteristics of the included studies

Author	Publication year	Study location	Study year	C.A.B group	N	Age (years)	Gender (M/F)	BMI	ICU stay	Operative time	In-hospital stay
Wippermann P et al. [34]	2005	Germany	NA	Off-pump	10	54.3±14.1	NA	26±8	1.2±0.4	NA	7.1±1.5
Yamaguchi A et al. [35]	2005	Japan	NA	On-pump	10	64.1±12.1	NA	26±3	1.4±0.5	NA	15.7±2.6
Vallely MP et al. [33]	2010	Australia	2000.3-2000.6	Off-pump	10	68.5±5.0	8/2	NA	NA	323±64	20.0±2.2
Serrano CV Jr et al. [29]	2010	Brazil	NA	On-pump	10	64.1±9.4	9/1	NA	NA	365±40	22.6±3.6
Rogers CA et al. [6]	2013	Italy	2007.2-2009.9	Off-pump	93	62.9±11.6	6/4	NA	NA	NA	NA
Philippidis P et al. [25]	2010	UK	NA	On-pump	10	62.6±9.7	7/3	NA	NA	NA	NA
Okubo N et al. [23]	2003	Japan	NA	Off-pump	20	62.5±6.0	26/14	NA	2.0±1.8	198±45	2.0±1.8
Murakami T et al. [22]	2005	Japan	NA	On-pump	20	63.1±4.9	27/14	NA	4.1±3.0	201±51	4.1±3.0
Massoudy P et al. [20]	2008	Germany	2005.2-2005.9	Off-pump	100	66.7±8.0	80/13	28.0±3.9	23.0 (19.5-26.4)	3.3 (3.0-4.0)	6 (5-7)
Johansson-Synergren M et al. [17]	2004	Sweden	1999.1-2001.1	Off-pump	26	63.1±8.7	84/7	27.6±4.1	22.4 (18.2-25.2)	4.1 (3.5-4.7)	5 (5-6)
Andrasi TB et al. [14]	2014	Germany	NA	Off-pump	10	66.0±10.3	15/5	NA	NA	NA	5.8±1.4
Ascione R et al. [15]	2000	UK	NA	On-pump	10	62.4±10.2	14/6	NA	NA	NA	6.2±0.7
Caputo M et al. [19]	2002	UK	NA	On-pump	10	72.4±5.9	9/1	NA	NA	260±30.6	NA
Ghorbel MT et al. [5]	2010	UK	NA	Off-pump	8	61.4±10.4	8/2	NA	NA	273.9±43.7	NA
Heijmans JH et al. [16]	2007	Netherlands	NA	On-pump	20	70.2±1.7	8/0	NA	1.0±0.0	256±31.0	19.3±4.2
Karu I et al. [18]	2010	Estonia	NA	Off-pump	7	62.8±6.0	7/0	NA	1.0±0.0	256.2±28.2	14.6±3.6
Mazzone A et al. [21]	2003	Italy	1998.10-2000.7	Off-pump	101	66.5±10.7	80/20	27.5±4.5	NA	247±59	NA
Mei YQ et al. [36]	2007	China	NA	On-pump	26	62.2±1.7	8/18	27.5±3.7	NA	222±54	NA
Nesher N et al. [3]	2006	Israel	2004	Off-pump	26	62.5±1.9	10/16	26.8±0.7	1.4±0.5	NA	10.3±1.0
Al-Rutzeih S et al. [30]	2003	UK	NA	Off-pump	10	71.8±1.9	5/5	NA	1.0±0.6	NA	9.2±0.5
				On-pump	10	71.0±3.6	5/5	NA	NA	NA	NA
				Off-pump	30	59.0±10.1	24/6	NA	1.00±0.00	NA	5.93±1.53
				On-pump	30	62.7±7.9	24/6	NA	1.21±0.41	NA	6.97±1.92
				Off-pump	20	62.7±10.6	17/3	NA	1.2 (0.9-1.4)	184 (158-11)	7.1 (5.5-8.7)
				On-pump	20	62.9±6.9	19/1	NA	2.4 (0.6-4.2)	230 (209-50)	9.0 (6.2-11.8)
				Off-pump	5	71.4±10.2	5/0	30.3±2.6	36.2±15.7	NA	5.0±2.2
				On-pump	5	68.0±10.3	5/0	31.1±5.1	60.4±38.7	NA	12.0±10.7
				Off-pump	20	63.7±12.8	14/6	26.9±2.8	26.0±17.1	113±33	6.3±1.7
				On-pump	20	61.4±9.5	16/4	27.9±3.5	29.0±13.8	162±24	6.3±1.9
				Off-pump	10	66±13	9/1	NA	1.0±0.0	NA	8.1±3.4
				On-pump	10	59±7	9/1	NA	1.3±0.5	NA	9.2±2.7
				Off-pump	20	68±7	18/2	NA	23±4	192±43	8±2
				On-pump	21	66±9	18/3	NA	40±7	262±57	12±4
				Off-pump	22	67.8±7.77	18/4	NA	2.14±1.04	230±50.40	NA
				On-pump	20	64.52±8.14	15/5	NA	2.93±2.05	290.25±63.17	NA
				Off-pump	60	67±1	44/16	26±4	NA	218±96	5.3±8
				On-pump	60	68±5	46/14	27±3	NA	228±63	6.1±3
				Off-pump	10	63.8±8.4	2/8	NA	NA	NA	NA

