Systematic Review

The Impact of Genetic Variation on Sensitivity to Opioid Analgesics in Patients with Postoperative Pain: A Systematic Review and Meta-Analysis

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Background: Individual response to opioid analgesics varies among patients.

Objective: This study sought to clarify the impact of distinct genetic variations on pain, opioid consumption, and opioid side effects in patients with postoperative pain.

Study Design: A systematic review and meta-analysis of associations between genetic single-nucleotide polymorphisms (SNPs) and opioids used for acute postoperative pain.

Setting: This meta-analysis examined all studies involving an association between genetic polymorphisms and the analgesic efficacy or clinical outcome of opioid analgesics for postoperative pain.

Methods: A literature search was performed up to January 31, 2014, using the PubMed, EMBase, ISI Web of Science, and Cochrane Library databases.

Results: Fifty-nine studies were included in this systematic review, and 23 studies (a total of 5,902 patients) were included in the final meta-analysis. The results showed that human μ-opioid receptor gene (OPRM1) 118G allele variant carriers consumed more opioids for analgesia (SMD = -0.17, 95% CI = [-0.25, -0.10], $P < 0.00001$), but reported higher pain scores (MD = -0.11, 95% CI = [-0.17, -0.04], $P = 0.002$) and less nausea and vomiting (odds ratio = 1.30, 95% CI = [1.08, 1.55], $P = 0.005$) than the homozygous 118AA patients during the first 24 hour but not the 48 hour postoperative period. Moreover, CYP3A4*1G carriers consumed less opioids than homozygous CYP3A4*1/*1 patients during the first 24 hours postoperative period (MD = 45.12, 95% CI = [36.17, 54.06], $P < 0.00001$). No significant differences were found in CYP3A5*3, ABCB1 C3435T, and G2477T/A genetic polymorphisms.

Limitations: Some potential non-genetic factors can modify the effects of gene SNP on pain and opioid consumption during the postoperative period, such as age, gender, mood, anxiety, and drug-drug interactions. But further analyses could not be performed in the present meta-analysis due to limited information.

Conclusion: The results indicate that among the genetic SNPs we studied which include those affecting analgesic drug metabolism, transport of analgesic agents across the blood-brain barrier, and their activity at target receptors and ion channels and in the modulation of neurotransmitter pathways, the A118G allele variant of OPRM1 has the most potent influence on pain management of postoperative patients. Opioid receptor gene information may provide valuable information for clinicians to properly manage the analgesic use of opioids individually for better pain management.

Key words: Postoperative pain, meta-analysis, single-nucleotide polymorphism, opioid

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Opioids are the most common analgesics used for moderate to severe pain. The sensitivity to pain and responses to analgesics, including analgesic effects and side effects, such as miosis, drowsiness, nausea, vomiting, constipation, and respiratory depression, are highly variable in patients. For example, morphine provides good analgesia without troublesome side effects for most patients. However, some patients experience either inadequate analgesia despite escalating doses or intolerable dose-limiting side-effects (1-3). The amount of analgesic opioids that is used for postoperative pain control, even following the same surgery, also varies substantially among patients (4-6). Interindividual variability in the sensitivity to analgesic opioids has been explained mostly by genetic factors (7,8). Therefore, providing conclusive evidence of the association between genetic variants and the analgesic effects of opioids is important. However, no meta-analyses of which we are aware have focused on the association between distinct gene polymorphisms and postoperative pain and opioid analgesics. A growing body of evidence in this field has made summarizing each candidate gene's contribution to postoperative analgesic and side effects difficult.

The present article summarizes the literature of genetic studies of postoperative pain to clarify the effects of genetic variants on pain, the analgesic effects of opioids, and adverse effects during the postoperative period in patients with postoperative pain.

1. Methods

1.1. Literature Search Strategy

We performed a systematic search of PubMed (1970 to January 31, 2014), EMBase (1966 to January 31, 2014), ISI Web of Science (1899 to January 31, 2014), and the Cochrane Library (1996 to January 31, 2014) for all studies that showed an association between genetic polymorphisms and the analgesic efficacy or clinical outcome of opioid analgesics using the following search combinations: "gene," "genetic," "polymorphism," "postoperative pain," "postoperative analgesia." The bibliographies of the identified original papers or review articles were also retrieved to provide a complete literature search.

1.2. Data Selection

Four researchers (ZY Ren, XQ Xu, J He, and L Shi) independently assessed the articles for their eligibility for inclusion. Studies were included if they were random-

ized or cohort studies in perioperative patients who took opioids for analgesia and presented the results of at least one of the following endpoints stratified by genetic polymorphisms: (i) pain score, (ii) opioid dosage requirements and typical clinical effects of opioids subdivided into (iii) analgesia and so-called side effects, including (iv) respiratory depression, (v) psychotropic effects, such as sedation, (vi) tolerance or addiction to opioid analgesics, (vii) nausea and vomiting, (viii) constipation, and (ix) "other side effects," such as blurred vision, decreases in heart rate or blood pressure, and itching. Different μ-opioid agonists and patient populations who underwent surgery (Table 1) were included in the meta-analysis. If the same patient population was used in more than one publication, then only the final dataset was chosen to avoid data replication.

1.3. Data Extraction

The data were independently extracted from eligible papers by 4 researchers (ZY Ren, XQ Xu, J He, and L Shi) who subsequently cross-checked the data and resolved discrepancies. When data were reported in a format that did not allow inclusion in the meta-analysis, the authors of those papers were contacted directly and asked to release the data. For each study, the following data were extracted: first author, year of publication, number of patients, age, gender, genetic variants, setting, analgesic opioids use information, and clinical outcome. We determined whether the genotype frequencies agreed with Hardy-Weinberg equilibrium by calculating the χ^2 goodness-of-fit. If the data were not provided in a tabular format, then they were calculated from the corresponding paragraphs or supplementary appendices. Any disagreements were resolved by further discussion or consultation.

The endpoints of our meta-analysis included pain score, opioid consumption, and side effects during the first 24 or 48-hour postoperative period. The detailed process of identifying eligible studies and the reasons for exclusion are presented in Fig. 1. Because only a limited number of studies involved side effects other than nausea and vomiting, the endpoint for side effects in the present analysis included only nausea and vomiting.

1.4. Statistical Analysis

The data were extracted from each individual study and pooled using Review Manager 5.1.0 to calculate the mean difference (MD), standard mean difference (SMD), and odds ratio (OR) as the parameters of pain score, opioid consumption, and drug side effects,

Table 1. *Characteristics of the studies included in the meta-analysis.*

No.	Author (year)	Male/ Female	Age (years)	Setting	Hardy-Weinberg	Variant	Opioid administered	Clinical adverse events (no.)
1	Sia et al. (2008) (6)	0/585	32.5 (4.7)	Post cesarean analgesia	No	OPRM1 A118G	morphine	nausea, 40 vomiting, 32
2	Mamie et al. (2013) (42)	51/117	11.4	orthopedic or abdominal surgery	Yes	OPRM1 A118G ABCB1 C3435T COMT Val158Met NTRK1 His40Tyr POMC Arg236Gln CYP2D6	morphine	ND
3	Hayashida et al. (2008) (31)	79/59	63.1 (9.8)	major open abdominal surgery	Yes	OPRM1 A118G OPRM1 IVS2+G691C OPRM1 IVS3+G5953A OPRM1 IVS3+A8449G OPRM1 TAA+A2109G	fentanyl and morphine	ND
4	Zhang et al. (2010b) (24)	0/174	41.1 (5.5)	total abdominal hysterectomy or myomectomy	Yes	OPRM1 A118G	remifentanil	nausea and vomiting, 48
5	Chou et al. (2006b) (20)	31/89	63.3 (10.9)	total knee arthroplasty	No	OPRM1 A118G	morphine	nausea, 7 vomiting, 22
6	Fukuda et al. (2010) (30)	40/68	25.7 (6.7)	sagittal split mandibular osteotomy	Yes	OPRM1 A118G OPRM1 IVS2+G691C OPRM1 IVS3+G5953A OPRM1 IVS3+A8449G OPRM1 TAA+A2109G	fentanyl	ND
7	Coulbault et al. (2006) (5)	44/30	56 (12)	abdominal surgery with a colorectal or coloanal anastomosis	Yes	OPRM1 A118G ABCB1 G2677T/A ABCB1 C3435T UGT2B7 T802C	morphine	nausea and vomiting, 23
8	Zwisler et al. (2011) (27)	38/228	51.2	thyroidectomy (partial and complete), parathyroidectomy, mastectomy, and hysterectomy (vaginal and abdominal)	Yes	OPRM1 A118G ABCB1 C3435T ABCB1 G2677T/A	alfentanil or sufentanil or oxycodone	nausea/ vomiting AUC 0-24 h, 0.2
9	Tan et al. (2009)(38)	0/994	32.5 (4.8)	elective caesarean delivery	Yes	OPRM1 A118G OPRM1 -T172G	morphine	vomiting, 123
10	Zhang et al. (2011) (25)	0/165	25-50	undergoing elective total abdominal hysterectomy or myomectomy under general anesthesia	Yes	OPRM1 A118G	remifentanil	nausea, 47 vomiting, 27
11	Chou et al. (2006a)(4)	0/80	45.7 (6.7)	abdominal total hysterectomy	No	OPRM1 A118G	morphine	vomiting, 12
12	Sia et al. (2013)(22)	0/973	47.8 (5.4)	abdominal hysterectomy	Yes	OPRM1 A118G	morphine	ND
13	Zhang et al. (2013) (23)	76/52	52.5 (12.6)	radical gastrectomy	Yes	OPRM1 A118G	fentanyl	nausea 47 vomiting 27
14	Liao et al. (2013) (21)	60/37	52.3 (13.1)	radical gastrectomy	Yes	OPRM1 A118G CYP3A4*18B	fentanyl	nausea, 37 vomiting, 18

