

## Systematic Review

# The Effect of Genetic Variation on the Sensitivity to Opioid Analgesics in Patients With Postoperative Pain: An Updated Meta-analysis

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**Background:** Responsiveness to opioid analgesics differs among patients with acute postoperative pain.

**Objective:** Our study presents the most recent evidence on the effect of genetic variations on postoperative pain, opioid consumption, nausea, and vomiting in patients treated with opioids.

**Study Design:** An updated systematic review and meta-analysis on the association between single-nucleotide polymorphisms and opioids administered to patients with acute postoperative pain.

**Methods:** PubMed, Embase, ISI Web of Science, and the Cochrane Library databases were searched for articles published from February 1, 2014, through December 31, 2021.

**Results:** Added to the previous meta-analysis, 39 studies (a total of 7,455 patients) were included in the final meta-analysis. Highlights of the findings include: 1) human  $\mu$ -opioid receptor gene 118G allele carriers required more opioids during the first postoperative 24 hours (standard mean difference [SMD] = -0.27; 95% CI, -0.40 to -0.14;  $P < 0.0001$ ) and 48 hours (SMD = -0.52; 95% CI, -0.83 to -0.20;  $P = 0.001$ ), and reported higher pain scores during the first 24 hours but not at the 48-hour postoperative period (SMD = -0.09, 95% CI, -0.15 to -0.03;  $P = 0.002$ ) compared to homozygous 118AA patients. 2) patients with the CYP3A4 \*1G allele required fewer opioids during the first 24-hour postoperative period (SMD = 0.59; 95% CI, 0.05 to 1.14;  $P = 0.03$ ) compared to patients with the homozygous CYP3A4\*1/\*1 allele. 3) Adenosine triphosphate-binding cassette subfamily B member-1 (ABCB1) 3435T allele carriers required more opioids during the 48-hour postoperative period (SMD = -0.21; 95% CI, -0.38 to -0.04;  $P = 0.02$ ) compared to homozygous CC carriers. 4) Catechol-O-methyl transferase 158A allele carriers required fewer opioids during the first 24-hour postoperative period (SMD = 0.33; 95% CI, 0.15 to 0.51;  $P = 0.0004$ ) compared to homozygous GG carriers. No significant differences were observed in patients with CYP2D6\*10 and ABCB1 G2677A/T genetic polymorphisms.

**Limitations:** Several loci were not analyzed in detail due to insufficient clinical data. Furthermore, nongenetic factors that affected analgesic efficacy and the clinical outcome of postoperative pain were not discussed and were not the aim of this meta-analysis.

**Conclusions:** In combination with previous systematic reviews and meta-analyses, our results indicate that the A118G allele variant of OPRM1 and the \*1\*1G allele variant of CYP3A4 have a profound influence on individual differences in opioid reactivity in patients with postoperative pain. Our results, together with the identification of additional single nucleotide polymorphisms in future studies, may provide a theoretical basis for precise clinical analgesia.

**Key words:** Single nucleotide polymorphism, postoperative pain, opioid, meta-analysis

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**O**pioid receptor agonists, also known as opioids, are well-established for the treatment of postoperative analgesia. The World Health Organization analgesic ladder for pain management of patients with cancer has been shown to relieve pain in 80% of these patients (1). However, the increased use of these highly potent drugs poses clinical safety problems after extended use, in addition to high rates of side effects, drug dependence, and addiction. In a randomized systematic review, about 80% of patients analyzed from 11 different studies experienced adverse events under opioid therapy (2).

Due to the differences in patient characteristics, the postsurgical use of opioids can lead to different clinical responses. These include differences in opioid consumption and opioid-related effects (3). Concerning clinical outcomes, we focused more on the side effects after opioid administration, such as nausea, vomiting, constipation, and typical symptoms of opioid-induced bowel dysfunction. The long-term adverse effects include endocrine dysfunctions, respiratory depression, respiratory problems, and direct or indirect effects on the immune system (4,5). Studies have suggested that different clinical responses are the result of numerous factors but are mainly genetic (6). Hence, providing evidence for genetic factors contributing to individual patient differences in clinical opioid use is crucial.

Based on our publication search, there are no meta-analyses that summarize the relationship between single nucleotide polymorphisms (SNPs) at multiple gene loci and postoperative analgesia, opioid consumption, and side effects, except for systematic reviews and meta-analyses previously performed by us (7). Considering that our previous meta-analyses were performed 8 years ago, and with the advancement of the field in recent years, our current study systematically summarizes the effect of SNPs on postoperative analgesia, opioid consumption, and side effects together with the latest studies. This was done to provide an additional theoretical basis for optimizing postoperative analgesia.

## METHODS

This meta-analysis protocol abided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and is registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42022338858)

## Literature Search Strategy

We performed a systematic search of PubMed, Embase, ISI Web of Science, and the Cochrane Library for articles published from February 1, 2014 through December 31, 2021, for all studies that showed an association between genetic polymorphisms and analgesic efficiency or clinical outcome of opioid analgesics using the following search combinations: "gene," "genetic," "polymorphism," "postoperative pain," "postoperative analgesia."

## Data Selection

Articles retrieved from the above databases were first filtered using EBM AI-Reviewer (an artificial intelligence tool for literature screening based on PICOS [population, intervention, comparison, outcomes, studies] principles) and then divided into 2 types: irrelevant and preliminary, which eliminated incomplete or duplicate articles. Three authors (ZX Li, WY Li, and F Ye) independently assessed the 2 types of articles for inclusion in the meta-analysis. Studies were included if they were randomized for postoperative adult patients who took opioids for analgesia and presented the results of at least one of the following endpoints stratified by genetic polymorphisms: 1) pain scores at 24 or 48 hours postsurgery; 2) opioid dosage requirements or consumption at 24 or 48 hours postsurgery; and 3) side effects: nausea, vomiting or postoperative nausea and vomiting (PONV) within 48 hours (few studies elaborated other side effects). Different opioid analgesics, surgery types, interventions, and patient populations are included in the meta-analysis (Table 1) (If the Visual Analog Scale (VAS) was greater than 10, it was divided by 10). Patient demographics and clinical statistics were collected and assessed to identify repetition, and only the final dataset was selected to prevent data replication.

## Data Extraction

Data were independently extracted from eligible articles by 3 authors (ZX Li, WY Li, and F Ye) who subsequently cross-checked the data. For each study, the following items were extracted: first author, year of publication, and genetic variants. The data were extracted from tabular format or were calculated from the main manuscript or supplementary appendices. When data were not presented in a direct format for inclusion, the evidence-based medicine data conversion formulas were used for conversion. Any disagreements between the authors were resolved by discussion or

Table 1. Details of the studies included in the meta-analysis.

No.	Author	Year	Men/ Women	Hardy- Weinberg	Setting	Opioid	Administration Method	Variant	NOS
1	Chou W Y et al (8)	2006 <sup>a</sup>	0/80	No	total abdominal hysterectomy	morphine	PCIA	OPRM1 A118G	8
2	Chou W Y et al (17)	2006 <sup>b</sup>	31/89	No	total knee arthroplasty	morphine	PCIA	OPRM1 A118G	8
3	Coulbault L et al (18)	2006	44/30	Yes	abdominal surgery with a colorectal or coloanal anastomosis	morphine	IV	OPRM1 A118G, ABCB1 C3435T, ABCB1 G2677A/T	8
4	Hayashida M et al (19)	2008	80/58	Yes	major open-abdominal surgery	morphine or fentanyl	epidural space injection	OPRM1 A118G	7
5	Sia A T et al (9)	2008	0/585	No	cesarean	morphine	PCIA	OPRM1 A118G	7
6	Fukud K et al (20)	2010	40/68	Yes	Sagittal split mandibular osteotomy	fentanyl	PCIA	OPRM1 A118G	8
7	Sia A T et al (44)	2010	0/620	Yes	cesarean delivery	morphine	PCIA	ABCB1 C3435T	8
8	Zhang W et al (34)	2010 <sup>a</sup>	0/143	Yes	total abdominal hysterectomy or myomectomy	fentanyl	PCIA	CYP3A4 *1/*1G	9
9	Zhang W et al (10)	2010 <sup>b</sup>	0/174	Yes	total abdominal hysterectomy or myomectomy	fentanyl	PCIA	OPRM1 A118G	8
10	Kolesnikov Y et al (30)	2011	45/57	No	abdominal surgery for either abdominal radical prostatectomy or hysterectomy	fentanyl	PCIA	OPRM1 A118G	9
11	Yuan R et al (35)	2011	83/93	Yes	abdominal surgery	fentanyl	PCA	CYP3A4 *1/*1G	8
12	Zhang W et al (11)	2011	0/165	Yes	total abdominal hysterectomy or myomectomy	fentanyl	PCIA	OPRM1 A118G	8
13	Chen L K et al (32)	2012	0/129	Yes	total abdominal hysterectomy	morphine	PCIA	OPRM1 A118G	8
14	Zwisler S T et al (12)	2012	N/A (totally 268)	Yes	thyroidectomy, parathyroidectomy, mastectomy and hysterectomy (vaginal and abdominal)	oxycodone	PCA	OPRM1 A118G, ABCB1 C3435T, ABCB1 G2677A/T	8
15	Boswell M V et al (31)	2013	0/158	NID	cesarean delivery	hydrocodone		OPRM1 A118G	8
16	Candiotti K et al (40)	2013	94/58	Yes	elective nephrectomy	morphine	PCIA	ABCB1 C3435T	8
17	Kim K M et al (21)	2013	0/196	Yes	abdominal hysterectomy or laparoscopic assisted vaginal hysterectomy	fentanyl	PCIA	OPRM1 A118G, ABCB1 C3435T, ABCB1 G2677A/T	8
18	Liao Q et al (22)	2013	60/37	Yes	radical gastrectomy	fentanyl	PCIA	OPRM1 A118G	9
19	Sia A T et al (13)	2013	0/1001	Yes	total hysterectomy	morphine	PCA	OPRM1 A118G	8
20	Zhang F et al (14)	2013	76/52	Yes	radical gastrectomy	fentanyl	PCIA	OPRM1 A118G	8
21	Bastami S et al (23)	2014	0/40	Yes	abdominal hysterectomy	morphine	PCIA	OPRM1 A118G, ABCB1 C3435T, ABCB1 G2677A/T	8
22	Candiotti K A et al (45)	2014	94/58	Yes	elective nephrectomy	morphine	IV	COMT Val158Met	9
23	Dong H et al (37)	2015	59/52	Yes	elective nephrectomy	tramadol	PCIA	CYP2D6 *1/*10	7

Table 1 (cont). Details of the studies included in the meta-analysis.