(Contd...)

**TABLE 1. (Continued)**

Author	Publication year	Study location	Study year	CAB group	N	Age (years)	Gender (M/F)	BMI	ICU stay	Operative time	In-hospital stay
Parolari A et al. [24]	2007	Italy	2004.1-2005.6	On-pump	10	63.9±10.9	1/9	NA	NA	NA	NA
				Off-pump	14	66±3.7	12/2	NA	NA	NA	NA
Quaniers JM et al. [26]	2006	Belgium	1999.11-2002.2	On-pump	15	67±3.1	11/4	NA	NA	NA	NA
				Off-pump	40	62±11	35/5	NA	2.9±2.1	197±38	12±11.2
Rasmussen BS et al. [27]	2007	Denmark	NA	On-pump	40	64±8	37/3	NA	2.6±1.6	208±41	11.1±3.9
				Off-pump	17	68±6	14/3	27.7±3.0	22.2±1.0	176±34	NA
Schulze C et al. [28]	2000	Germany	NA	On-pump	16	67±4	13/3	27.0±2.6	22.3±1.2	168±39	NA
				Off-pump	13	64±9.3	10/3	NA	2±2	NA	NA
Szerafin T et al. [31]	2005	Austria	NA	On-pump	13	66.4±8.9	10/3	NA	3±2	NA	NA
				Off-pump	15	58.6±2.6	9/6	27.7±0.86	32.2±9.8	218±11	10.3±3
Wan JY et al. [4]	2004	China	NA	On-pump	15	59.9±2.2	9/6	26.8±1.1	22.4±1.6	223.9±8.7	6.6±0.3
				Off-pump	18	63.61±10.47	15/3	NA	18.94±4.57	143.61±29.20	6.06±1.21
Untch BR et al. [32]	2008	USA	NA	On-pump	19	65.37±9.08	11/8	NA	18.74±2.88	167.10±36.91	6.26±0.99
				Off-pump	13	59±12	9/4	NA	NA	NA	NA
				On-pump	26	62±10	15/11	NA	NA	NA	NA

NA: Not available; ICU: Intensive care unit stay; BMI: Body mass index; M: Male; F: Female; CAB: coronary artery bypass

different regions, including China, Brazil, Italy, Japan, Israel, and England. A total of 1340 participants were considered. Among these participants, there were 664 off-pump CAB and 676 on-pump CAB patients. The majority of the patients were elderly (>60 years), and no significant difference was found in the age between the two groups. The baseline information showed that most of the patients were male, with mean BMI >24. In most of the included studies operative time, ICU stay, and hospital stay were slightly longer in on-pump CAB group compared to off-pump CAB group.