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

No.	Author (year)	Male/ Female	Age (years)	Setting	Hardy-Weinberg	Variant	Opioid administered	Clinical adverse events (no.)
15	Kim et al. (2013) (32)	0/196	45.3 (4.9)	abdominal hysterectomy or laparoscopic assisted vaginal hysterectomy	Yes	OPRM1 A118G ABCB1 2677G>A/T ABCB1 3435C>T CYP3A4*18 CYP3A5*3	fentanyl	ND
16	Boswell et al. (2013) (35)	0/158	27.6 (5.9)	cesarean section	ND	OPRM1 A118G	hydrocodone/ morphine	nausea, 33 vomiting, 7
17	Kolesnikov et al. (2011) (151)	45/57	54.6 (11.1)	abdominal radical prostatectomy or hysterectomy	OPRM1 No COMT Yes	OPRM1 A118G COMT Val158Met	morphine	ND
18	Chen et al. (2013)(45)	0/129	ND	total abdominal hysterectomy	Yes	OPRM1 A118G	morphine	nausea, 81 vomiting, 58
19	Yuan et al. (2011)(61)	83/93	45.9 (11.1)	lower abdominal surgery	Yes	CYP3A4*1G	fentanyl	nausea and vomiting, 50
20	(Zhang et al. (2010a) (73)	0/143	406 (6.0)	abdominal total hysterectomy or myomectomy	Yes	CYP3A4*1G	fentanyl	nausea and vomiting, 41
21	Slanar et al. (2012) (51)	0/156	39.6 (14.2)	knee arthroscopy	Yes	CYP2D6 MDR1 ABCB1 C3435T	tramadol	nausea and vomiting, 6
22	Sia et al. (2010) (86)	0/620	32.4 (4.7)	caesarean section	Yes	ABCB1 C3435T ABCB1 C1236T ABCB1 G2677T/A	morphine	nausea, 44 vomiting, 36
23	(Candiotti et al. (2013) (88)	94/58	53.7 (16.3)	nephrectomy	Yes	ABCB1 C3435T	morphine/ oxycodone	ND

respectively. We calculated the SMD to standardize the data, such as when opioid consumption was represented in different units. Candidate genes for the review and meta-analysis were selected if 2 or more studies evaluated the data and such data were available. Individual and pooled results are illustrated as point estimates and 95% confidence intervals (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 of the included studies was assessed by the Q-statistic, with a *P* < 0.05 or I^2 > 50% considered significant heterogeneity.

2. Review and Meta-Analysis Results

2.1. Human μ-opioid Receptor Gene (OPRM1)

Three opioid receptors (μ, δ, and κ) are involved in

numerous biological processes. The μ-opioid receptor (MOR), a member of the G-protein-coupled receptor superfamily, has been identified as the major site of the analgesic action of opiate drugs. Animal studies have indicated that MOR gene knockout mice present morphine-induced analgesic inefficacy (9). In humans, variations in the MOR gene also affect opiate-related analgesia (10,11). Among over 3,000 polymorphisms in OPRM1 (www.1000genomes.org), the most commonly studied single-nucleotide polymorphism (SNP) is A118G, which leads to a substitution of the amino acid asparagine to aspartate at position 40. Therefore, the SNP of the human MOR gene (OPRM1) (12), which is located on human chromosome 6q24–q25, has been investigated for its clinical value in pain modulation (7).

2.1.1. A118G and Postoperative Pain

A118G variation eliminates a putative N-linked

Fig. 1. *Flow chart of the identification of eligible studies.*
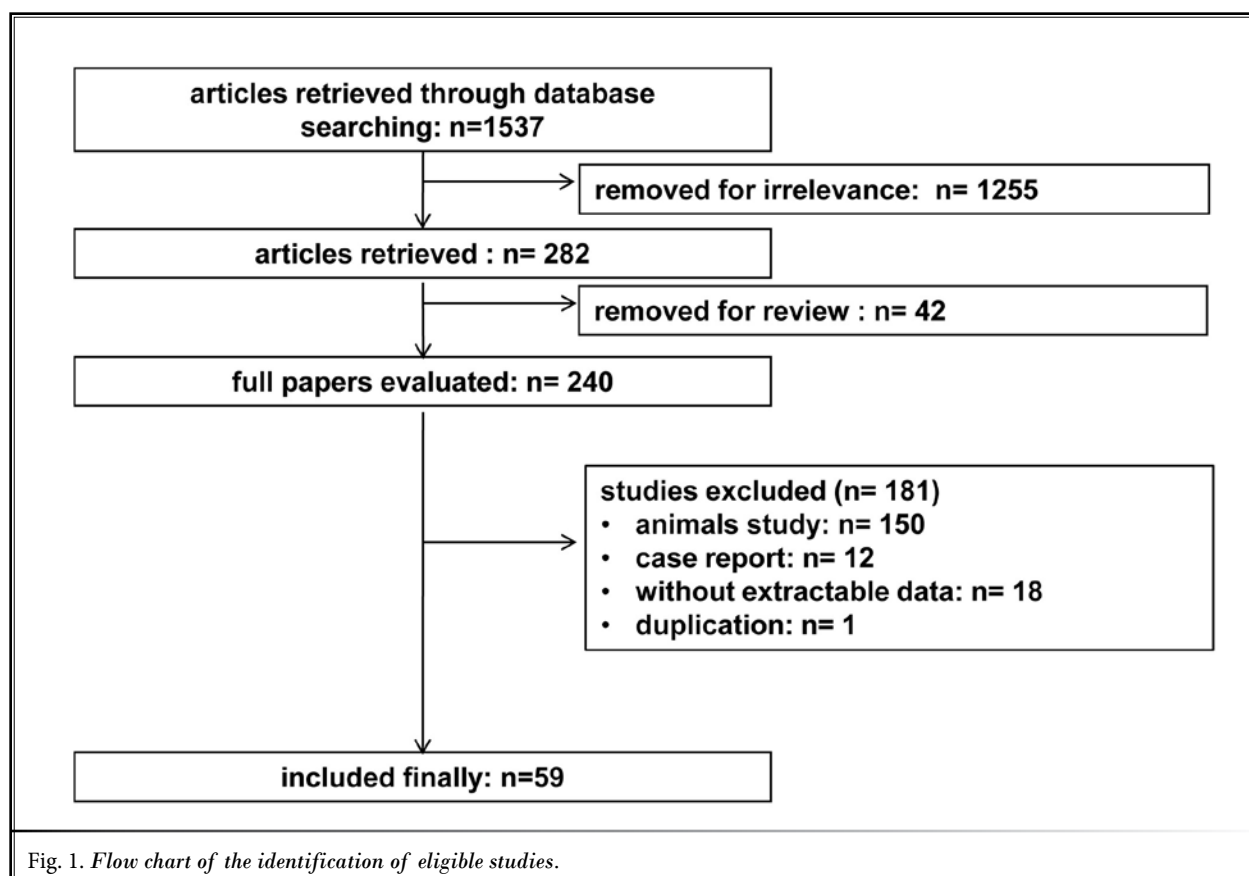
glycosylation site in the receptor (13) and affects the ligand-receptor binding process, which is regarded as the mechanism that underlies discrepancies in the sensitivity to analgesic opioids, such as pain sensitivity (14) and analgesic requirements (15-17). Moreover, the frequency of the polymorphism (the G allele) varies depending on the population that is studied, from 16% in northern and western Europeans to 46.5% in Asians (NCBI HapMap SNP frequency data available at: www. ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1799971). Emerging evidence suggests the clinical relevance (15) and therapeutic predictive value (18) of SNPs of OPRM1, and inclusion of the OPRM1 variant 118A>G into concepts of personalized therapeutic pain management has been increasingly contemplated. A previous meta-analysis assessed the OPRM1 118A>G genetic variant and the analgesic effects of opioids on patients with various pain, including acute postoperative pain, chronic non-cancer pain, and cancer pain, but reported no statistically significant association between the OPRM1 118A>G polymorphism and pain or opioid dosing (19). To our knowledge, no meta-analysis has focused on the association between the OPRM1 A118G SNP and analgesic opioid consumption in acute postoperative pain.

Meta-analysis of A118G and pain scores: Pain score data were available from independent samples in 8 studies for the AA vs. G variation during the 24-hour postoperative period (4,6,20-25) and four studies during the 48-hour postoperative period (4,20,21,23). Two studies were excluded because the pain scores were either in the form of AUC0-24-hour or median and semi-interquartile range (26,. The study by Wu and co-workers (28) was excluded because the pain scores were obtained after bolus fentanyl. Two other studies were excluded because they lacked data from the specific postoperative period (i.e., 24 or 48 hour) (26,29). The final analysis included 1,004 homozygous 118AA patients and 1,318 118G allele carriers during the 24-hour postoperative period and 213 homozygous 118AA patients and 212 118G allele carriers during the 48-hour postoperative period. Actual 24-hour pain was reported using ordinal scales (11 points, ranging from 0 for no pain to 10 for maximum pain) in most of the studies. The pain scores were transformed to 11 points
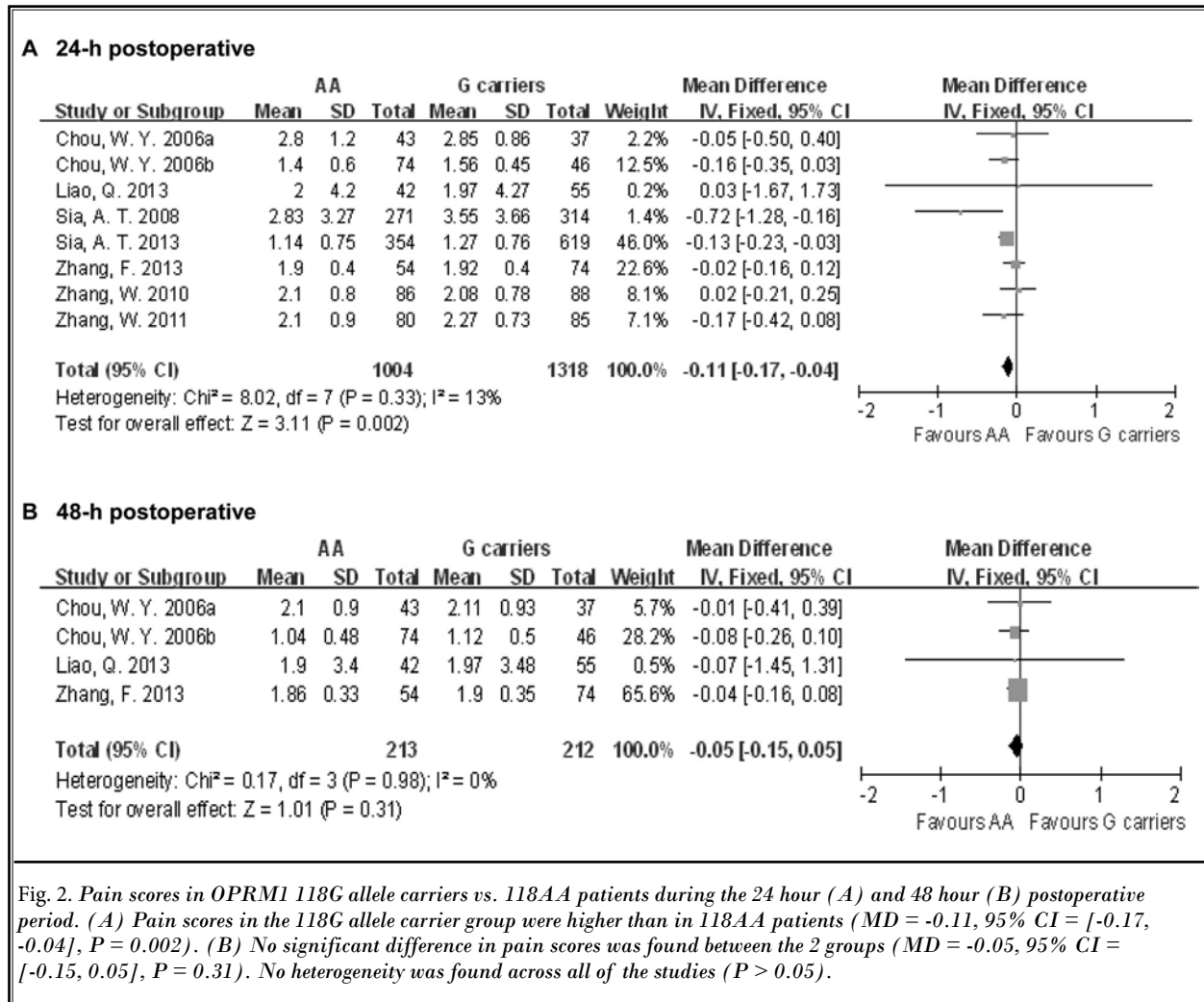
Fig. 2. *Pain scores in OPRM1 118G allele carriers vs. 118AA patients during the 24 hour (A) and 48 hour (B) postoperative period. (A) Pain scores in the 118G allele carrier group were higher than in 118AA patients (MD = -0.11, 95% CI = [-0.17, -0.04], P = 0.002). (B) No significant difference in pain scores was found between the 2 groups (MD = -0.05, 95% CI = [-0.15, 0.05], P = 0.31). No heterogeneity was found across all of the studies (P > 0.05).*