No.	Author	Year	Men/ Women	Hardy- Weinberg	Setting	Opioid	Administration Method	Variant	NOS
24	Lee S -H et al (24)	2015	0/416	ND	general anesthesia	remifentanyl		OPRM1 A118G	8
25	Wei X -B et al (38)	2015	49/65	ND	general anesthesia	morphine	PCIA	CYP2D6 *1/*10	8
26	Wu S -B et al (39)	2015	123/84	No	radical gastrectomy	fentanyl	PCIA	CYP2D6 *1/*10	8
27	Zhang F et al (46)	2015	69/46	Yes	radical gastrectomy	fentanyl	PCIA	COMT Val158Met	8
28	Dzambazovska- Trajkovska V et al (41)	2016	N/A (total 100)	ND	abdominal surgery with colorectal anastomosis because of colorectal carcinoma	fentanyl	PCA	ABCBI C3435T	8
29	Wang Y et al (25)	2016	30/90	Yes	cancer surgery	sufentanyl	PCA	OPRM1 A118G, ABCBI C3435T, ABCBI G2677A/ T, CYP3A4 *1/*1G	9
30	Zhou Y et al (26)	2017	87/72	ND	radical resection of lung cancer	fentanyl	PCA	OPRM1 A118G	8
31	Pettini E et al (33)	2018	0/63	ND	cesarean delivery	morphine	IV	OPRM1 A118G	9
32	Zhang J et al (15)	2018	0/240	ND	lower segment caesarean delivery surgeries	fentanyl	PCEA	OPRM1 A118G, CYP3A4 *1/*1G	9
33	Pu J et al (27)	2019	22/8 (oxycodone), 19/10 (sufentanyl)	Yes	laparoscopic surgery for gastric or intestinal cancer	oxycodone, sufentanyl	PCA	OPRM1 A118G, CYP3A4 *1/*1G, CYP2D6 *1/*10	8
34	Wang L et al (28)	2019	0/266	Yes	cesarean delivery	sufentanyl	PCIA	OPRM1 A118G, COMT Val158Met	8
35	Zhang X et al (42)	2019	N/A (totally 100)	Yes	thoracoscopic lobectomy	sufentanyl	PCIA	ABCBI C3435T	8
36	Zhao Z et al (16)	2019	132/93	Yes	thoracoscopic-assisted radical resection of lung cancer	sufentanyl	PCEA	OPRM1 A118G, ABCBI C3435T, ABCBI G2677A/T	9
37	Hou Y et al (36)	2020	79/71	Yes	hip replacement	sufentanyl	IV	CYP3A4 *1/*1G	8
38	Zhang F et al (43)	2021	N/A (totally 135)	Yes	radical Gastrectomy	fentanyl	PCIA	ABCBI C3435T	8
39	Chou W -Y et al (29)	2021	28/83	ND	total knee replacement	morphine	PCA	OPRM1 A118G	8

NOS, Newcastle-Ottawa Scale; PCIA, patient-controlled intravenous analgesia; IV, intravenous; PCA, patient-controlled analgesia; [this is not in the Table]ND, not discussed; VAS, visual analog scale; PCEA, patient-controlled epidural analgesia.

consultation. The detailed process of identifying eligible studies and exclusion reasons is presented in Fig. 1. We updated all study information that was included in our prior meta-analysis.

### Study Quality Assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). The NOS assesses the quality of studies using a star system based on the following 3 domains: selection of the study groups (1-4 points), comparability of cohorts (1-2 points), and assessment of exposure and outcome (1-3 points). Total scores range from 0 (lowest) to 9 (highest). Studies with scores  $\geq 8$  were considered to have high quality, those with scores of 6–7 were considered to have intermediate quality, and those with scores  $< 6$  were considered to have low quality.

### Statistical Analysis

Data extracted from each study were pooled using RevMan 5.4.1 (The Nordic Cochrane Centre for The Cochrane Collaboration) to calculate the mean difference (MD), standard mean difference (SMD), and odds ratio (OR) for parameters of pain score, opioid consumption, and drug side effects, respectively.

For data reflecting opioid consumption, we calculated the SMD to standardize the data to resolve issues related to different data units. Candidate gene loci for the meta-analysis were selected if 3 or more studies recorded the data and such data were available.

Results were illustrated as point estimates and 95% CIs, with 2-sided  $P$  values using a fixed-effects model or random-effects model based on heterogeneity. A  $P$  value  $< 0.05$  was considered statistically significant. Heterogeneity across all the included studies was assessed using  $Q$ -statistic, with a  $P < 0.05$  or  $I^2 > 50\%$  considered to have significant heterogeneity. Sensitivity analyses were performed in the included studies by excluding studies with an NOS score  $\leq 7$  to assess the stability of the core results. The presence of publication bias was evaluated using funnel plots.

### Meta-Analysis Results

#### Study Characteristics

Briefly, a total of 7,506 patients were included in our meta-analysis. The included studies' NOS scores ranged from 7 to 9, indicating moderate to high quality. The main characteristics of the 39 eligible studies are summarized in Table 1.

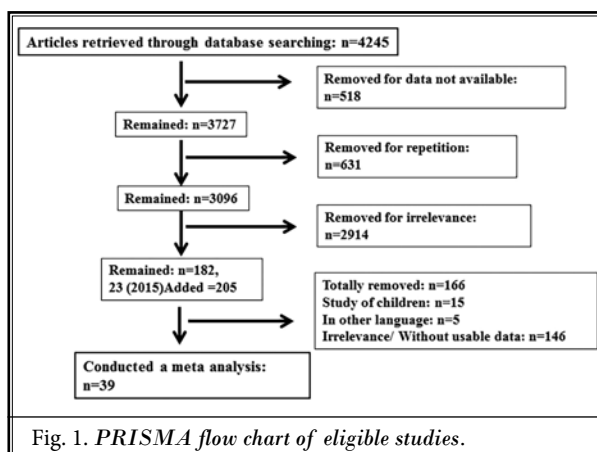


Fig. 1. PRISMA flow chart of eligible studies.

### Study Quality Assessment

All studies we analyzed scored from 7 to 9 using the NOS scoring system. Three studies scored 7 points, 28 studies scored 8 points and 8 studies scored 9 points. Most studies had good performance in sample selection and comparability, but failed in outcome. Study-specific quality assessment scores are summarized in Supplemental Table 1.

### Human $\mu$ -opioid Receptor Gene (*OPRM1*) A118G/rs1799971

#### Pain

Data on pain scores were available from independent samples in 10 studies for the AA vs G variant during the 24-hour postoperative period (8-17) and 4 studies during the 48-hour postoperative period (8,14,16,17). The final analysis included 1,398 homozygous 118AA patients and 1,558 118G allele carriers during the 24-hour postoperative period and 286 homozygous 118AA patients and 267 118G allele carriers during the 48-hour postoperative period. To unify the data, the pain scores were transformed to 11 points (ranging from 0 for no pain to 10 for maximum pain) if the original data were presented on a 100-point scale (ranging from 0 for no pain to 100 for maximum pain).

No heterogeneity was observed across the studies ( $\chi^2$ ;  $P > 0.05$ ; 11.18 [Fig. 2A], 0.17 [Fig. 2B]), hence the fixed-effects model was selected. The presence of the G allele was associated with higher pain scores compared to AA homozygotes during the first 24-hour postoperative period (fixed-effects model: MD = -0.09; 95% CI, -0.15 to -0.03;  $P = 0.002$ ; Fig. 2A). No significant differences were observed when comparing G allele carriers and homozygous AA carriers in the 48-hour