**Pooled analysis**

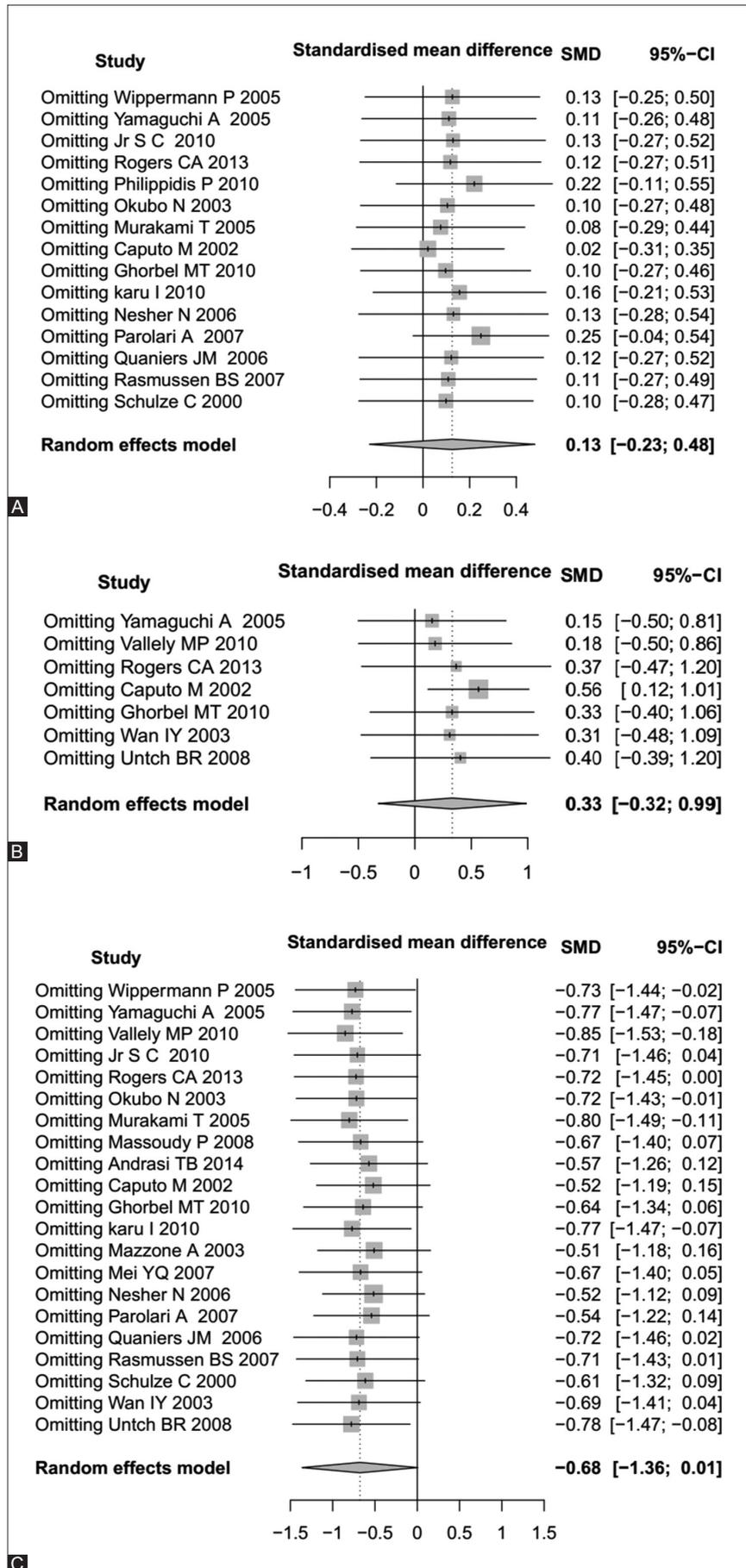
The pre and postoperative concentrations (at 12 and 24 hours) of IL-6, 8, and 10 were considered as outcomes. Due to inapparent heterogeneity ( $p = 0.1234$ ,  $I^2 = 40.2\%$ ), pooling analysis of preoperative IL-8 concentration was performed using fixed effects model. The remaining outcomes were pooled using random effects model. The pooled results were summarized in Table 2. The postoperative concentration of IL-10 at 12 hours in off-pump CAB group was significantly lower compared to on-pump CAB group (SMD = -1.3640, 95% CI = -2.0086--0.7193). However, there were no obvious differences in the preoperative concentrations of IL-10 and those assessed 24 hours postoperatively, between off-pump and on-pump CAB groups. In addition, there were no significant differences in the pre and postoperative concentrations of IL-6 and 8 between the two groups. All of the pooled results showed no significant publication bias.