if the original data were presented on a 100-point scale, ranging from 0 for no pain to 100 for maximum pain.

Heterogeneity was not detected across studies (χ^2, $P > 0.05$; Fig. 2A, B), so a fixed-effect model was chosen. Presence of the G allele was associated with higher pain scores compared with AA homozygotes during the first 24-hour postoperative period (fixed-effects model: MD = -0.11, 95% CI = -0.17, -0.04, $P = 0.002$; Fig. 2A). No significant difference was observed when comparing G carriers and homozygous AA carriers in the 48-hour postoperative period (fixed-effects model: MD = -0.05, 95% CI = -0.15, 0.05, $P = 0.31$; Fig. 2B).

Meta-analysis of A118G and opioid consumption: Opioid consumption data were available from 13 studies for the first 24-hour postoperative period (4-6,20,22,24,25,27,29-32) and 5 studies during the 48-hour postoperative period (4,20,31-33). Two studies were

excluded because the results were presented in the form of median and semi-interquartile range (31,34). The study by Janicki et al (26) was excluded because it lacked data from the exact postoperative time point. Finally, the studies included 1,500 homozygous 118AA patients and 1,644 118G allele carriers for the 24-hour postoperative period and 313 118AA homozygotes and 282 118G allele carriers for the 48-hour postoperative period, with several different kinds of opioids and dosing parameters. Opioid doses were reported as total 24- or 48-hour postoperative opioid consumption.

During the first 24-hour, 118G allele carriers exhibited significantly more opioid consumption compared with AA homozygotes (fixed-effects model: SMD = -0.17, 95% CI = [-0.25, -0.10], $P < 0.00001$; Fig. 3A). No significant heterogeneity was found across studies (χ^2, $P = 0.24$; Fig. 3A). However, we did not find the same
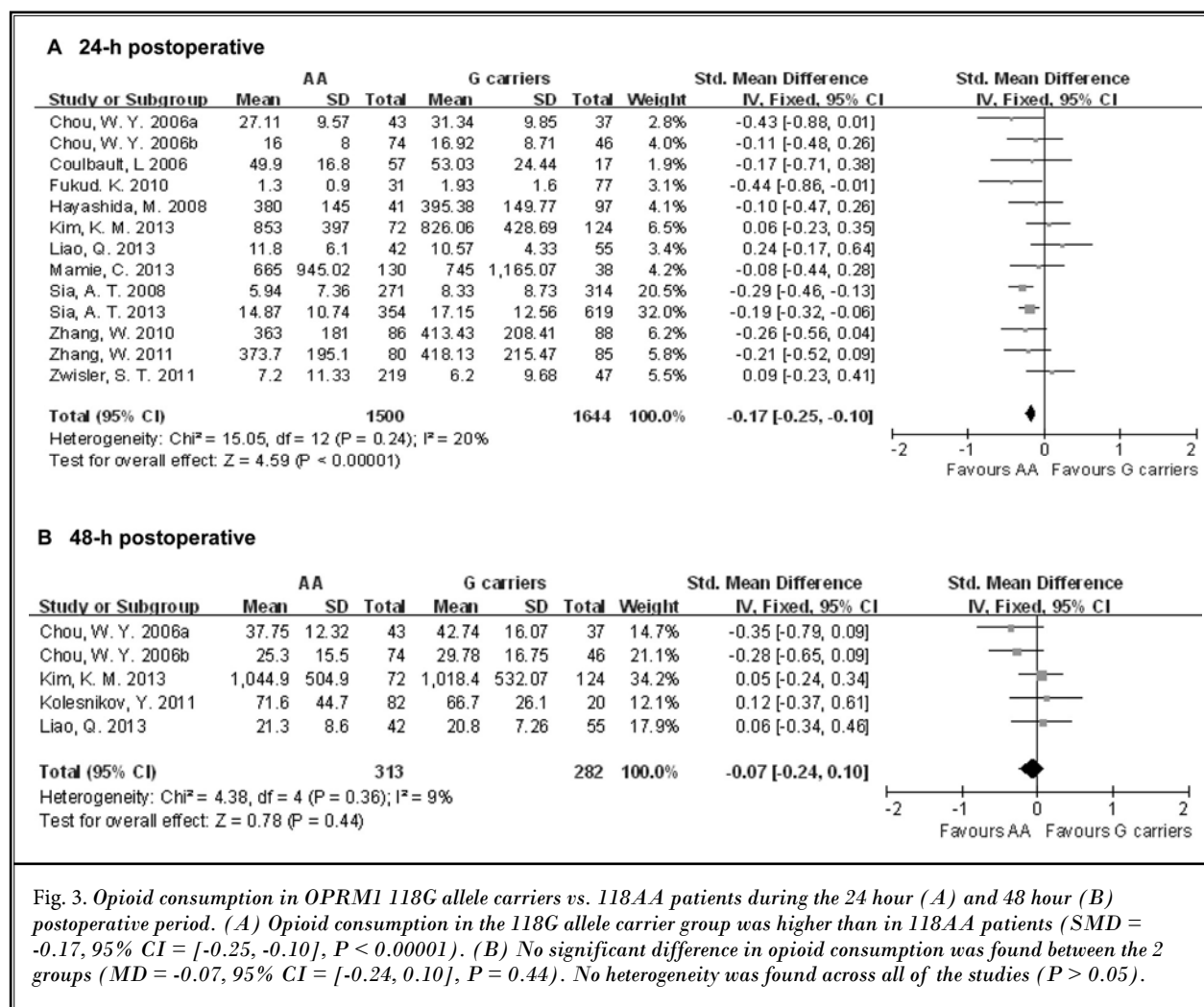
Fig. 3. *Opioid consumption in OPRM1 118G allele carriers vs. 118AA patients during the 24 hour (A) and 48 hour (B) postoperative period. (A) Opioid consumption in the 118G allele carrier group was higher than in 118AA patients (SMD = -0.17, 95% CI = [-0.25, -0.10], P < 0.00001). (B) No significant difference in opioid consumption was found between the 2 groups (MD = -0.07, 95% CI = [-0.24, 0.10], P = 0.44). No heterogeneity was found across all of the studies (P > 0.05).*

trend between AA homozygotes and G allele carriers during the 48-hour postoperative period (fixed-effects model: SMD = -0.07, 95% CI = [-0.24, 0.10], P = 0.36; Fig. 3B). No heterogeneity was found across all of the included studies (χ^2, P = 0.44; Fig. 3B).

Meta-analysis of A118G and side effects: Data for side effects, including nausea and vomiting, were available from 11 independent studies (4-6,20,23-25,35-38). Data for nausea and vomiting were presented as 2 subgroups. Data for nausea and vomiting were pooled in the papers of Coulbault et al (5) and Zhang et al (24); they were used only once in our analysis to avoid data repetition. And the same statistical results were observed when these data were presented as either nausea or vomiting. The nausea subgroup included 851 homozygous 118AA patients and 779 118G allele carriers, whereas the vomiting subgroup included 1,140

homozygous 118AA patients and 1316 118G allele carriers. No significant heterogeneity was observed across all of the included studies (χ^2, P = 0.05; Fig. 4). The presence of the 118G allele was associated with a significantly lower rate of vomiting compared with homozygous 118AA patients (fixed-effects model: OR = 1.38, 95% CI = [1.07, 1.77], P = 0.01; Fig. 4), but no significant difference was observed in the nausea subgroup (fixed-effects model: OR = 1.21, 95% CI = [0.93, 1.58], P = 0.16; Fig. 4). However, the overall effect was significant (fixed-effects model: OR = 1.30, 95% CI = [1.08, 1.55], P = 0.005; Fig. 4), indicating a lower incidence of postoperative nausea or vomiting (PNOV) among 118G allele carriers.