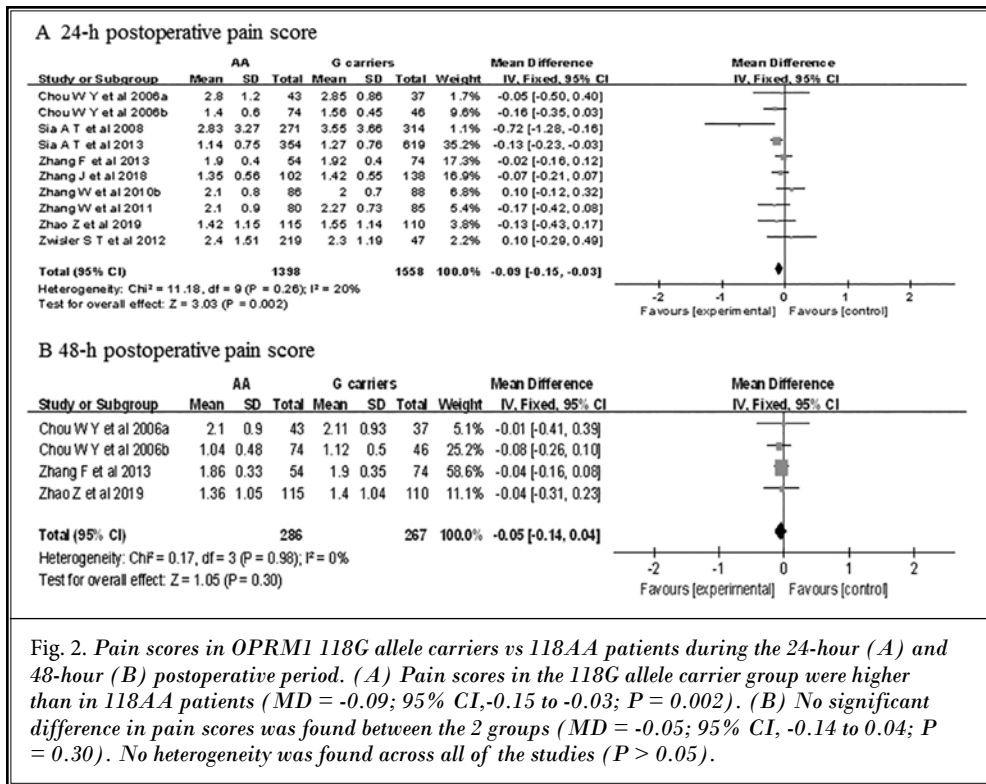


Fig. 2. Pain scores in OPRM1 118G allele carriers vs 118AA patients during the 24-hour (A) and 48-hour (B) postoperative period. (A) Pain scores in the 118G allele carrier group were higher than in 118AA patients (MD = -0.09; 95% CI, -0.15 to -0.03; P = 0.002). (B) No significant difference in pain scores was found between the 2 groups (MD = -0.05; 95% CI, -0.14 to 0.04; P = 0.30). No heterogeneity was found across all of the studies (P > 0.05).

postoperative period (fixed-effects model: MD = -0.05; 95% CI, -0.14 to 0.04; P = 0.30; Fig. 2B).

**Opioid Consumption**

Data on opioid consumption were available from independent samples in 22 studies for the AA vs G carrier during the 24-hour postoperative period (8-29) and 11 studies during the 48-hour postoperative period (8,15-17,21,22,25,26,28-30). The final analysis included 2,175 homozygous 118AA patients and 2,567 118G allele carriers during the 24-hour postoperative period, and 855 homozygous 118AA patients and 864 118G allele carriers during the 48-hour postoperative period. Because different opioids and dosing parameters were used, to unify the data, opioid doses were reported as total 24-hour or 48-hour postoperative opioid consumption.

Heterogeneity was detected across the studies ( $\chi^2$ ; P < 0.05; 89.16 [Fig. 3A], 96.36 [Fig. 3B]), hence a random-effects model was used. More opioid consumption was observed in 118G allele carriers compared to AA homozygotes during the first 24-hour postoperative period (random-effects model: SMD = -0.27; 95% CI, -0.40 to -0.14; P < 0.0001; Fig. 3A). Similarly, 118G allele carriers exhibited more opioid consumption compared to AA homozygotes during the 48-hour postoperative period (random-effects

model: SMD = -0.52; 95% CI, -0.83 to -0.20; P = 0.001; Fig. 3B).

**Side Effects**

Data for nausea were available from 14 independent studies (9-11,14-18,22,26,27,29,31,32) and data for vomiting were available from 15 independent studies (8-11,14-18,22,26,27,29,31,32). The final analysis included 1,228 homozygous 118AA patients and 1,198 118G allele carriers for nausea, while there were 1,271 homozygous 118AA patients and 1,235 118G allele carriers for vomiting.

No heterogeneity was observed across the studies ( $\chi^2$ ; P > 0.05; Figs. 4A, 4B), hence a fixed-effects model was used. No significant differences were observed between G carriers and homozygous AA carriers for the rate of nausea (fixed-effects model: OR = 1.16; 95% CI, 0.93 to 1.44; P = 0.19; Fig. 4A) and vomiting (fixed-effects model: OR = 1.13; 95% CI, 0.89 to 1.43; P = 0.33; Fig. 4B).

Similarly, when we considered these 2 effects together, i.e., postoperative nausea or vomiting (PONV), data were available from 17 independent studies (8-11,14-18,22,24,26,27,29,31-33). The final analysis included 1,475 homozygous 118AA patients and 1,511 118G allele carriers. Heterogeneity was detected across the studies ( $\chi^2$ ; P < 0.05; Fig. 4C), and the overall effect showed no significant difference (random-effects model: OR = 1.21; 95% CI, 0.90 to 1.64; P = 0.21; Fig. 4C).

**Cytochrome (CYP)**

**CYP3A4 \*1/\*10G**

**Pain**

Data on pain scores during the 24-hour postoperative period for the \*1\*1 vs \*1G variant were available

Genetic Effects on Postoperative Pain and Opioid Consumption

from independent samples in 4 studies (15,34-36). The final analysis included 398 homozygous \*1\*1 patients and 311 \*1G allele carriers during the 24-hour postoperative period. To unify the data, the pain scores were transformed to 11 points if the original data were presented on a 100-point scale.

No heterogeneity was observed across the studies ( $\chi^2$ ;  $P > 0.05$ ; Fig. 5A), hence a fixed-effects model was used. No significant differences were observed when comparing \*1G allele carriers and homozygous \*1\*1

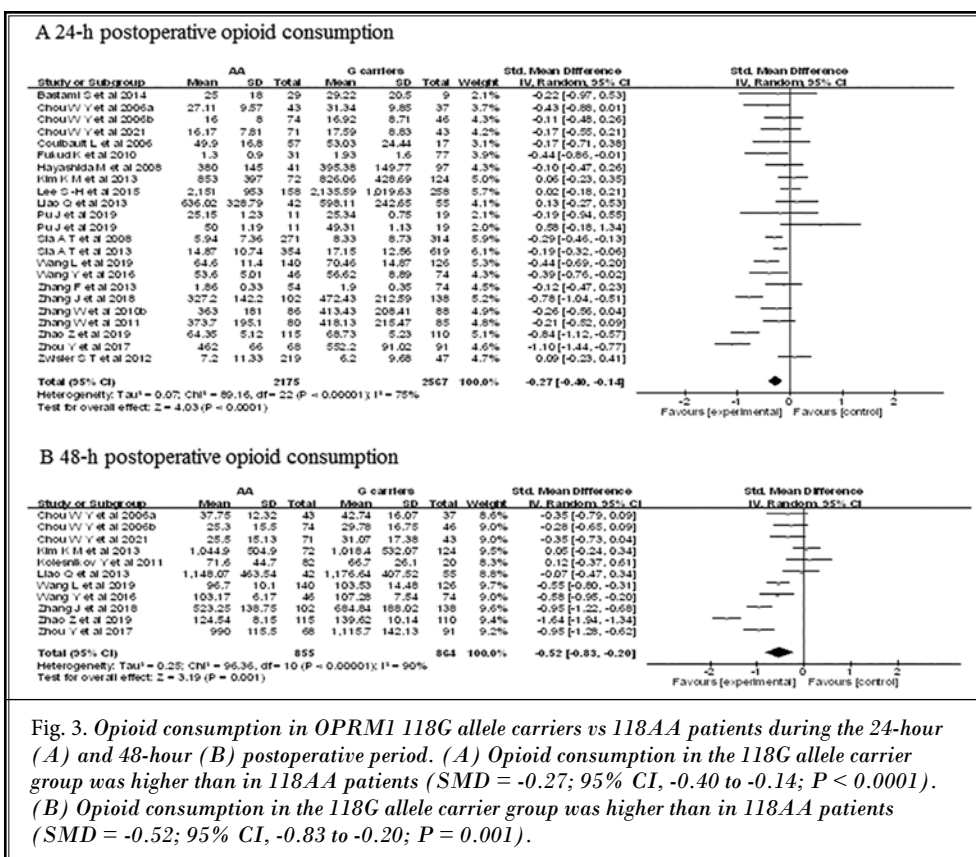
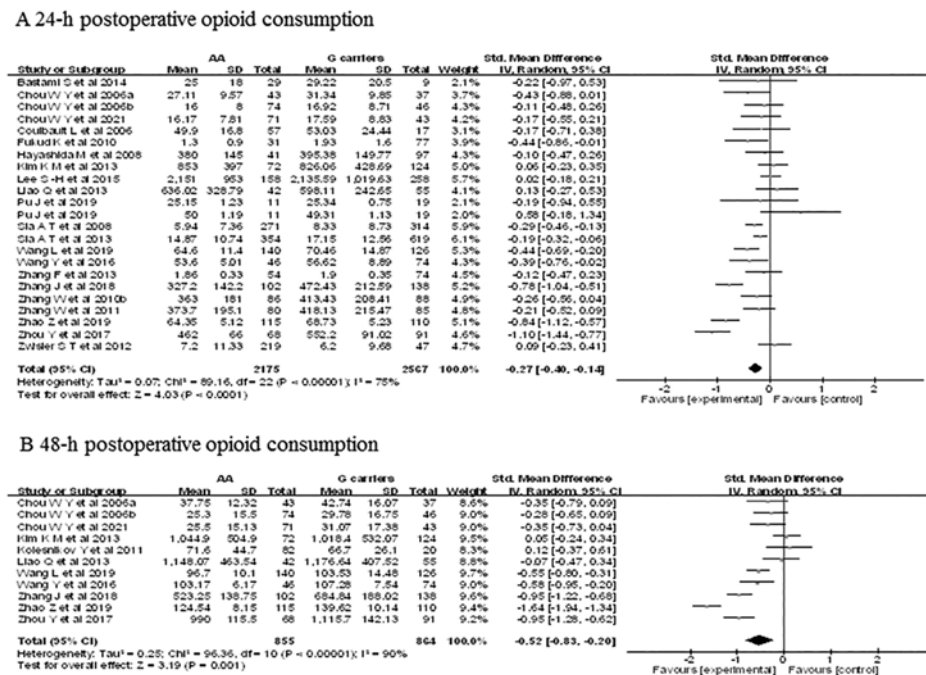


Fig. 3. Opioid consumption in OPRM1 118G allele carriers vs 118AA patients during the 24-hour (A) and 48-hour (B) postoperative period. (A) Opioid consumption in the 118G allele carrier group was higher than in 118AA patients (SMD = -0.27; 95% CI, -0.40 to -0.14;  $P < 0.0001$ ). (B) Opioid consumption in the 118G allele carrier group was higher than in 118AA patients (SMD = -0.52; 95% CI, -0.83 to -0.20;  $P = 0.001$ ).