**Sensitivity analyses**

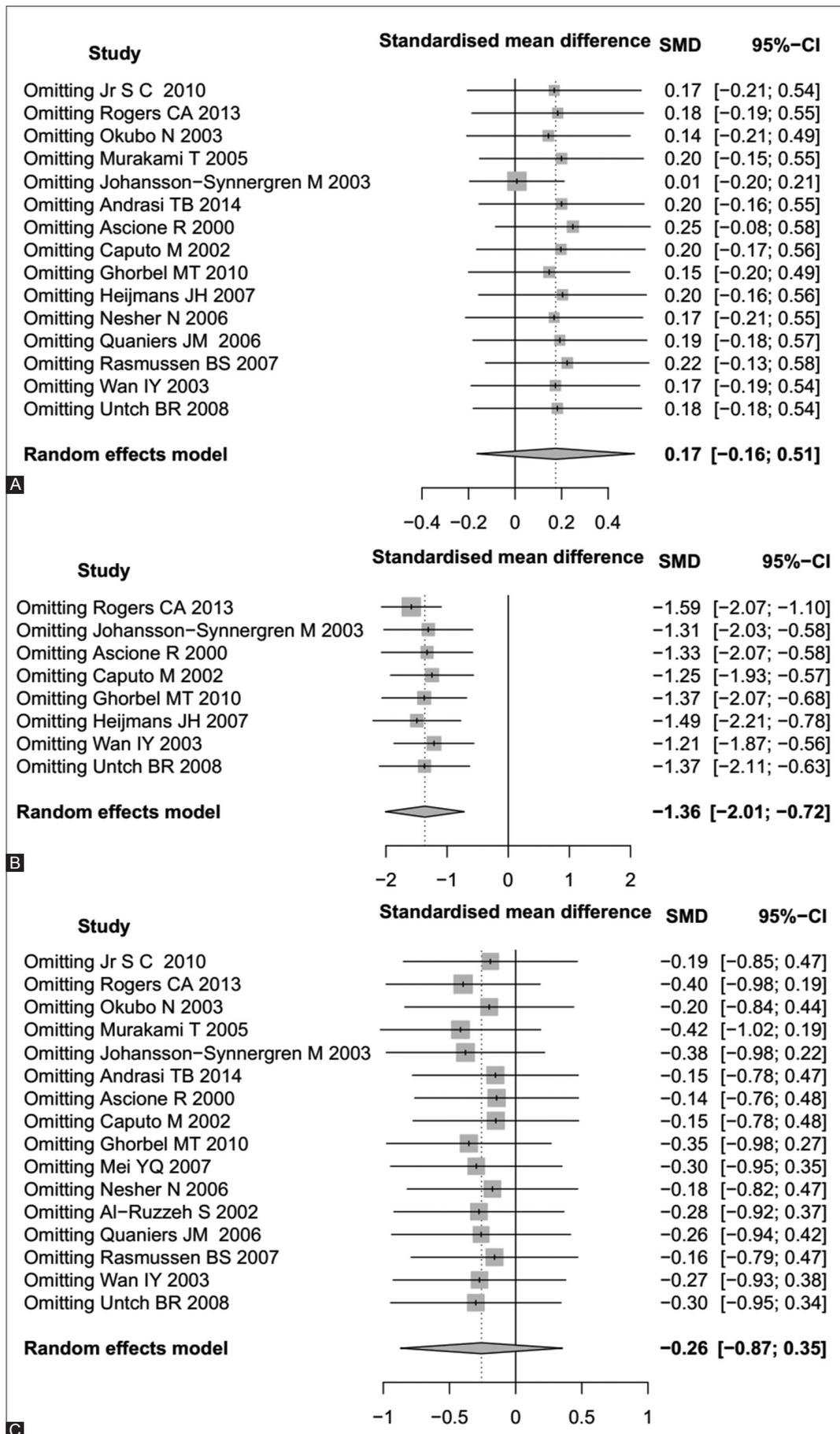
The results of sensitivity analyses are shown in Figures 2, 3, and 4. After omitting the studies by Caputo et al. [19] and Valley et al. [33], the outcomes were reversed for the IL-6 concentration (SMD = 0.56, 95% CI = 0.12-1.01 [Figure 2B]) and IL-8 concentration (SMD = 0.70, 95% CI = 0.27-1.13 [Figure 4B]) 12 hours after operation. Other results of sensitivity analysis were consistent with the overall pooled results.

**DISCUSSION**

Off-pump CAB surgery is likely to have some advantages over on-pump CAB surgery, such as reduced operative time and cost [1]. However, whether off-pump CAB surgery can significantly reduce the postoperative inflammation, is controversial. In this study, we found that only concentration of IL-10, 12 hours after operation, was significantly lower in off-pump CAB group compared to on-pump CAB group. There were no significant differences in the concentrations of IL-6, 8, and other concentrations of IL-10 between



**FIGURE 2.** Sensitivity analyses of interleukin-6 (IL-6) in preoperative conditions (A), at 12 hours postoperatively (B), and at 24 hours postoperatively (C).