2.1.2. Other SNPs and Postoperative Pain

Among 3,324 SNPs in the MOR gene, many of them

Study or Subgroup	AA Events	Total	G carriers Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.1.1 nausea						
Boswell, M. V. 2013	27	131	6	27	3.8%	0.91 [0.33, 2.47]
Chen, L. K. 2013	34	56	47	73	7.8%	0.85 [0.42, 1.75]
Chou, W. Y. 2006b	6	74	1	46	0.6%	3.97 [0.46, 34.10]
Coulbault, L 2006	17	57	6	17	3.2%	0.78 [0.25, 2.45]
Liao, Q. 2013	14	42	23	55	6.5%	0.70 [0.30, 1.60]
Sia, A. T. 2008	26	271	14	314	5.7%	2.27 [1.16, 4.45]
Zhang, F. 2013	16	54	31	74	9.0%	0.58 [0.28, 1.23]
Zhang, W. 2010	28	86	20	88	6.5%	1.64 [0.84, 3.22]
Zhang, W. 2011	28	80	19	85	5.8%	1.87 [0.94, 3.72]
Subtotal (95% CI)		851		779	48.8%	1.21 [0.93, 1.58]
Total events	196		167			

Heterogeneity: Chi² = 14.04, df = 8 (P = 0.08); I² = 43%
Test for overall effect: Z = 1.41 (P = 0.16)

Study or Subgroup	AA Events	Total	G carriers Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.1.2 vomiting						
Boswell, M. V. 2013	5	131	2	27	1.6%	0.50 [0.09, 2.70]
Chen, L. K. 2013	24	56	34	73	8.2%	0.86 [0.43, 1.73]
Chou, W. Y. 2006a	7	43	5	37	2.2%	1.24 [0.36, 4.31]
Chou, W. Y. 2006b	17	74	5	46	2.3%	2.45 [0.83, 7.16]
Coulbault, L 2006	17	57	6	17	0.0%	0.78 [0.25, 2.45]
Liao, Q. 2013	8	42	10	55	3.4%	1.06 [0.38, 2.97]
Sia, A. T. 2008	10	271	11	314	4.8%	1.06 [0.44, 2.52]
Tan, E. C. 2009	65	389	58	605	18.4%	1.89 [1.29, 2.77]
Zhang, F. 2013	8	54	19	74	6.6%	0.50 [0.20, 1.26]
Zhang, W. 2010	28	86	20	88	0.0%	1.64 [0.84, 3.22]
Zhang, W. 2011	17	80	10	85	3.7%	2.02 [0.87, 4.73]
Subtotal (95% CI)		1140		1316	51.2%	1.38 [1.07, 1.77]
Total events	161		154			

Heterogeneity: Chi² = 12.98, df = 8 (P = 0.11); I² = 38%
Test for overall effect: Z = 2.52 (P = 0.01)

Total (95% CI)		1991		2095	100.0%	1.30 [1.08, 1.55]
Total events	357		321			

Heterogeneity: Chi² = 27.60, df = 17 (P = 0.05); I² = 38%
Test for overall effect: Z = 2.80 (P = 0.005)

0.01 0.1 1 10 100
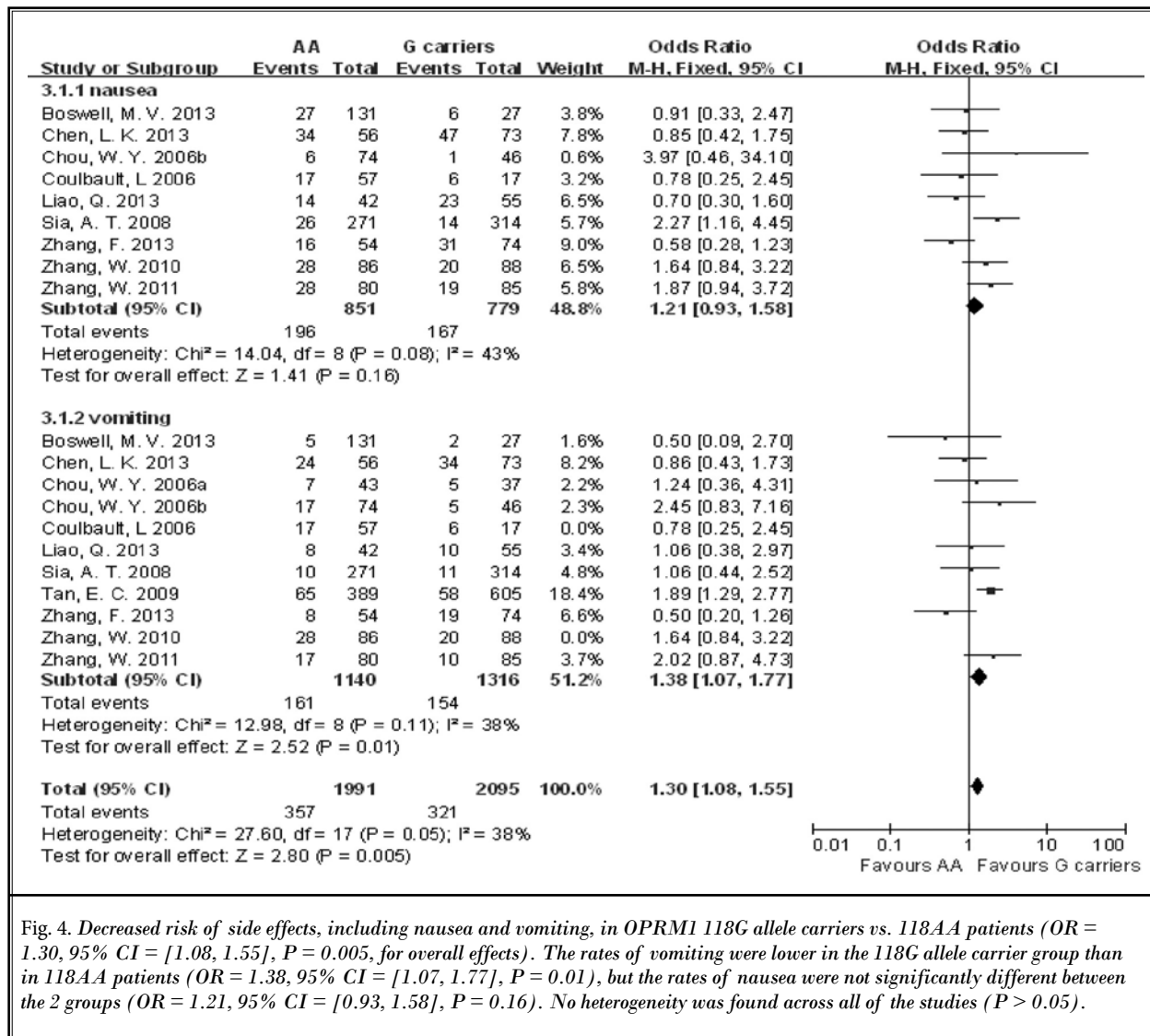Favours AA Favours G carriers

Fig. 4. *Decreased risk of side effects, including nausea and vomiting, in OPRM1 118G allele carriers vs. 118AA patients (OR = 1.30, 95% CI = [1.08, 1.55], P = 0.005, for overall effects). The rates of vomiting were lower in the 118G allele carrier group than in 118AA patients (OR = 1.38, 95% CI = [1.07, 1.77], P = 0.01), but the rates of nausea were not significantly different between the 2 groups (OR = 1.21, 95% CI = [0.93, 1.58], P = 0.16). No heterogeneity was found across all of the studies (P > 0.05).*

have extremely low frequencies, making exploration of the association with pain difficult at the population level (39). However, the minor allele frequencies of 1,395 genetic variants are greater than 1% in the global population (39). Besides SNPs, there are 4 substantial linkage disequilibrium (LD) blocks in the MOR gene (40). A118G, IVS2+G691C (rs2075572), IVS3+G5953A (rs599548), IVS3+A8449G (rs9384179), and TAA+A2109G (rs558025) are 5 tag SNPs that represent the 4 LD blocks of the OPRM1 gene. The IVS2+G691C SNP in intron 2, representing the second LD block, has been studied with regard to nicotine dependence (41) , acute drug dose (42), and heroin addiction (43). The frequency of the minor allele varies from 54.5% to 81.9% in differ-

ent ethnic populations (44). Hayashida et al (31) investigated the influence of IVS2+G691C on clinical pain management and found that the IVS2+G691C variant had no impact on postoperative opioid consumption. Fukuda et al (33) examined associations between fentanyl sensitivity and IVS3+A8449G, which is located in intron 3 and represents a complete LD block with more than 30 SNPs from intron 3 to the 30 untranslated region. They found that individuals who carry the G allele consumed less fentanyl compared with patients without the G allele during the 24-hour postoperative period, but no statistically significant difference in pain scores was found between the 2 groups. These results are inconsistent with Hayashida et al (31), who did

not report a relationship between IVS3+A8449G and postoperative opioid requirements. Another 2 SNPs, IVS3+G5953A in intron 3 and TAA+A2109G, representing the fourth LD block, also did not influence postoperative pain management (31). T172G (rs6912029) in exon 1 is a promoter SNP and has been studied in methadone maintenance patients (46,47) and opiate-dependent individuals (48). In a relatively large sample that consisted of different ethnicities, Tan and co-workers (38) concluded that the T172G variant had no impact on postoperative pain management, including pain score, opioid consumption, and adverse effects. A paper published by Ochroch et al (49) investigated the relationship between 20 SNPs in the MOR gene and postoperative pain scores 3 days after thoracotomy, indicating that 4 SNPs (i.e., rs634479, rs499796, rs548646, and rs679987) were associated with postoperative pain, and 5 SNPs (i.e., rs9322447, rs606148, rs599945, rs613341, and rs616585) approached statistical significance, but these results require further confirmation in a relatively larger sample.

2.2. Cytochrome P450 System

Cytochrome P450 (CYP450) comprises a series of enzyme families, including 57 putatively functional human enzymes (50), and plays an important role in catalyzing the oxidative biotransformation of most drugs, including opiates (51,52). Most enzymes of CYP450 are expressed mainly in the liver and consist of 3 families (i.e., CYP1, CYP2, and CYP3). The CYP1 family has 2 subfamilies: CYP1A and CYP1B. CYP1A-related genes (CYP1A1 and CYP1A2) are located on chromosome 15q24.1, which contains 7 exons and 6 introns (53). The CYP1B subfamily has only one type (CYP1B1), which is located on chromosome 2p22.2 (47). The CYP2 family consists of 4 subfamilies: CYP2A, CYP2B, CYP2C, and CYP2D. The CYP2A subfamily mainly includes CYP2A6, CYP2A7, and CYP2A13, which are located on chromosome 19q13.2 (48). The CYP2B subfamily has only one functional CYP2B6 gene located on chromosome 19 (54). CYP2B6 can be induced and activated during pregnancy, resulting in an increased incidence of methadone clearance (54). The CYP2D gene is located on chromosome 22q13.1. CYP2D has one functional gene (CYP2D6) and 2 pseudogenes (CYP2D7 and CYP2D8) (55). Codeine is metabolized by CYP2D6 to the active morphine metabolite, which has 3000-fold greater affinity for the MOR than codeine (56-58). The CYP3 enzyme has only one subfamily (CYP3A), which is located on chromosome 7q22.1. The impact of CYP3A on opiate metabolism has been investigated mainly with regard to fentanyl (50,51,59) and oxycodone (45,52,60). Concerning the crucial role of the CYP450 family in opiate metabolism, we tested the association between these genetic variants and postoperative pain.