Fig. 4. Nausea (A) and vomiting (B) during the postoperative period in OPRM1 118G allele carriers vs 118AA patients. No significant difference in nausea (A) ( $OR = 1.16$ ; 95% CI, 0.93 to 1.44;  $P = 0.19$ ) and vomiting occurrence (B) ( $OR = 1.13$ ; 95% CI, 0.89 to 1.43;  $P = 0.33$ ) was found between the 2 groups. No heterogeneity was found across all of the studies ( $P > 0.05$ ). (C) Postoperative nausea and vomiting (PONV) in OPRM1 118G allele carriers vs AA patients. No significant difference in PONV was found between the 2 groups ( $OR = 1.21$ ; 95% CI, 0.90 to 1.64;  $P = 0.21$ ).



patients in the 24-hour postoperative period (fixed-effects model: MD = 0.03; 95% CI, -0.05 to 0.12;  $P = 0.45$ ; Fig. 5A).

**Opioid Consumption**

Data on opioid consumption during the 24-hour postoperative period for the \*1\*1 vs \*1G variants were available from independent samples in 5 studies (15,25,27,34,35). The final analysis included 407 homozygous \*1\*1 patients and 331 \*1G allele carriers during the 24-hour postoperative period. To unify the data, opioid doses were reported as a total of 24-hour postoperative opioid consumption.

Heterogeneity was detected across the studies ( $\chi^2$ ;  $P < 0.05$ ; Fig. 5B), hence a random-effects model was used. More opioid consumption was observed for \*1\*1 homozygotes compared to \*1G allele carriers during the first 24-hour postoperative period (fixed-effects model: SMD = 0.59; 95% CI, 0.05 to 1.14;  $P = 0.03$ ; Fig. 5B).

**PONV**

PONV data were available from 3 independent studies (34-36). The final analysis included 271 homozygous \*1\*1 patients and 198 \*1G allele carriers.

No heterogeneity was observed across the studies ( $\chi^2$ ;  $P > 0.05$ ; Fig. 5C), hence a fixed-effects model was used. No significant difference in PONV was observed when comparing \*1G carriers and homozygous \*1\*1 patients (fixed-effects model: OR = 1.20; 95% CI, 0.78 to 1.85;  $P = 0.41$ ; Fig. 5C).

**CYP2D6 \*1/\*10**

**Pain**

Data on pain scores were available from independent samples in 3 studies for the \*1\*1 vs \*10 variant during the 24-hour and 48-hour postoperative period (37-39). The final analysis included 111 homozygous \*1\*1 patients and 309 \*10 allele carriers during the 24-hour and 48-hour postoperative period. To unify the data, the pain scores were transformed

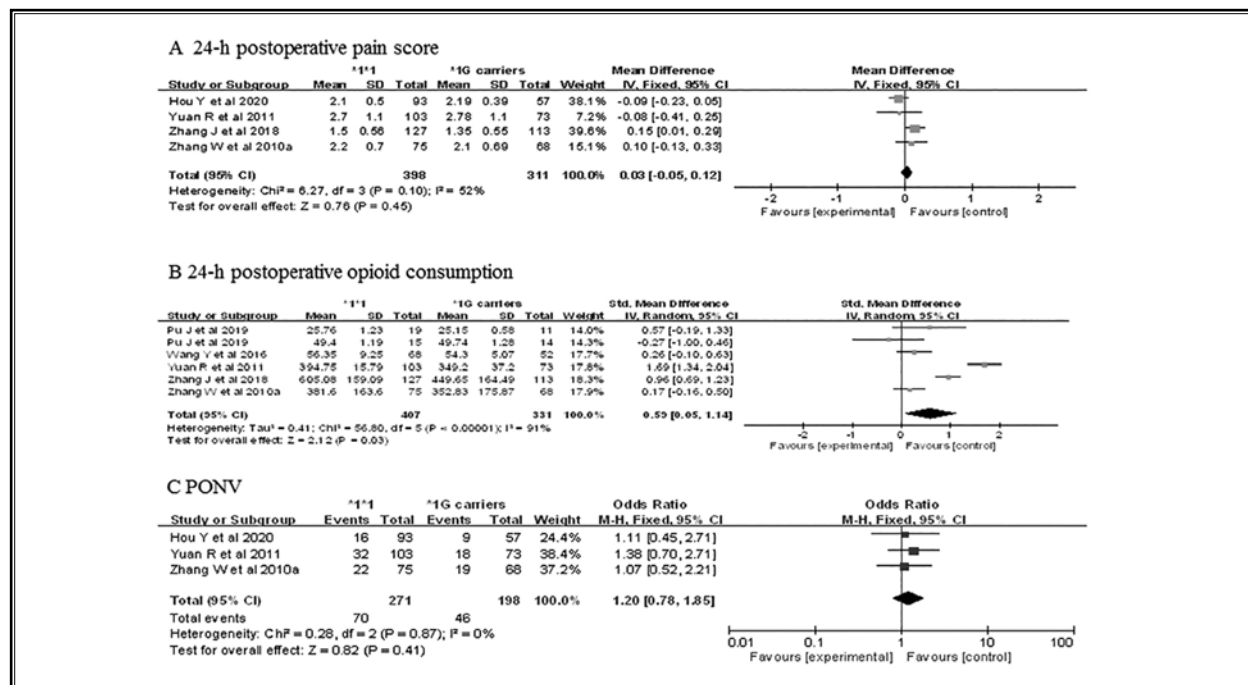


Fig. 5. Pain scores in CYP3A4 \*1G allele carriers vs \*1\*1 patients during the 24-hour postoperative period (A). No significant difference in pain scores was found between the 2 groups (MD = 0.03; 95% CI, -0.05 to 0.12;  $P = 0.45$ ). No heterogeneity was found across all of the studies ( $P > 0.05$ ). (B) Increased opioid consumption in CYP3A4 \*1\*1 patients vs \*1G allele carriers during the 24-hour postoperative period. Opioid consumption in \*1\*1 patients was higher than the \*1G allele carrier group (SMD = 0.59; 95% CI, 0.05 to 1.14;  $P = 0.03$ ). (C) PONV in CYP3A4 \*1G allele carriers vs \*1\*1 patients. No significant difference in PONV was found between the 2 groups (OR = 1.20; 95% CI, 0.78 to 1.85;  $P = 0.41$ ). No heterogeneity was found across all of the studies ( $P > 0.05$ ).



to 11 points if the original data were presented on a 100-point scale.

No heterogeneity was observed across the studies ( $\chi^2$ ;  $P > 0.05$ ; Figs. 6A, 6B), hence a fixed-effects model was used. No significant difference was observed when comparing \*10 allele carriers and homozygous \*1\*1 carriers in the 24-hour (fixed-effects model: MD = -0.15, 95% CI = [-0.39, 0.10],  $P = 0.24$ ; Fig. 6A) and 48-hour postoperative period (fixed-effects model: MD = -0.02; 95% CI, -0.22 to 0.17;  $P = 0.80$ ; Fig. 6B).

### Opioid Consumption

Data on opioid consumption were available from independent samples in 4 studies for the \*1\*1 vs. \*10 variant during the 24-hour postoperative period (27,37-39) and 3 studies during the 48-hour postoperative period (37-39). The final analysis included 124 homozygous \*1\*1 patients and 355 \*10 allele carriers during the 24-hour postoperative period and 111 homozygous \*1\*1 patients and 309 \*10 allele carriers during the 48-hour postoperative period. To unify the data, opioid doses were reported as total 24-hour or 48-hour postoperative opioid consumption.

No heterogeneity was observed across the studies ( $\chi^2$ ;  $P > 0.05$ ; Figs. 7A, 7B), hence a fixed-effects model was used. No significant difference was observed when comparing \*10 allele carriers and homozygous \*1\*1 carriers in the 24-hour (fixed-effects model: SMD = -0.12; 95% CI, -0.33 to 0.09;  $P = 0.26$ ; Fig. 7A) and 48-

hour postoperative period (fixed-effects model: SMD = 0.05; 95% CI, -0.17 to 0.27;  $P = 0.65$ ; Fig. 7B).

### Adenosine Triphosphate-binding Cassette Subfamily B Member-1 (ABCB1)

#### ABCB1 C3435T/rs1045642

##### Pain

Data on pain scores were available from independent samples in 5 studies for the CC vs T variant during the first 24-hour postoperative period (16,40-43). The final analysis included 283 homozygous CC patients and 428 T allele carriers. Pain scores were transformed to 11 points if the original data were presented on a 100-point scale.

Heterogeneity was detected across the studies ( $\chi^2$ ;  $P < 0.05$ ; Fig. 8A), hence a random-effects model was used. No significant difference in pain scores during the 24-hour postoperative period was observed when comparing T allele carriers and the homozygous CC group (random-effects model: SMD = -0.54; 95% CI, -0.05 to 1.13;  $P = 0.07$ ; Fig. 8A).