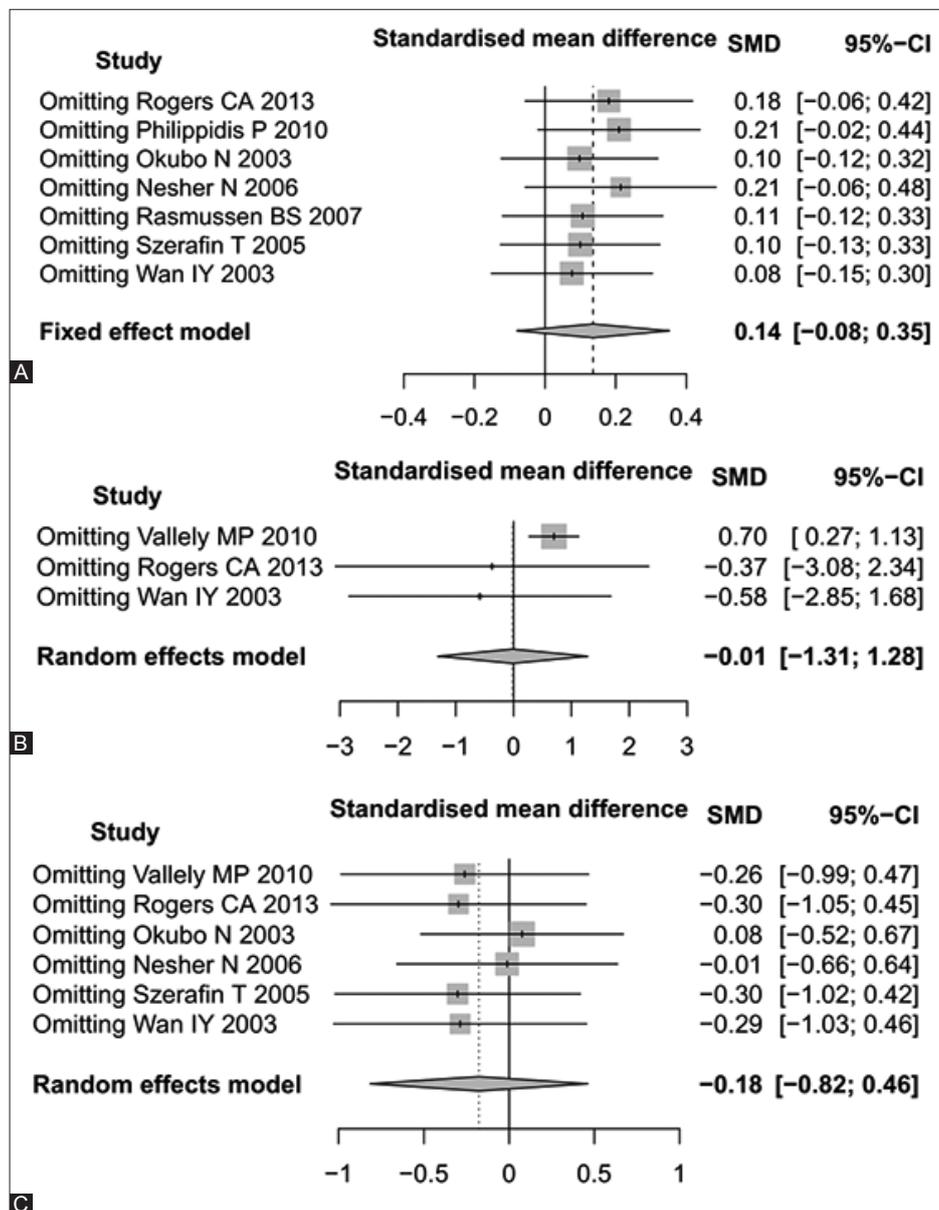


**FIGURE 3.** Sensitivity analyses of interleukin-10 (IL-10) in preoperative conditions (A), at 12 hours postoperatively (B), and at 24 hours postoperatively (C).