2.2.1. CYP2D6 and Postoperative Pain

CYP2D6 is a unique functional protein in the CYP2D subfamily. To date, more than 100 allelic variants of CYP2D6 have been identified (www.cypalleles.ki.se/). Because of genetic polymorphisms, the products can be divided into 4 phenotypes: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM), and ultrarapid metabolizer (UM). Distinct CYP2D6 variants play differential roles in opiate metabolism. Persson et al reported that most EM patients had satisfactory analgesia when using codeine after hysterectomy, with the exception of one patient who had severe hip damage (47). VanderVaart and co-workers suggested that codeine had no effect on analgesia in PM patients, whereas UM patients achieve immediate pain relief but have severe side effects (48). Tramadol is a synthetic opioid with a lower incidence of morphine-like effects (63), such as abuse potential (64) and the depression of respiration (32). It is metabolized by CYP450 to 11 desmethylated compounds, of which O-desmethyltramadol predominates and possesses analgesic properties (44,56). O-desmethyltramadol and the MOR have strong affinity, which is 200-fold greater than tramadol (65). PM patients require more tramadol than EM patients and have a lower response rate to tramadol compared with EM patients (66). This is inconsistent with another study that found that tramadol consumption, side effects, and pain scores at specific postoperative time points were not significantly different between CYP2D6 genotypes (67). Wang et al (68) focused on the relationship between tramadol and the CYP2D6*10 C188T polymorphism, which is the most common allele, with a frequency that ranges from 51% to 70% in the Chinese population, indicating that heterozygous CYP2D6*10 carriers require less tramadol than homozygotes. Morphine is a traditionally used analgesic, and morphine requirements vary widely among individuals. UM patients consumed less morphine and had lower pain scores than other phenotypes in the acute postoperative period (52). CYP2D6 catalyzes oxycodone to form oxymorphone (53), which has a 10- to 40-times higher affinity than the prototype (69). However, no significant difference was found in oxycodone consumption between PM and EM patients during the

acute postoperative period (53). Additionally, Wesmiller et al (70) found that the CYP2D6 genotype influenced the occurrence of postoperative nausea and vomiting, and PM patients had a lower rate of occurrence of nausea and vomiting and higher pain score. In summary, gene variants of CYP2D6 contribute to individual postoperative pain management.

2.2.2. CYP3A4 and Postoperative Pain

Among the CYP3A subfamily, the most studied variant was CYP3A4. The CYP3A4 gene has approximately 40 alleles (www.cypalleles.ki.se/). Variations in CYP3A4 result in changes in enzyme activity, and 30 – 85% of the interindividual variability in CYP3A4 activity depends on genetic factors (71,72). Numerous studies have explored the relationship between pain management and CYP3A4 (21,32,61-64,73), all of which were conducted in the Asian population.

CYP3A4*1G and postoperative pain: CYP3A4*1G (20230G>A) has a G-to-A substitution in intron 10 (64). It is a high-frequency allele in Asians (0.249 in Japanese [32] and 0.221 in Chinese [64]). Several studies (63,73-75) have discussed the relationship between CYP3A4*1G and pain management in the Chinese population. The CYP3A4*1G variant allele leads to decrease in enzyme activity (76,77). During the first 24-hour postoperative period, fentanyl consumption was lower in the *1G/*1G genotype compared with the *1/*1 and *1/*1G genotypes (32,78), and the plasma concentration of fentanyl was higher in the *1G/*1G group (61). These results were inconsistent with the findings reported by Dong et al (63), in which no significant difference in fentanyl consumption was observed in the 24 and 48-hour postoperative periods. Similarly, pain scores and adverse effects were not significantly different among the 3 genotypes (61,63,73).

Meta-analysis of CYP3A4*1G and pain scores: Available data were retrieved from 2 independent studies (61,73). One study was excluded because the data were presented in the form of median and semi-interquartile range (63). The final meta-analysis included 178 homozygous *1/*1 and 141 *1G carriers. No heterogeneity was detected in either the 0 hour group (χ^2, $P = 0.81$; Fig. 5A) or 24-hour group (χ^2, $P = 0.38$; Fig. 5B). The results of the meta-analysis revealed that pain scores were not significantly different between *1/*1 homozygotes and *1G carriers at 0 hour (fixed-effects model: MD = 0.06, 95% CI = [-0.22, 0.33], $P = 0.67$; Fig. 5A) or 24-hour (fixed-effects model: MD = 0.04, 95% CI = [-0.15, 0.23], $P = 0.66$; Fig. 5B).
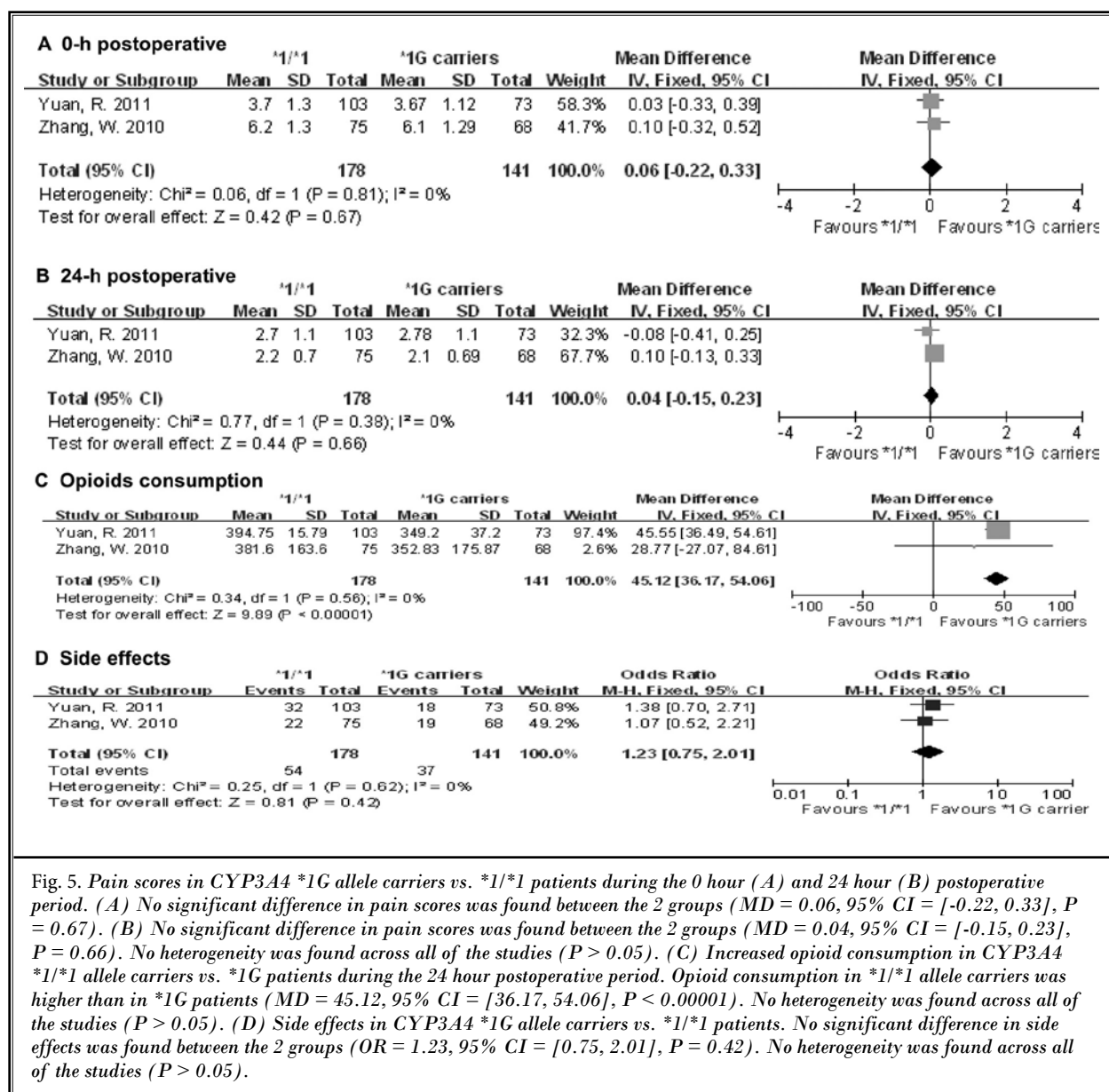
Meta-analysis of CYP3A4*1G and fentanyl con-sumption: The same studies were included as mentioned above. Similarly, 178 homozygous *1/*1 and 141 *1G carriers were included in this meta-analysis. One study was excluded because the results were presented in the form of median and semi-interquartile range (63). Individuals who carried the *1G allele required less fentanyl during the first 24-hour postoperative period than individuals with the wildtype *1/*1 genotype (fixed-effects model: MD = 45.12, 95% CI = [36.17, 54.06], $P < 0.00001$; Fig. 5C), with no heterogeneity detected (χ^2, $P = 0.56$; Fig. 5C).

Meta-analysis of CYP3A4*1G and side effects: Side effects mainly include PONV. The data were derived from 2 studies (61,73). Among 178 homozygous *1/*1 carriers, 54 reported PONV, whereas among 141 *1G carriers, 37 reported PONV. No significant difference was found in the incidence of PONV between the *1G/*1G and *1/*1G groups (fixed-effects model: OR = 1.23, 95% CI = [0.75, 2.01], $P = 0.42$; Fig. 5D). No heterogeneity was detected (χ^2, $P = 0.62$; Fig. 5D).