##### Opioid Consumption

Data on opioid consumption were available from independent samples in 9 studies for the CC vs T variant during the 24-hour postoperative period (12,16,18,21,23,25,40,43,44) and 3 studies during the 48-hour postoperative period (16,21,25). The final anal-

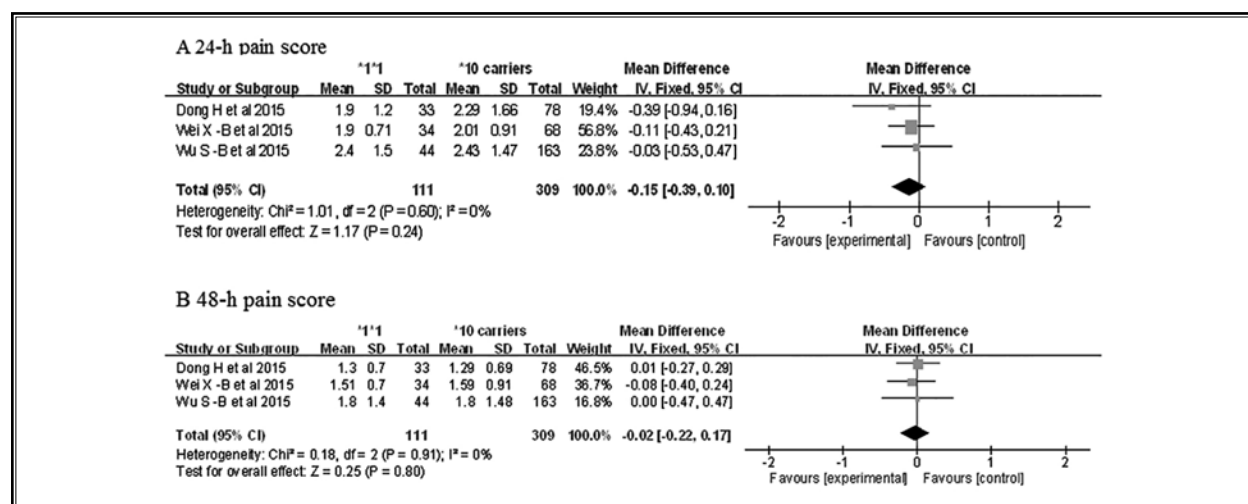


Fig. 6. Pain scores in CYP2D6 \*10 allele carriers vs \*1\*1 patients during the 24 hour (A) and 48 hour (B) postoperative period. No significant difference in pain scores was found between the 2 groups during the 24-hour (MD = -0.15; 95% CI, -0.39 to 0.10;  $P = 0.24$ ) and 48-hour (MD = -0.02; 95% CI, -0.22 to 0.17;  $P = 0.80$ ) postoperative period. No heterogeneity was found across all of the studies ( $P > 0.05$ ).

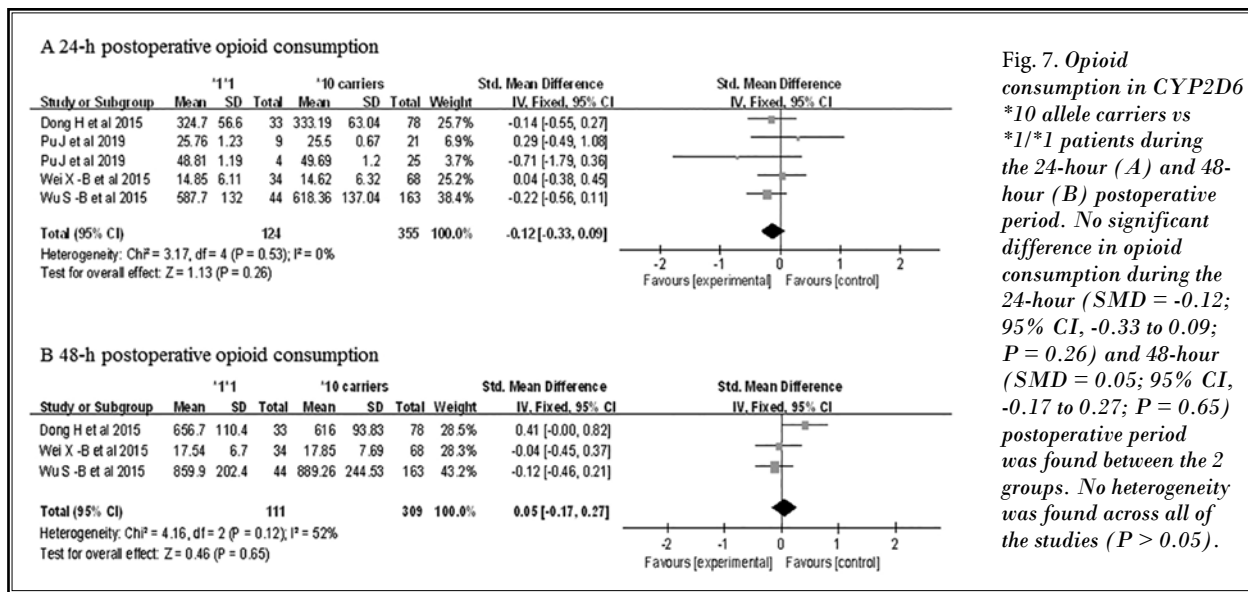


Fig. 7. Opioid consumption in CYP2D6 \*10 allele carriers vs \*1/\*1 patients during the 24-hour (A) and 48-hour (B) postoperative period. No significant difference in opioid consumption during the 24-hour (SMD = -0.12; 95% CI, -0.33 to 0.09; P = 0.26) and 48-hour (SMD = 0.05; 95% CI, -0.17 to 0.27; P = 0.65) postoperative period was found between the 2 groups. No heterogeneity was found across all of the studies (P > 0.05).

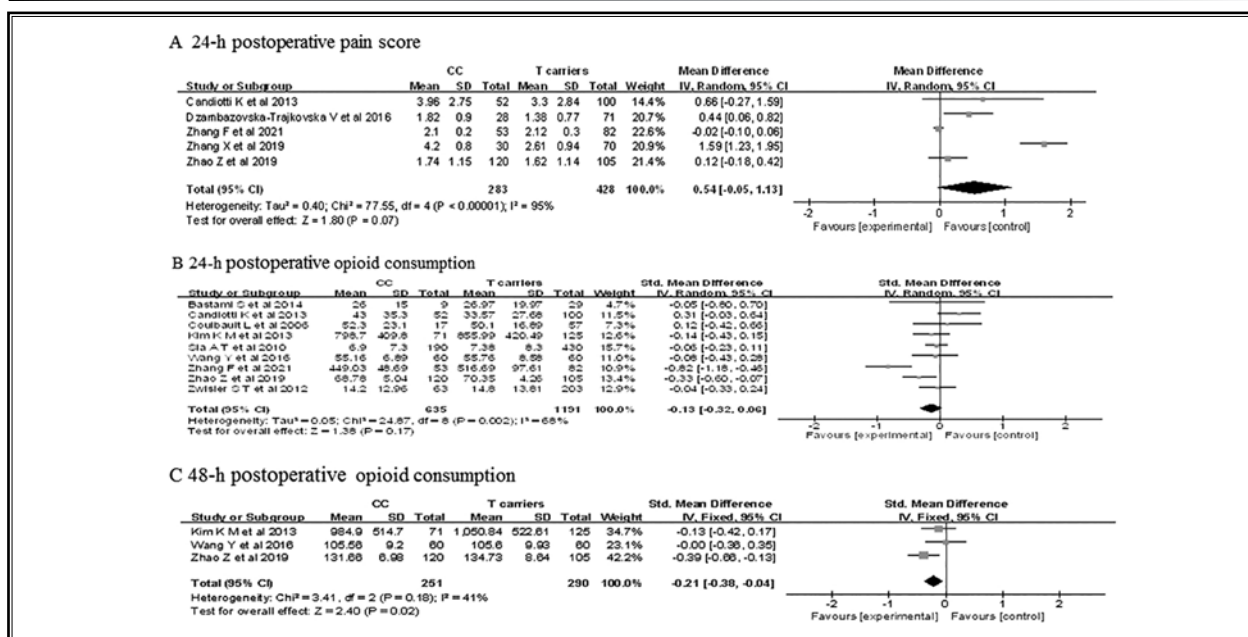


Fig. 8. (A) Pain scores in ABCB1 3435 T allele carriers vs CC patients. No significant difference in pain scores during the 24-hour postoperative period was found between the 2 groups (MD=0.54; 95% CI, -0.05 to 1.13; P = 0.07). Opioid consumption in ABCB1 3435 allele carriers vs CC patients during the 24-hour (B) and 48-hour (C) postoperative period. (B) No significant difference in opioid consumption was found between the 2 groups (SMD = -0.13; 95% CI, -0.32 to 0.06; P = 0.17). (C) Opioid consumption in the T allele carrier group was higher than in CC patients (SMD = -0.21; 95% CI, -0.38 to -0.04; P = 0.02). No heterogeneity was found across all of the studies (P > 0.05).

ysis included 635 homozygous CC patients and 1,191 T allele carriers during the 24-hour postoperative period, and 251 homozygous CC patients and 290 T allele carriers during the 48-hours postoperative period. To unify the data, opioid doses were reported as total opioid

consumption during the 24-hour or 48-hour postoperative period.

For the 24-hour postoperative period, heterogeneity was detected across the studies ( $\chi^2$ ; P < 0.05; Fig. 8B), hence a random-effects model was used. No significant

difference in opioid consumption was observed when comparing T allele carriers and homozygous CC carriers during the first 24-hour postoperative period (random-effects model: SMD = -0.13; 95% CI, -0.32 to 0.06;  $P = 0.17$ ; Fig. 8B). For the 48-hour postoperative period, no heterogeneity was found across all the studies ( $\chi^2$ ;  $P > 0.05$ ; Fig. 8C), hence a fixed-effects model was used. T allele carriers exhibited more opioid consumption compared to CC homozygotes during the 48-hour postoperative period (fixed-effects model: SMD = -0.21; 95% CI, -0.38 to -0.04;  $P = 0.02$ ; Fig. 8C).

### ABCB1 G2677A/T /rs2032582

#### Opioid Consumption

Data on opioid consumption were available from independent samples in 7 studies for the GG vs A/T carriers during the first 24-hour postoperative period (12,16,18,21,23,25,44). The final analysis included 457 homozygous GG patients and 1,074 A/T allele carriers. To unify the data, opioid doses were reported as a total of 24-hour postoperative opioid consumption.