**TABLE 2.** Overall pooled analyses of pre and postoperative IL-6, 8 and 10 between off- and on-pump CAB groups

IL	Sample size		Test of association			Model	Test of heterogeneity <sup>a,b</sup>			Egger's test for publication bias <sup>c</sup>	
	Off-pump	On-pump	SMD [95%CI]	Z	p		Q	p	I <sup>2</sup> (%)	t	p
IL-6											
Pre	304	307	0.1251 [-0.2294; 0.4795]	0.6915	0.4892	Random	57.66	<0.001	75.7	0.0684	0.9465
Post 12 hours	103	120	0.3315 [-0.3241; 0.9871]	0.9910	0.3217	Random	30.6	<0.001	80.4	0.9821	0.3712
Post 24 hours	411	420	-0.6778 [-1.3618; 0.0062]	1.9422	0.0521	Random	346.64	<0.001	94.2	0.5332	0.6001
IL-10											
Pre	344	360	0.1747 [-0.1643; 0.5137]	1.0103	0.3124	Random	62.86	<0.001	77.7	0.4941	0.6294
Post 12 hours	159	176	-1.3640 [-2.0086; -0.7193]	4.1471	<0.0001	Random	45.44	<0.001	84.6	1.4479	0.1978
Post 24 hours	356	370	-0.2583 [-0.8703; 0.3538]	0.8271	0.4082	Random	201.86	<0.001	92.6	0.8034	0.4352
IL-8											
Pre	167	170	0.1362 [-0.0796; 0.352]	1.2373	0.216	Fixed	10.03	0.1234	40.2	1.6846	0.1529
Post 12 hours	55	59	-0.0148 [-1.3102; 1.2805]	0.0225	0.9821	Random	18.89	<0.001	89.4	1.333	0.4097
Post 24 hours	140	144	0.1773 [-0.8160; 0.4614]	0.5441	0.5863	Random	29.72	<0.001	83.2	0.3886	0.7174

<sup>a</sup>Random-effects model was used when the p for heterogeneity test was <0.10, otherwise the fixed-effect model was used. <sup>b</sup>p<0.1 is considered statistically significant for Q statistics. <sup>c</sup>Egger's test was used to evaluate publication bias, p<0.05 was considered statistically significant. CI: confidence interval; CAB: Coronary artery bypass; SMD: Standardized mean differences; IL: Interleukin



**FIGURE 4.** Sensitivity analyses of interleukin-8 (IL-8) in preoperative conditions (A), at 12 hours postoperatively (B), and at 24 hours postoperatively (C).

off-pump and on-pump CAB groups, suggesting that off-pump CAB surgery has no advantage over on-pump CAB surgery, in reducing postoperative inflammatory responses in patients.

Nevertheless, in our analysis, IL-6, 8, and 10 levels were significantly decreased in off-pump CAB group at 24 hours postoperatively. However, the IL concentrations at 12 hours postoperatively showed inconsistent results, which might be related to a small number of included studies or divergent effects of different types of ILs on the inflammatory response during surgery. For example, in patients with coronary artery disease serum levels of IL-6 are significantly higher, but the concentration of IL-10 is significantly lower compared to healthy people [37]. Furthermore, the physical condition of a patient is also an important factor influencing the IL levels. Shi *et al.* [38] found that IL-6 could induce obesity-related inflammatory response. In addition, some pro-inflammatory markers, including IL-6, were positively related to the obesity-independent insulin resistance and metabolic syndrome features [39-41]. Therefore, more clinical characteristics of participants should be considered when carrying out experiment design in these studies.

In this study, significant heterogeneities were observed in all outcomes except preoperative IL-8 concentrations. The following reasons could be the source of this heterogeneity: (1) participants from different regions may differ with regard to culture, living environment, and customs; (2) potential factors that may increase inflammatory responses, such as comorbidity interference, were not excluded; (3) many of the included studies compared only postoperative IL levels between off-pump and on-pump CAB groups. Therefore, the diversity of baseline levels between the two groups could be the source of heterogeneity.

This is the first meta-analysis systematically comparing the preoperative and postoperative IL-6, 8 and 10 concentrations between off-pump and on-pump CAB groups. No publication biases were found in the outcomes. However, there are several limitations in this study. First, the subgroup analyses and meta-regression analysis could not be conducted due to the incomplete covariates provided in the included studies. Second, only the outcomes in pre and postoperative periods were pooled. The post-discharge outcomes were not analyzed due to lack of data. Thus, further studies with a strict experimental design are required to verify our observation.

In the present meta-analysis, the sensitivity analyses showed that most of the pooled results were stable after omitting one study. However, the studies by Caputo *et al.* [19] and Valley *et al.* [33] showed a large effect on the pooled results. This may be due to the small sample sizes. Thus, more studies with larger sample size and strict

experimental design should be performed to evaluate the inflammatory response between off-pump and on-pump CAB patients.

Overall, there are no significant differences in the concentrations of IL-6, 8 and 10 between off-pump and on-pump CAB groups, suggesting that the off-pump CAB surgery may have no beneficial effect on the reduction of inflammatory response in these patients. However, this result should be verified by other studies with high quality and large samples.

## DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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