Other variants of CYP3A4 and postoperative pain: Other variants of CYP3A4 include CYP3A4*18 and CYP3A4*18B. CYP3A4*18 is a promoter SNP and has been extensively studied because of its role in transcriptional regulation in vitro (79). Tan et al (64) suggested that CYP3A4*18 had no effect on postoperative fentanyl consumption in the Malaysian Malay population. This is consistent with findings in Koreans by Kim et al (32), in which the CYP3A4 genetic polymorphism had no relationship with postoperative fentanyl dose. Additionally, pain scores and adverse effects were not influenced by CYP3A4*18 (64). This phenomenon requires further confirmation in a larger sample. A recent study investigated the effect of CYP3A4*18B on postoperative pain in the Chinese population (21). CYP3A4*18B, which has a high frequency in Asians, has a G-to-A substitution in intron 10 and is correlated with increased enzyme activity (74,75). One study by Liao et al (21) indicated that CYP3A4*18B had no effect on postoperative pain score and untoward effects. They found no significant difference in fentanyl requirements among 3 genotypes during the 24-hour postoperative period, whereas the *18B allele was associated with less fentanyl consumption at 48 hours (21).

2.2.3. CYP3A5 and Postoperative Pain

The expression of CYP3A5 in the liver differs among ethnicities (76). The variants of CYP3A5 can influence protein expression and enzyme activity. CYP3A5*3 is the most common variant that induces a mutation in

A 0-h postoperative

| Study or Subgroup | *1/*1 | | | *1G carriers | | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Yuan, R. 2011	3.7	1.3	103	3.67	1.12	73	58.3%	0.03 [-0.33, 0.39]	
Zhang, W. 2010	6.2	1.3	75	6.1	1.29	68	41.7%	0.10 [-0.32, 0.52]	
Total (95% CI)			178			141	100.0%	0.06 [-0.22, 0.33]	

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.67)

B 24-h postoperative

| Study or Subgroup | *1/*1 | | | *1G carriers | | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Yuan, R. 2011	2.7	1.1	103	2.78	1.1	73	32.3%	-0.08 [-0.41, 0.25]	
Zhang, W. 2010	2.2	0.7	75	2.1	0.69	68	67.7%	0.10 [-0.13, 0.33]	
Total (95% CI)			178			141	100.0%	0.04 [-0.15, 0.23]	

Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)

C Opioids consumption

| Study or Subgroup | *1/*1 | | | *1G carriers | | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Yuan, R. 2011	394.75	15.79	103	349.2	37.2	73	97.4%	45.55 [36.49, 54.61]	
Zhang, W. 2010	381.6	163.6	75	352.83	175.87	68	2.6%	28.77 [-27.07, 84.61]	
Total (95% CI)			178			141	100.0%	45.12 [36.17, 54.06]	

Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 9.89 (P < 0.00001)

D Side effects

| Study or Subgroup | *1/*1 | | *1G carriers | | | Odds Ratio | Odds Ratio |
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Yuan, R. 2011	32	103	18	73	50.8%	1.38 [0.70, 2.71]	
Zhang, W. 2010	22	75	19	68	49.2%	1.07 [0.52, 2.21]	
Total (95% CI)		178		141	100.0%	1.23 [0.75, 2.01]	
Total events	54		37				

Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)

*Fig. 5. Pain scores in CYP3A4 *1G allele carriers vs. *1/*1 patients during the 0 hour (A) and 24 hour (B) postoperative period. (A) No significant difference in pain scores was found between the 2 groups (MD = 0.06, 95% CI = [-0.22, 0.33], P = 0.67). (B) No significant difference in pain scores was found between the 2 groups (MD = 0.04, 95% CI = [-0.15, 0.23], P = 0.66). No heterogeneity was found across all of the studies (P > 0.05). (C) Increased opioid consumption in CYP3A4 *1/*1 allele carriers vs. *1G patients during the 24 hour postoperative period. Opioid consumption in *1/*1 allele carriers was higher than in *1G patients (MD = 45.12, 95% CI = [36.17, 54.06], P < 0.00001). No heterogeneity was found across all of the studies (P > 0.05). (D) Side effects in CYP3A4 *1G allele carriers vs. *1/*1 patients. No significant difference in side effects was found between the 2 groups (OR = 1.23, 95% CI = [0.75, 2.01], P = 0.42). No heterogeneity was found across all of the studies (P > 0.05).*
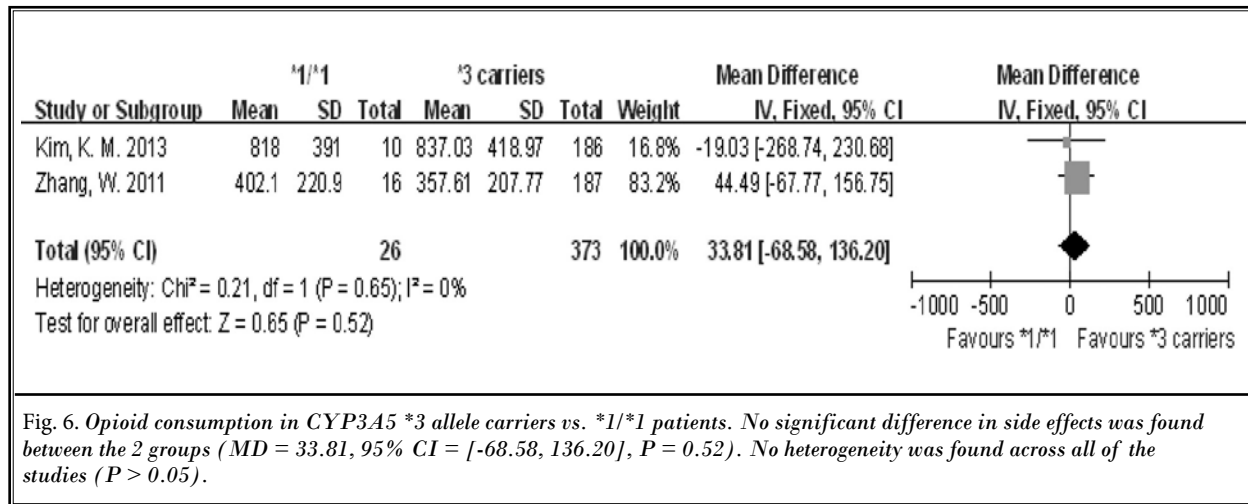
intron 3, resulting in aberrant splicing and truncation (76). CYP3A5*3 presents a high frequency in Asians (32,77,78). Fentanyl consumption was not significantly correlated with CYP3A5*3 in Chinese and Koreans (32,62), but a trend toward an association between decreased fentanyl consumption and CYP3A5*1/*3 and CYP3A5*3/*3 polymorphisms was detected in Chinese (62). When combined with CYP3A4*1G, CYP3A5*1/*3 and CYP3A5*3/*3 genotypes presented significantly lower fentanyl requirements than wildtypes (62). These results suggest an interaction among CYP450 genes.

Meta-analysis of CYP3A5*3 and opioid consumption: Data were obtained from 2 studies (32,62) that included 26 homozygous *1/*1 and 373 *3 carriers. No heterogeneity was detected across studies (χ^2, P = 0.65; Fig. 6). When the data were pooled, wildtype and mutation carriers presented no significant difference in fentanyl consumption (fixed-effects model: MD = 33.81, 95% CI = [-68.58, 136.20], P = 0.52; Fig. 6).

2.3. P-glycoprotein

P-glycoprotein (P-gp) is encoded by the adenosine

Fig. 6. *Opioid consumption in CYP3A5 *3 allele carriers vs. *1/*1 patients. No significant difference in side effects was found between the 2 groups (MD = 33.81, 95% CI = [-68.58, 136.20], P = 0.52). No heterogeneity was found across all of the studies (P > 0.05).*

triphosphate (ATP)-binding cassette subfamily B member-1 (ABCB1) gene. It is a transporter for drug efflux (80) that is expressed in biological barriers, including the blood-brain barrier (BBB) and intestinal wall (81). P-gp is considered the major constituent of the BBB that can restrict the disposition of certain opioids in the brain (80). A number of opioids, including morphine and fentanyl, are all substrates of P-gp (82). Therefore, ABCB1 is highly associated with the function of P-gp, and any mutation in this gene could lead to abnormal opioid-induced analgesia.

ABCB1 and pain: The SNP of ABCB1 can influence the expression and activity of P-gp. C3435T and G2677T are the most extensively investigated SNPs that have minor allele frequencies in the European population (approximately 50% and 42 – 45%, respectively) (83,84). The P-gp expression level was affected by distinct genotypes and led to different analgesic effects. Many studies have suggested that C3435T is associated with opioid consumption in the management of either acute or chronic pain (18,85). However, Sia et al (86) found that the ABCB1 C3435T SNP is irrelevant for opioid consumption, but they found that homozygous TT patients had a higher risk of persistent pain than wildtype CC patients. Kim et al suggested that ABCB1 2677G>T/A and 3435C>T were not related to variability of the analgesic response to fentanyl (32). In another study, no significant difference was found in opioid dose requirements between distinct variants (5).

Meta-analysis of ABCB1 C3435T and opioid consumption: Opioid consumption data were available from 7 studies (5,27,32,51,86-88). One study was excluded for a lack of available data for specific post-

operative periods (89). The studies finally included 456 homozygous CC patients and 1,176 T allele carriers. No heterogeneity was detected across studies (χ^2, $P = 0.48$; Fig. 7A). When the data were pooled, wildtype and mutation carriers did not exhibit significant differences in opioid consumption (fixed-effects model: SMD = -0.01, 95% CI = [-0.12, 0.10], $P = 0.82$; Fig. 7A).

Meta-analysis of ABCB1 G2477T/A and opioid consumption: Opioid consumption data were available from 4 studies (5,27,32,86). One study was excluded for a lack of available data for specific postoperative periods (89). One study was excluded because the results were presented in the form of median and semi-interquartile range (90). The studies finally included 286 homozygous GG patients and 862 other allele carriers. No heterogeneity was detected across studies (χ^2, $P = 0.66$; Fig. 7B). When the data were pooled, homozygous GG patients and other mutation carriers did not exhibit significant differences in opioid consumption (fixed-effects model: SMD = -0.01, 95% CI = [-0.15, 0.13], $P = 0.88$; Fig. 7B).

2.4. Catechol-O-methyltransferase

The catechol-O-methyltransferase (COMT) gene is located on chromosome 22 (22q11.1–q11.2), including 6 exons (91). A functional G-to-A transition that results in a Val-to-Met amino-acid substitution has been implicated in the regulation of pain (92). The COMT enzyme can metabolize catecholamines (e.g., dopamine, epinephrine, and norepinephrine) of glial cells and postsynaptic neurons in the central nervous system and other tissues (93). Previous studies showed that lower COMT activity results in an increase in pain sensitivity in both animals and humans (94,95).