Heterogeneity was detected across the studies ( $\chi^2$ ;  $P < 0.05$ ; Fig. 9A), hence a random-effects model was used. Comparing A/T carriers and GG homozygotes, no significant difference in opioid consumption was observed (random-effects model: SMD = -0.21; 95% CI, -0.73 to 0.31;  $P = 0.42$ ; Fig. 9).

### Catechol-O-methyltransferase (COMT) Val158Met/ G1947A/rs4680

#### Opioid Consumption

Data on opioid consumption were available from independent samples in 3 studies for the GG vs A variant during the 24-hour postoperative period (28,45,46). The final analysis included 216 homozygous GG patients and 317 118A allele carriers during the 24-hour postoperative period. To unify the data, opioid doses were reported as a total of 24-hour postoperative opioid consumption.

No heterogeneity was observed across the studies ( $\chi^2$ ;  $P > 0.05$ ; Fig. 9B), hence a fixed-effects model was used. During the first 24-hour postoperative period, 118A allele carriers exhibited lower opioid consumption compared to GG homozygotes (fixed-effects model: SMD = 0.33; 95% CI, 0.15 to 0.51;  $P = 0.0004$ ; Fig. 10).

### Sensitivity Analysis and Publication Bias Analysis

We performed a sensitivity analysis by excluding the studies with a NOS score  $\leq 7$  (9,19,37). The summary results were not significantly affected by these studies, confirming that the summary results are robust.

We used several strategies to investigate possible publication bias (7). Figure 11 presents funnel plots and a regression-based Egger test bias probability of the statistically significant meta-analysis. No significant publication bias was found for OPRM1 A118G, CYP3A4 \*1\*1G, CYP2D6 \*1\*10, ABCB1 C3435T, ABCB1 G2677A/T and COMT rs4680 in the present study. However, because of the limited number of articles included in the final analysis, publication bias could not be assessed for CYP3A4, CYP2D6, and COMT rs4680 gene SNPs.

## DISCUSSION

### OPRM1 A118G

The opioid response is mediated by receptors in the central nervous system, which bind opioids with high affinity (47). Opioid receptors are part of the G-protein coupled receptors (GPCRs); the 3 most common types include the  $\mu$ -opioid receptor (MOR),  $\delta$ -opioid receptor (DOR), and  $\kappa$ -opioid receptor (KOR), encoded by the OPRM1, OPRD1, and OPRK1 genes, respectively (48). The OPRM1 gene is located on chromosome 6q24-25 (49), occupying a 200kb region (48). The most common and well-studied SNP in this gene is A118G, which results in asparagine to aspartate at position 40 (47), which subsequently leads to reduced expression of MOR (50, 51). Hence this variant has been repeatedly associated with the efficacy of treatment for pain (48). In addition, epigenetic mechanisms may also be

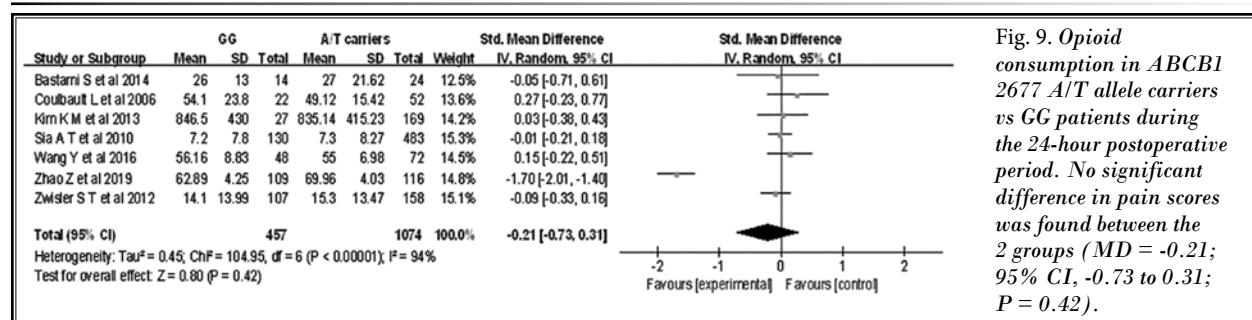


Fig. 9. Opioid consumption in ABCB1 2677 A/T allele carriers vs GG patients during the 24-hour postoperative period. No significant difference in pain scores was found between the 2 groups (MD = -0.21; 95% CI, -0.73 to 0.31;  $P = 0.42$ ).

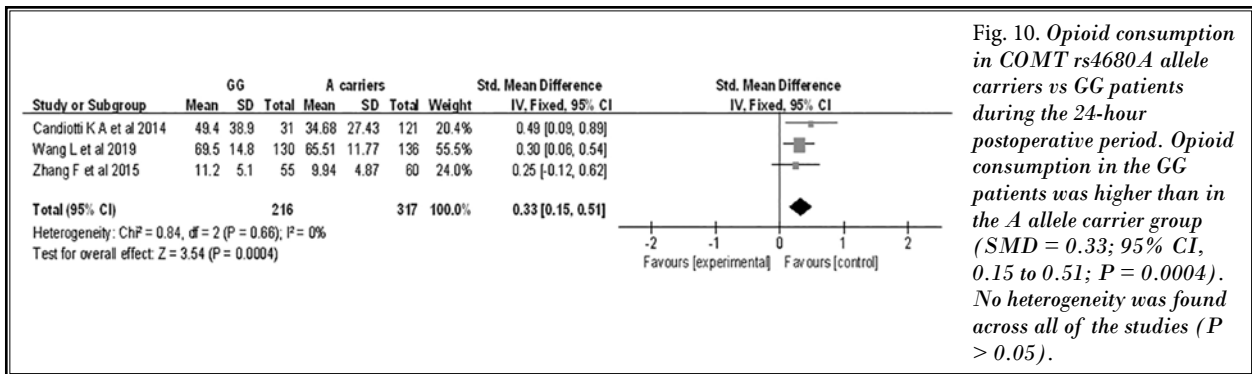


Fig. 10. Opioid consumption in COMT rs4680A allele carriers vs GG patients during the 24-hour postoperative period. Opioid consumption in the GG patients was higher than in the A allele carrier group (SMD = 0.33; 95% CI, 0.15 to 0.51; P = 0.0004). No heterogeneity was found across all of the studies (P > 0.05).

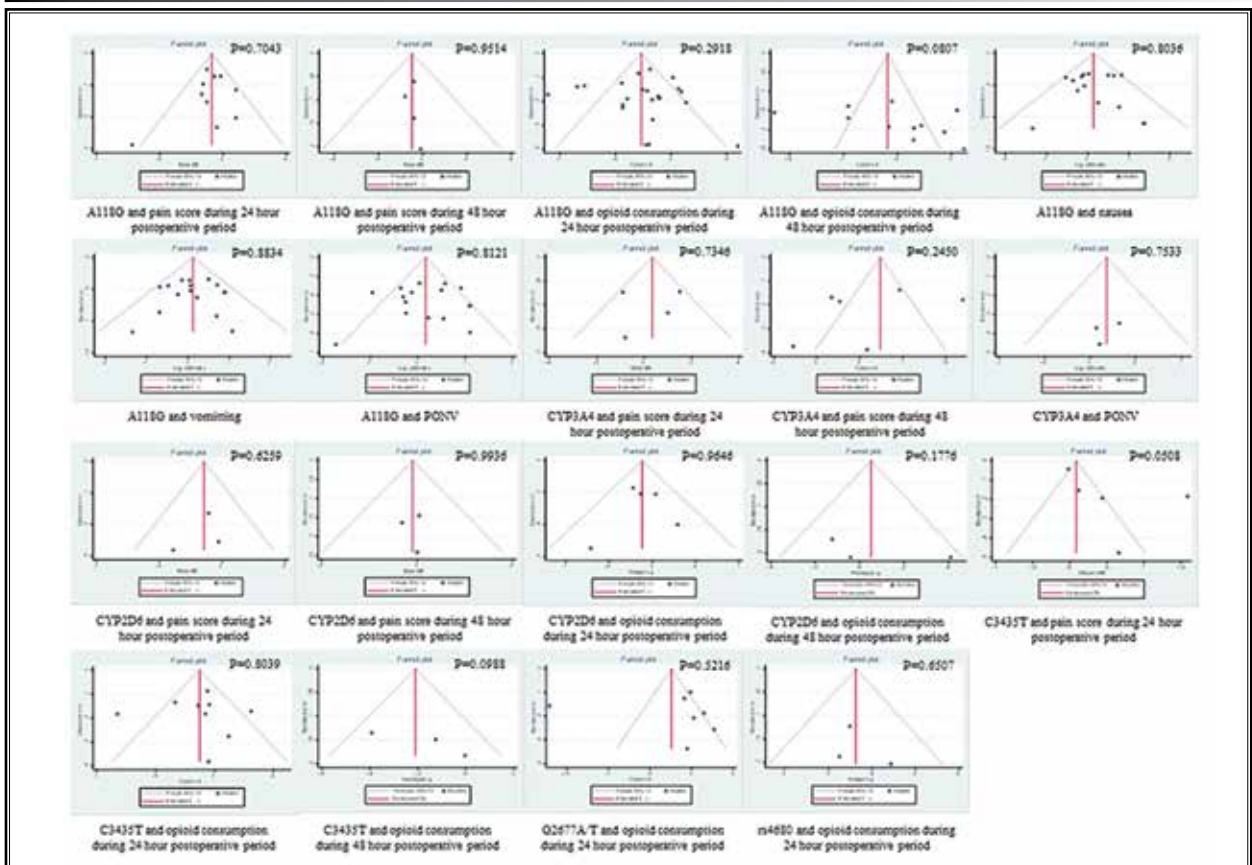


Fig. 11. Funnel plots of statistically significant meta-analyses. No significant publication bias was evident for OPRM1 A118G, CYP3A4 \*1\*1G, CYP2D6 \*1\*10, ABCB1 C3435T, ABCB1 G2677A/T and COMT rs4680 in the present study.

involved in the inhibition of receptor proteins in 118G allele carriers (50). 118G allele carriers have been found to have fewer cell-surface receptor-binding sites, reduced downstream signal transduction, and lower mRNA expression levels (52-54). The downregulation of receptor expression levels and signal transduction will result in patients feeling more pain, which in turn would require more analgesics.