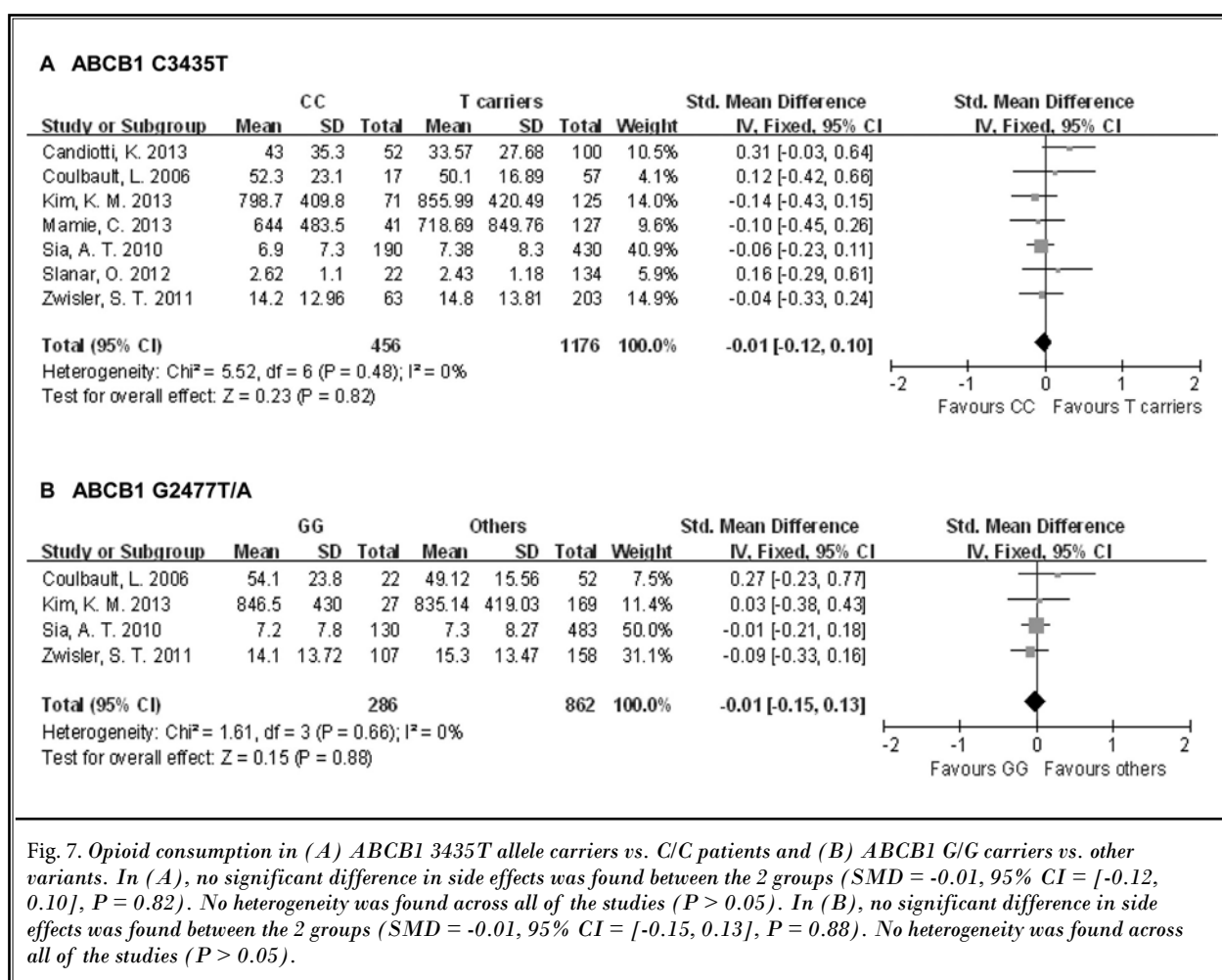Catechol-O-methyltransferase Val158Met and pain:

The most common SNP of COMT is COMT G1947A, also called COMT Val158Met. The methionine at codon 158 reduces enzyme thermostability. Homozygous 1947AA carriers exhibit a 3- to 4-fold reduction of enzyme activity than G allele carriers, resulting in a decrease in the degradation of catecholamines in individuals with the A allele (96) and have increased pain sensitivity (97). Osteoarthritis patients with the Val158Met variant exhibited higher pain levels (98), and lower COMT enzyme activity leads to an increase in pain sensitivity when exposed to mechanical or thermal stimulation (99). Reyes-Gibby et al (17) investigated the combined effect of the COMT Val158Met variant and OPRM1 A118G polymorphism. The results indicated that patients with the 118AA and Met/Met genotype consumed less opioids to relieve pain than any of the other genotypes tested (17).

2.5. Serotonergic System

Serotonin receptors: Serotonin is among the most important analgesic substances for modulating the pain response. Increased serotonin levels can act on postsynaptic receptors, activate serotonin receptors and downstream signaling pathways, and result in the generation of pain.

2.5.1. Serotonin-1A Receptor and Pain

The 5-HT1A gene (HTR1A) is located on chromosome 5q11.2–13. It spans approximately 1200 bp without introns. Fifty important SNPs are known to date, and most of them are in almost complete linkage disequilibrium (LD). Among all of the SNPs, -1019C/G (rs6295), which determines the transcription rate of the HTR1A gene, has been shown to significantly affect serotonergic neurotransmission (100-102). Allele

Fig. 7. *Opioid consumption in (A) ABCB1 3435T allele carriers vs. C/C patients and (B) ABCB1 G/G carriers vs. other variants. In (A), no significant difference in side effects was found between the 2 groups (SMD = -0.01, 95% CI = [-0.12, 0.10], P = 0.82). No heterogeneity was found across all of the studies (P > 0.05). In (B), no significant difference in side effects was found between the 2 groups (SMD = -0.01, 95% CI = [-0.15, 0.13], P = 0.88). No heterogeneity was found across all of the studies (P > 0.05).*

frequency distributions are significantly different between Caucasians and Asians. The G allele has been identified in approximately 50% of Caucasians but only 21% of Asians (103,104). 5-HT1AR agonists has been investigated for their therapeutic potential in pain relief (105). Repeated morphine administration leads to tolerance and even hyperalgesia, but repeated administration of a 5-HT1AR agonist can reverse this effect by inducing the loss of hyperalgesia and increasing analgesia (106).

2.5.2. Serotonin-2A Receptor and Pain

The 5-HT$_{2A}$ receptor gene is mapped on chromosome 13q14–21 and consists of 3 exons that span over 60 kb. The promoter region has 2 important SNPs (-1438A/G [rs6311] and -102T/C [rs6313]) that show strong LD (107,108). The -1438G (102C) allele was reported to be present in almost 50% of different populations, including Caucasians and Asians (109). Abbott et al (110) reported that treatment with 5-HT$_{2A}$/2C antagonists and a 5-HT$_{2A}$ antagonist decreased the pain response. Tokunaga et al (111) also reported that the pain response was attenuated by treatment with a 5-HT$_{2A}$ receptor antagonist. 5-HT$_{2A}$ receptor activation has been implicated in the process of pain modulation. Previous studies suggested that patients with irritable bowel syndrome (IBS) or fibromyalgia and the T/T genotype exhibited higher pain sensitivity than patients with other genotypes (112-114).

Aoki et al (115) investigated the relationship between the 102T/C polymorphism and individual differences in analgesic requirements in patients with postoperative pain. They suggested that women with the T/T genotype tended to have greater analgesic requirements than those with other genotypes (115).

2.6. Ion-Channel Function

Pain is felt through the activation of nociceptors on sensory neurons that detect high-threshold stimuli, including extremes of temperature and mechanical force or chemical exposure (e.g., acids or prostaglandins). Such signals are then transmitted to the central nervous system (116,117). Ligand-gated ion channels or voltage-gated ion channels play a pivotal role in detecting and transmitting stimulus signals. Early findings indicated that ion channel variants may modulate the risk, severity, and persistence of pain after injury (118). In the present review, we discuss and highlight the role of ion channels in pain modulation.

2.6.1. TRP Channels and Pain

Numerous transient receptor potential (TRP) channels have been shown to be expressed on sensory neurons. Vanilloid-1 (TRPV1) was the first TRP receptor discovered and is a nonselective cation channel that is activated by noxious stimuli, leading to pain mediated by discharges in C-polymodal and Aδ mechanoheat nociceptors (119,120). In animals, genetic variability in TRPV1 has been reported to be associated with an increase in surgical pain (121-123). Recently, Ochroch and colleagues (49) examined the association between distinct genetic variants and pain in 90 patients on postoperative day 3, but no significant difference was detected between TRPV1 and postoperative pain.

2.6.2. Voltage-gated Sodium Channels and Pain

Voltage-gated sodium channels (Nav) are crucial in the process of nociceptor excitability and signal transmission. Diverse channels (e.g., Nav1.7, Nav1.8, and Nav1.9) are preferentially expressed in peripheral neurons and execute distinct functions related to the regulation of pain (124-126). Before the congenital insensitivity to pain phenotype was discovered in 2006, people did not realize the importance of mutations in the SCN9A gene (127,128). SCN9A encodes the Nav1.7 voltage-gated sodium channel and is mainly expressed in dorsal root ganglion neurons and sympathetic ganglion neurons (129). Many studies have identified mutations in SCN9A that contribute to the development of pain disorders, ranging from abnormal pain sensitivity to the partial loss of pain perception (127-131). The 3312G>T SNP that is located within exon 16 of the SCN9A gene leads to an amino acid substitution and is associated with the incidence of congenital insensitivity to pain (132). Duan et al (133) explored the role of 3312G>T in the SCN9A gene in predicting individual baseline pain perception and postoperative pain sensitivity in the general population. The results suggested that patients who carry the SCN9A 3312T allele have lower postoperative pain sensitivity and a decreased likelihood of developing inadequate analgesia than those who carry the 3312G allele (133).

2.7. Publication Bias Analysis

We applied a series of strategies to investigate possible publication biases. Fig. 8 presents funnel plots of the statistically significant meta-analysis. No publication bias was evident for OPRM1 A118G, ABCB1 C3435T, or ABCB1 2477T in the present study. However,

because of the limited number of articles included in the final analysis, publication bias cannot be assessed for CYP3A4 and CYP3A5 gene SNPs.

3. Discussion

Our meta-analysis showed that OPRM1 118G allele carriers consumed more opioids for analgesia but reported higher pain scores and less nausea and vomiting than homozygous 118AA patients during the first 24-hour postoperative period but not 48-hour postoperative period. CYP3A4*1G carriers consumed less opioids than homozygous CYP3A4*1/*1 patients. Our results indicate that 118G allele carriers have lower sensitivity to opioid analgesics, including both opioid-induced analgesic effects and side effects, together with less satisfactory pain management than 118AA homozygotes. In terms of CYP3A4, *1G carriers had higher sensitivity to opioid-induced analgesia compared with *1/*1 homozygotes.

With emerging evidence of the clinical relevance (15) and therapeutic predictive value (18) of OPRM1 SNPs, the inclusion of the OPRM1 118A>G variant in personalized therapeutic concepts for pain has been increasingly contemplated. A meta-analysis targeted the OPRM1 118A>G variant and its effects on opioids, but no significant association was found (19). This was opposite to our results. One important reason may be the heterogeneity across datasets and population stratification in the study by Walter and Lotsch (19) that mixed cancer pain, non-cancer pain, and postoperative pain, whereas our meta-analysis included only postoperative pain. It could be more difficult to derive gene-opioid effect relationships from data of patients with different types of pain, for the mechanism, severity, and nature differ substantially. Secondly, in cancer patients, pain is much more severe and persistent. Pain sensitivity varies after long-term opioid analgesic medication, which can also produce abnormal pain perception, either hyperalgesia or hypoalgesia (134-136). Additionally, pain assessment at different time points, such as incident pain, end-of-dose failure pain, uncontrolled persistent pain, and well-managed cancer pain, substantially affect pain ratings (137). As a result, pain and opioids consumption in cancer pain patients may not be comparable to that in postoperative patients. Song et al (138) conducted a meta-analysis of the association between the OPRM1 A118G polymorphism and epidural analgesia with fentanyl during labor. Contrary to the aforementioned meta-analysis results, this study reported that 118G carriers required less fentanyl but reported higher an-

algesic satisfaction than AA homozygotes during labor. A large number of paradoxical reports in this field still exist in the literature (3,16,19). A recently published meta-analysis by Hwang et al (139) supported our finding. Hwang and his colleagues found that the OPRM1 118G carriers required a higher mean opioid dose than AA homozygotes. One more interesting finding was that the subgroup analysis revealed the A118G affects the requirement for postoperative morphine but not fentanyl (139). Hwang's finding suggests that pharmacogenetic effect of A118G SNP on response to opioid agonists may be ligand dependent, which may explain the contradictory reports of Song et al (138).

Our meta-analysis showed that 118G allele carriers had decreased sensitivity to opioids, reflected by more opioid consumption, less nausea and vomiting, and higher pain ratings. This can be partially interpreted by related basic research findings. Results from *in vitro* experiments and an analysis of postmortem human brains reported lower MOR expression for the 118G allele compared with the 118A prototypic receptor, which had a "gene dose"-dependent reduction of receptor number as the number of 118G alleles increased (140-142). Genetic influences on pain sensitivity and pain modulation have been strongly supported by a large amount of animal literature, with highly pain-sensitive animals exhibiting less responsiveness to analgesics (143-145), indicating high pain sensitivity may both enhance pain intensity and reduce the general effectiveness of endogenous and exogenous analgesia. This was also observed in human experimental pain (146,147), with a decrease in opioid-induced miosis (148,149) in carriers of the MOR variant N40D. This is consistent with an interesting phenomenon, in which the alfentanil concentration-dependent analgesic effect linearly decreased with pain-related brain activation. This suggests that the increase in opioid requirements in pain patients who carry the MOR variant N40D (4,15) is mainly attributable to a reduction of the sensory intensity of pain.

The results for the 48-hour postoperative period were not significantly different between OPRM1 118G allele carriers and homozygous 118AA patients for several reasons, although there has presented a trend the same as the 24 hours cohort. Firstly, the smaller sample size may limit the statistical significances; secondly, for postoperative patients, pain at the 48-hour postoperative period is less terrible than that at the 24-hour postoperative period. Therefore, many associations may not be identified.
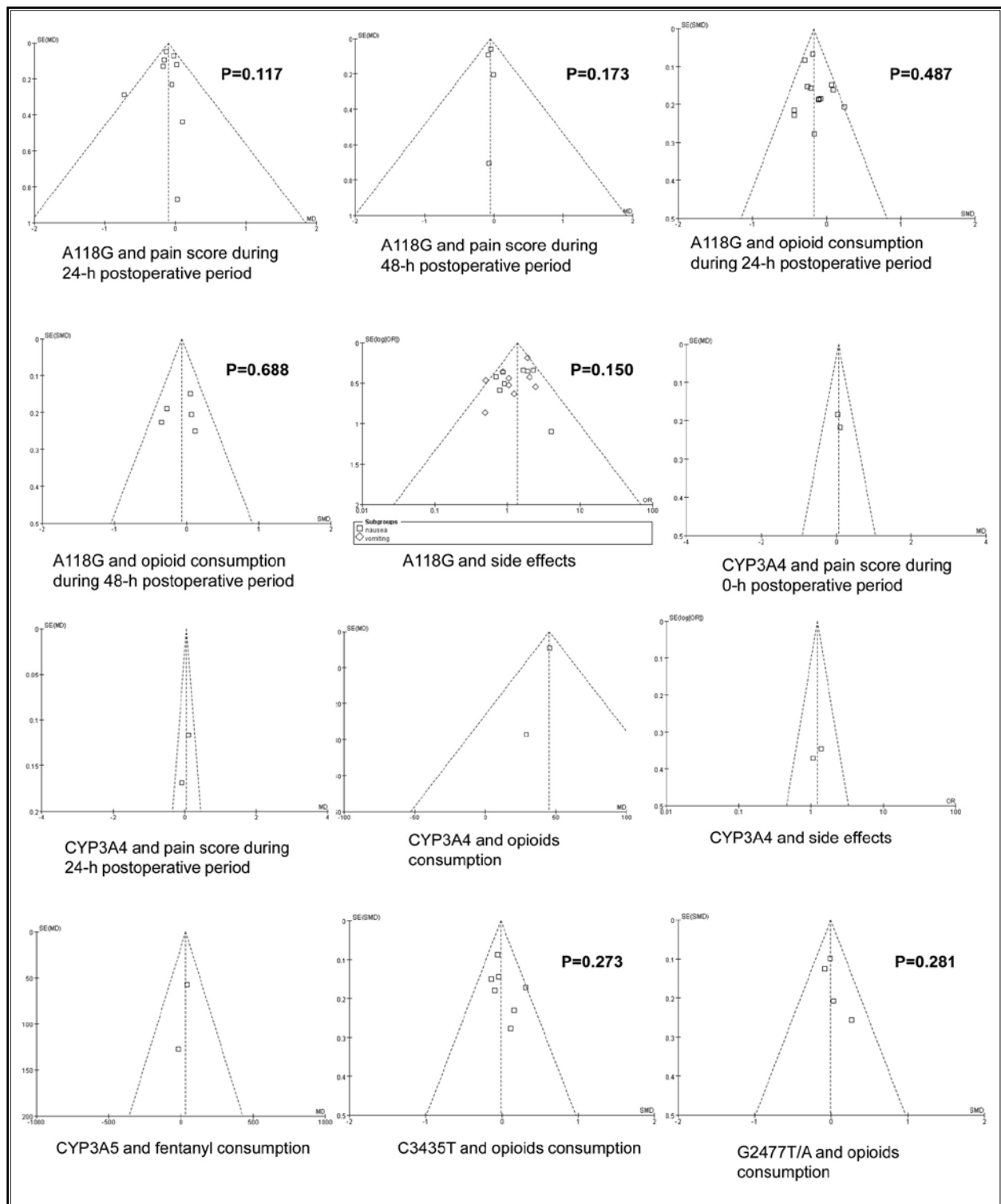
Fig. 8. *Funnel plots of statistically significant meta-analyses. No significant publication bias was evident for OPRM1 A118G, ABCB1 C3435T, and ABCB1 2477T in the present study.*

In our meta-analysis, we found that CYP3A4 *1G carriers consumed less opioids than homozygous CYP3A4 *1/*1 patients. However, to our knowledge, no meta-analysis has focused on the association between the CYP3A4 SNP and postoperative pain and opioid analgesics. Moreover, few studies published prior to January 2014 targeting the CYP3A4 SNP and pain modulation. Therefore, the results need to be further confirmed in larger samples.

The finding that the A118G SNP of OPRM1 has the most potent influence on postoperative pain management undoubtedly provides important insight into the multiplicity of genentic factors that contribute to the often marked interindividual differences in responses to opioid analgesics for patients with postoperative pain. These genetic factors include those affecting analgesic drug metabolism, transport of analgesic agents across the BBB, and their activity at target receptors and ion channels and in the modulation of neurotransmitter pathways. Compared with the multiplicity of routinely identifying a large number of genetic variants, the finding will contribute to the cost reduction in the effort to individualize pain medication. Clinical application of this finding to enable tailoring of analgesic dosing regimens in individual patients is relatively more reachable in the near future. It is important to highlight that identifying the genes encoding opioid receptors, maybe more SNPs of OPRM1, other than metabolizing enzymes, and transporters, will be of great value in clinical settings of postoperative pain control. Still, more clinical studies are necessary to investigate the cost-benefit ratio of this genetic evaluation.

Our meta-analysis has some limitations. Some potential non-genetic factors can modify the effects of genetic SNPs on pain and opioid consumption during the postoperative period, such as age, gender, mood, anxiety, and drug-drug interactions (150). Other factors, such as selective publication bias (i.e., the "winner curse"), may also be a factor. However, little information was provided in most studies on the interactions between such non-genetic factors and SNPs of genetic variant. Therefore, further analyses could not be performed in the present meta-analysis.

4. Conclusion

In summary, the present meta-analysis indicated that among the studied genetic SNPs that include those affecting analgesic drug metabolism, transport of analgesic agents across the BBB, and their activity at target receptors and ion channels and in the modulation of neurotransmitter pathways, the A118G allele variant of OPRM1 has more potent influence on pain management of postoperative patients. The 118G allele reduces the analgesic potency and the occurrence of side effects of opioids, and results in higher pain scores compared with the 118AA homozygotes. The identification of other SNPs of the OPRM1 gene might provide valuable information for clinicians to properly manage the analgesic use of opioids individually for better pain management.

Acknowledgements

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