As predicted, several studies showed that 118G allele carriers have reduced analgesic effects with morphine treatment (54,55), with G allele carriers requiring more medication to achieve analgesia (48,54). Our study is consistent with these findings. Our meta-analysis shows that pain scores during the 24-hour postoperative period in the 118G allele carrier group were higher compared to 118A patients. However, no

significant difference in pain scores during the 48-hour postoperative period was observed between the 2 groups and was consistent with our previous study (7). This is probably due to the limited number of studies.

Our meta-analysis shows that OPRM1 118G carriers consume more opioids during the 24-hour and 48-hour postoperative period. The results during the 24-hour period are the same as the previous study, however, the results during the 48-hour period switched from negative to positive, probably because of the higher number of studies (7). Two meta-analyses that looked at the effect of this locus on opioid consumption support our present study (56,57). Furthermore, one of the studies performed in 2014 (56) showed that the conclusion was more applicable to Asians through a subgroup analysis. However, a meta-analysis that showed the effects of the SNP on epidural analgesia with fentanyl during labor had an opposite result (58).

There may be 2 reasons for the findings. First, the study analyzed only one specific procedure, administration method, and analgesia, hence it is possible that the results of such a specific subgroup analysis would be different from the overall analysis. In addition, the limited number of patients included in the study may have affected the results.

Regarding side effects, if nausea and vomiting are considered separately, our meta-analysis showed no significant difference between 118AA homozygotes and 118G allele carriers. However, a previous study supports our results for nausea but found that 118G allele carriers are associated with a significantly lower rate of vomiting (7). To complicate the analysis, another meta-analysis supports our results for vomiting but found that 118G allele carriers are associated with less nausea compared to 118AA homozygotes (57). A more detailed meta-analysis found that postoperative vomiting was significantly associated with the A118G SNP in homozygotes (GG vs AA), dominant (G carriers vs AA), and recessive (GG vs A carriers) models, but no association was found in allele (G vs A), and heterozygote (AG vs AA) models. In addition, no associations were found for nausea in all 5 models (59).

Based on these results, we believe that analyzing these 2 side effects together is helpful to obtain a meaningful and consistent result. Considering PONV together, our meta-analysis shows that there is also no significant difference between 118AA homozygotes and 118G allele carriers, which is consistent with a previous meta-analysis that focused on this locus (58). However, a previous study found that 118G allele car-

riers present a lower incidence of PONV (7). The difference may be due to the larger number of articles between studies. We can conclude that the OPRM1 A118G SNP does not affect the incidence of nausea and vomiting for postoperative opioid analgesia.

### CYP

The cytochrome P450 (CYP) superfamily is responsible for the biotransformation of nearly 70% of drugs. Growing clinical evidence suggests that members of the CYP superfamily play a metabolic role and are directly associated with clinical efficacy (60), dose requirements, and adverse drug reactions. In terms of the association of postoperative analgesia and CYP SNPs, we focused on CYP3A4 \*1\*G (rs2242480) and CYP2D6 \*1\*10 (rs1065852) with relatively sufficient quantized clinical statistics for our meta-analysis.

### CYP3A4 \*1/\*1G

CYP3A4 is a well-studied member of CYP3A, the only subfamily of the CYP3 family. The CYP3A gene, located on chromosome 7q22.1 with a size of 231 kb (61), is abundantly expressed in the human liver and is the main CYP expressed in intestinal epithelial cells (62-64). It accounts for one-sixth to one-fourth of hepatic microsomal P450 (65) and plays an essential role in drug first-pass metabolism. CYP3A4 is directly involved in the N-demethylation of codeine, oxycodone, and buprenorphine, as well as the N-dealkylation of fentanyl (60). It generates metabolites that do not have opioid receptor agonistic activity, resulting in fewer opioids entering the nociceptive nerve synapses. The CYP3A4 \*1G (rs2242480) located on CYP3A4 intron 10 has been associated with the transcriptional regulation of CYP3A4. Recent experimental evidence suggests that the CYP3A4 \*1G allele increases the expression of an antisense lncRNA AC069294 of its downstream CYP3A4 fragment to inhibit CYP3A4 enzyme expression (66). Accordingly, patients with the \*1\*1 homozygous genotype tend to have higher CYP3A4 metabolic activity compared to CYP3A4 \*1G allele carriers and may need more analgesic agents to relieve postoperative pain.

Several clinical studies have supported this finding (67,68). However, the sample size of some clinical studies may not support the statistical conclusions for CYP3A4 because of the multiple potential polymorphisms that affect enzyme activity and the low proportion of patients with heterozygous or mutant homozygous genotypes at these sites (67-69). Our current meta-analysis reveals that CYP3A4 \*1\*1 patients

consume more opioids in the 24-hour postoperative period compared to \*1G carriers; this is consistent with a previous study (7).

However, opioid consumption in the 48-hour postoperative period did not have a similar correlation with CYP3A4 SNPs. In our meta-analysis, we failed to observe a significant association between postoperative pain and CYP3A4 SNPs. The results for postoperative pain scores are similar to a previous study (11). Possible reasons include: part of the clinical statistics included for meta-analysis used opioids that did not go through the CYP3A4 metabolic pathway (36), limited data were included in the meta-analysis, and a small sample size with limited statistical significance. Pain management applications, particularly the widespread use of patient-controlled analgesia in most of the included studies, may also explain differences in opioid consumption in the 24-hour postoperative period and mask potential postoperative pain implications under the same opioid doses.

#### **CYP2D6 \*1/\*10**

Similar to CYP3A4, CYP2D6 is also one of the most intensely investigated CYP members. The CYP2D6 gene is located on chromosome 22q13.1 and is composed of 9 exons with a 1,491 bp-long open reading frame encoding 497 amino acids (70). Unlike CYP3A4, CYP2D6 is low in hepatic CYP (2%-4%) and regulates the metabolism of about one-fourth of clinical drugs. It is worth mentioning that humans have only one functional CYP2D6 gene, while rodents, such as mice, have several. In about 7% of the White population, CYP2D6 genes are absent; this proportion is much lower in Asian populations. Complete deletions of CYP2D6 genes and allele deletions are often directly related to poor drug metabolism (71). Opioids such as codeine, dihydrocodeine, and oxycodone are activated by CYP2D6-mediated O-methylation (60,72-74). The CYP2D6 enzyme converts codeine into its active metabolite, morphine, to provide an analgesic effect (75). This means that individuals with poor CYP2D6 metabolism will show insensitivity to such opioids.

Among the SNPs that have been confirmed to influence CYP2D6 activity, the CYP2D6 \*10 (rs1065852) mutation is one of the most studied. The \*10 allele has a 100C > T SNP mutation which results in P34S substitution in the proline-rich ("PPGP") region near the highly conserved amino terminal of the CYP2D6 protein. This directly leads to a decrease in the stability and partial loss of activity of CYP2D6 (76,77). Although the effect of \*10 SNP on enzyme activity may be lower

than other SNPs that completely silence or completely inactivate CYP2D6 genes, they occur very frequently (more than one-third) in East Asian populations, such as the Chinese (78). Clinical evidence has shown that \*10 mutation carriers are associated with poor CYP2D6 metabolic activity (79-81). Hence, \*10 allele-carrying patients may consume more opioids for postoperative analgesia compared to \*1/\*1 homozygous individuals.

Regardless of these predictions, our meta-analysis failed to observe a significant association between CYP2D6\*10 polymorphisms and postoperative pain scores or opioid requirements, as did the meta-analysis performed by Choi et al (82), even though the few included studies used postoperative opioids that relied on activation via CYP2D6 metabolism. The reason is the mechanism is complex; there are dozens of sites affecting CYP2D6 metabolic activity. The influence of polymorphisms at \*10 sites alone is likely to be affected by differences in other sites. In addition, the small sample size was a major disadvantage. For these reasons, larger sample sizes are required to confirm or contradict our findings.

#### **ABCB1**

The ATP-binding cassette transporter (ABC transporter) belongs to the largest and oldest membrane protein families (83-85). The ABC transporter relies on the hydrolysis of ATP, which stimulates a direct association between the substrate and the substrate-binding protein (SBP) (83,84). Studies have identified more than 40 ABC transporters in the human body (85). They can be categorized into 7 subfamilies from ABCA to ABCG (mainly based on gene structure, amino acid sequence, domain organization, and phylogenetic analysis).

Of the ABC transporters, the P-glycoprotein (P-glycoprotein, ABCB1 or MDR1) plays a key role in multidrug resistance (MDR) development (86-89). The P-glycoprotein is encoded by the ABCB1 gene located on chromosome 7 at q21 with 28 exons encoding a protein of 1280AA. It can be expressed in cancer cells, and is widely found in various human tissues such as the liver, gut, and brain, which can mediate drug transport and plays a significant role in drug absorption and excretion (86-87). Previous studies have shown that inhibition of P-glycoprotein expression in the blood-brain barrier can significantly increase the brain exposure level to fentanyl and aggravate central sedation (90-92). P-glycoprotein recognizes and transports various drugs (89,91) including chemotherapy agents and immunosuppressants.

Callaghan et al (93) demonstrated that P-glycoprotein plays a role in the regulation of the net transfer of opioids into the central nervous system. Morphine and its active metabolites, such as morphine-6-glucuronide, are substrates of P-glycoprotein. P-glycoprotein can discharge these substrates from brain tissue into microvessels and finally into the bloodstream to reduce morphine levels in brain tissue. This suggests that during postoperative analgesia, individuals with lower P-glycoprotein activity will accumulate drugs and their metabolites due to reduced transport activity, resulting in lower opioid consumption. However, P-glycoprotein has not been demonstrated to affect analgesia, and hence may not be clinically significant (86).

In the next section, we selected 2 SNPs with relatively sufficient quantized clinical statistics, ABCB1 C3435T (rs1045642) and G2677T (rs2032582). These polymorphisms demonstrated a functional impairment of P-glycoprotein (94-96), which in turn affected the sensitivity of analgesic drugs.

#### **ABCB1 C3435T**

The C→T transversion at 3435 on exon 26 (C3435T) is a synonymous mutation. Quantifying P-glycoprotein levels using an immunochemical approach, Kerb, et al (97) were the first to report the TT genotype (i.e., the homozygote for the mutant T allele) reduced P-glycoprotein levels in the intestine. Meineke et al (99) demonstrated that patients carrying the TT genotype exhibited higher opioid cerebrospinal fluid levels of P-glycoprotein compared to C allele carriers.

Our meta-analysis, however, failed to observe changes in postoperative opioid consumption (43,99). During the first 24-hour postoperative period, the homozygous CC group did not show a significant difference in opioid consumption but was found to increase during the 48-hour postoperative period. Considering that only 3 groups of data were included in the meta-analysis, consumption differences could not be represented with high confidence. Possible reasons for no differences in the 24-hour period may include different drug delivery approaches, limited statistical significance, ethnic factors, and other mechanisms not considered.

Although the T allele results in lower P-glycoprotein expression levels, the allelic frequencies for ABCB1 variants have been shown to vary between ethnic populations (95,100). The frequency of the C allele in Whites has been reported to be around 43%-54%, while in Asians it is 34%-63%. C allele carriers with

African ethnicity were the largest, with a frequency of 73%-90%. This suggests an important genetic variable that needs to be considered for future analysis, i.e., different mutational rates may indicate differences in analgesia. Goto, et al reported that the ABCB1 C3435T polymorphism could affect the enterocyte expression levels of CYP3A4 instead of P-glycoprotein (101). This has not been discussed in a previous meta-analysis.

Furthermore, no significant differences were observed in the 24-hour pain scores. As predicted, reduced transport activity did not directly affect the final release of endogenous analgesic substances. Even if consumption changed, the somatosensory analgesia effect was stable (102). Additionally, patients had access to sufficient medication within the 24-48 postoperative period. This could have contributed to no significant differences in the pain scores.

#### **ABCB1 G2677A/T**

The G to T and G to A transversions at position 2677 in exon 21 are nonsynonymous SNPs, located on the intracellular region of P-glycoprotein after the transmembrane region 10. Based on the mutations, Ala at codon 893 (Ala893) translates to Ser (G2677T) and Thr (G2677A) respectively. Previous studies have suggested that the mutant allele reduces P-glycoprotein expression levels, however, no significant differences were observed. Our meta-analysis did not observe significant differences in expression levels during the first 24-hour postoperative opioid consumption. Possible reasons could be due to ethnic differences, similar to what was discussed for ABCB1 C3435T.

Multiple polymorphisms of the ABCB1 gene have been observed, with the selected 2, ABCB1 C3435T and G2677T, being in linkage disequilibrium (103). In our meta-analysis, the 2 transversions were not synthetically analyzed for limited quantized statistics and unstated mechanisms. Association analysis would be helpful to fully comprehend our findings.

#### **COMT Val158Met**

The COMT gene is located on chromosome 22q11.1–q11.2 (104). COMT catalyzes the transfer of the methyl group of S-adenosyl-L methionine to the phenolic group of the substrate that has a catechol structure (105). This makes it a key enzyme involved in the degradation of catecholamine neurotransmitters (dopamine, epinephrine, and norepinephrine) in the central nervous system and other tissues (106). Since catecholamine plays an important role in pain trans-

mission and modulation, its activity greatly affects pain sensitivity (107) and opioid consumption (108).

The most common SNP found in COMT is G1947A (7). The G to A substitution leads to a valine-to-methionine substitution, which results in a 3-to-4-fold reduction in the activity of the COMT enzyme (106). Decreased activity of COMT results in higher levels of catecholamines, which increases sensitivity to pain (107). Disappointingly, we did not perform a meta-analysis for pain scores in this locus due to insufficient data.

Zubieta et al (109) demonstrated that the change in enzyme activity due to COMT Val158Met SNP could influence downstream receptor repression. Using positron emission tomography to examine the brain, the authors found that individuals who express low enzyme activity (A allele carriers) have a higher density of MORs. These individuals would require fewer opioids for postoperative analgesia; this is consistent with our meta-analysis which shows that COMT 158A allele carriers consumed fewer opioids during the 24-hour postoperative period.

Another meta-analysis analyzed the locus and its influence on opioid consumption in patients with

postoperative pain. The authors found that 158AG carriers consumed fewer opioids compared with AA homozygotes during the 24-hour postoperative period. However, there was no difference in opioid consumption between AA homozygotes and GG homozygotes (110). Additional analysis with larger cohort numbers is required to resolve these inconsistencies.

## CONCLUSION

In conjunction with previous systematic reviews and meta-analyses, the A118G allele variant of OPRM1 and the \*1\*1G allele variant of CYP3A4 had a potent influence on the individual differences in opioid reactivity in postoperative pain patients. The 118G allele was found to reduce opioid analgesic potency, and hence register higher pain scores in patients compared to 118AA homozygotes. Additionally, \*1G allele carriers for CYP3A4 were associated with lower opioid consumption compared to \*1\*1 homozygotes. Other gene loci need to be investigated to conclusively determine their role in postoperative pain patients. Our results, and the identification of additional SNPs, may provide a theoretical basis for precise clinical analgesia.

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Supplementary Table 1. *Quality assessment scores of the included studies.*

Study				Selection				Comparability			Outcome			Quality Score
No.	Author	Reference No.	Year	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Quality Score		
1	Chou W Y et al	(11)	2006 <sup>a</sup>	1	1	1	1	1	1	1	1	8		
2	Chou W Y et al	(5)	2006 <sup>b</sup>	1	1	1	1	1	1	1	1	8		
3	Coulbault L et al	(7)	2006	1	1	1	1	1	1	1	1	8		
4	Hayashida M et al	(3)	2008	1	1	1	1	1	1	1	0	7		
5	Sia A T et al	(1)	2008	1	1	1	1	1	1	1	0	7		
6	Fukud K et al	(6)	2010	1	1	1	1	2	1	1	0	8		
7	Sia A T et al	(22)	2010	1	1	1	1	2	1	1	0	8		
8	Zhang W et al	(20)	2010 <sup>a</sup>	1	1	1	1	2	1	1	1	9		
9	Zhang W et al	(4)	2010 <sup>b</sup>	1	1	1	1	2	1	1	0	8		
10	Kolesnikov Y et al	(17)	2011	1	1	1	1	2	1	1	1	9		
11	Yuan R et al	(19)	2011	1	1	1	1	1	1	1	1	8		
12	Zhang W et al	(10)	2011	1	1	1	1	1	1	1	1	8		
13	Chen L K et al	(18)	2012	1	1	1	1	2	1	1	0	8		
14	Zwisler S T et al	(8)	2012	1	1	1	1	2	1	1	0	8		
15	Boswell M V et al	(16)	2013	1	1	1	1	2	1	1	0	8		
16	Candiotti K et al	(23)	2013	1	1	1	1	1	1	1	1	8		
17	Kim K M et al	(15)	2013	1	1	1	1	2	1	1	0	8		
18	Liao Q et al	(14)	2013	1	1	1	1	2	1	1	1	9		
19	Sia A T et al	(12)	2013	1	1	1	1	2	1	1	0	8		
20	Zhang F et al	(13)	2013	1	1	1	1	2	1	1	0	8		

Supplementary Table 1 continued. *Quality assessment scores of the included studies.*

Study				Selection				Comparability			Outcome			Quality Score
No.	Author	Reference No.	Year	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Quality Score		
21	Bastami S et al	13	2014	1	1	1	1	2	1	1	0	8		
22	Candiotti K A et al	23	2014	1	1	1	1	2	1	1	1	9		
23	Dong H et al	41	2015	1	1	1	1	1	1	1	0	7		
24	Lee S -H et al	84	2015	1	1	1	1	2	1	1	0	8		
25	Wei X -B et al	163	2015	1	1	1	1	2	1	1	0	8		
26	Wu S -B et al	166	2015	1	1	1	1	2	1	1	0	8		
27	Zhang F et al	180	2015	1	1	1	1	2	1	1	0	8		
28	Dzambazovska-Trajkovska V et al	43	2016	1	1	1	1	1	1	1	1	8		
29	Wang Y et al	159	2016	1	1	1	1	2	1	1	1	9		
30	Zhou Y et al	188	2017	1	1	1	1	2	1	1	0	8		
31	Pettini E et al	118	2018	1	1	1	1	2	1	1	1	9		
32	Zhang J et al	182	2018	1	1	1	1	2	1	1	1	9		
33	Pu J et al	122	2019	1	1	1	1	1	1	1	1	8		
34	Wang L et al	158	2019	1	1	1	1	2	1	1	0	8		
35	Zhang X et al	183	2019	1	1	1	1	1	1	1	1	8		
36	Zhao Z et al	185	2019	1	1	1	1	2	1	1	1	9		
37	Hou Y et al	58	2020	1	1	1	1	2	1	1	0	8		
38	Zhang F et al	181	2021	1	1	1	1	2	1	1	0	8		
39	Chou W -Y et al	34	2021	1	1	1	1	2	1	1	0	8		