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RESEARCH

Pharmacogenetics of opioid medications for relief of labor pain and post-cesarean pain: a systematic review and meta-analysis

Martina Giacon[1] · Sarah Cargnin[2] · Maria Talmon[1] · Salvatore Terrazzino[1]

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Abstract

Objective Several studies have attempted to identify genetic determinants of clinical response to opioids administered during labor or after cesarean section. However, their results were often contrasting. A systematic review and meta-analysis was conducted to quantitatively assess the association between gene polymorphisms and clinical outcomes of opioid administration in the treatment of labor pain and post-cesarean pain.

Methods A comprehensive search was performed up to December 2023 using PubMed, Web of Knowledge, Cochrane Library, and OpenGrey databases. The clinical endpoints of interest were pain score after opioid treatment, total opioid consumption, patient's analgesic satisfaction, and incidence of opioid side effects. Random-effects meta-analyses were conducted when data were available in at least three studies.

Results Twenty-six studies enrolling 7765 patients were included in the systematic review. Overall, a total of 12 candidate polymorphic genes (OPRM1, COMT, CYP2D6, CYP3A4, ABCB1, ABCC3, UGT2B7, CGRP, OPRK1, OPRD1, KCNJ6, KCNJ9) were considered by the included studies, among which the most investigated variant was OPRM1 rs1799971. Overall pooled results indicated that individuals carrying the G allele of *OPRM1* rs1799971 required higher opioid doses for pain management in comparison to rs1799971 AA subjects (standardized mean difference: 0.26; 95% CI: 0.09–0.44; $P = 0.003$). Such an association was confirmed in the subgroups of patients with labor pain and post-cesarean pain.

Conclusion The present meta-analysis provides strong evidence of an association between *OPRM1* rs1799971 and opioid dose requirement for relief of labor pain or post-cesarean pain. However, given the insufficient evidence for other polymorphic gene variants, large studies are still needed to investigate the impact of genetic variability on the efficacy and safety of opioid medications for relief of labor pain and post-cesarean pain (INPLASY Registration No. 202410040).

Keywords Labor pain · Post-cesarean pain · Opioids · Gene polymorphisms · Meta-analysis

Introduction

Labor pain and delivery pain are among the worst pains that women experience in their lives [1]. Although not life-threatening, labor pain has relevant short- and long-term consequences for the well-being of mother and fetus. Poorly controlled labor pain can exacerbate maternal stress and anxiety, prolong labor, and lead to fetal metabolic acidosis [2, 3]. A significant proportion of postpartum women experience uterine involution pain, perineal pain, and incisional pain following cesarean section, which evolve into chronic pain in 6.1 to 11.5% of women [4, 5]. Notably, patients who do not receive adequate analgesia before and after labor are at higher risk of postpartum depression and post-traumatic stress syndrome [6, 7]. Therefore, the provision of analgesics to mitigate such harmful effects is becoming increasingly common, especially in high-income countries [8].

Opioids are drugs often used for the management of labor and post-cesarean pain [9–11]. However, patient response to opioids is highly variable in terms of pain relief, occurrence, and severity of side effects [12]. There are several factors that can contribute to the inter-individual variability of opioid response. These include clinical factors, such as age, parity, stage of labor, ethnicity [13, 14], and genetic factors

✉ Salvatore Terrazzino
salvatore.terrazzino@uniupo.it

[1] Department of Pharmaceutical Sciences, University of Piemonte Orientale "A. Avogadro", Largo Donegani 2, 28100 Novara, Italy

[2] Department of Health Sciences, Università del Piemonte Orientale (UPO), 28100 Novara, Italy

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[15]. Among the polymorphic variants of genes involved in opioid pharmacokinetics (e.g., *CYP2D6*, *CYP3A4*, *ABCB1*, *COMT*) or pharmacodynamics (e.g., *OPRM1*), much interest has been focused on *OPRM1* rs1799971 (A118G), a functional single nucleotide polymorphism (SNP) in the gene encoding the mu opioid receptor (MOR). This SNP consists of an Asn40Asp amino substitution in the extracellular N-terminus of the receptor which leads to reduced MOR density on neuronal membranes and altered MOR-mediated responses [16]. Some studies have shown that carriers of *OPRM1* rs1799971 G allele require higher opioid doses to achieve pain relief during labor [17] or after a cesarean section [18–20], when compared to homozygotes for the rs1799971 A allele. Conversely, some other studies suggest that the *OPRM1* A118G polymorphism does not affect the opioid dose requirement in both clinical settings [21–23]. Given the conflicting results of previous studies and the increasing number of publications in this field, we herein conducted a systematic review of published studies aimed at quantitatively summarizing the evidence on the association between gene polymorphisms and clinical outcomes of opioid medications in the context of labor and post-cesarean pain management.

Methods

This meta-analysis follows the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. The MOOSE checklist is available in the Supplementary Materials (Supplementary Table 1).

Literature search and inclusion/exclusion criteria

The protocol was set a priori to the literature search and registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) (Registration No. 202410040, doi:https://doi.org/10.37766/inplasy2024.1.0040). A comprehensive search of electronic databases (PubMed, Web of Knowledge, Cochrane Library, and OpenGrey) was conducted up to November19th, 2024, to identify potentially eligible studies. A Boolean combination of the following keywords was used: (opioid* OR opiate* OR analges*) AND (polymorphism* OR SNP OR SNPs OR variant* OR pharmacogenetic* OR pharmacogenomic*) AND (labor OR labour OR birth OR childbirth OR afterbirth OR "after-birth" OR "post-childbirth" OR prebirth OR "pre-birth" OR "near-birth" OR delivery OR "post-delivery" OR postdelivery OR "pre-delivery" OR predelivery OR postpartum OR "post-partum" OR antepartum OR "ante-partum" OR intrapartum OR "intra-partum" OR peripartum OR "peri-partum" OR partum OR natal OR prenatal OR "pre-natal" OR postnatal OR "post-natal" OR neonatal OR "neo-natal" OR perinatal OR "peri-natal" OR antenatal OR "ante-natal" OR intranatal OR "intra-natal"). To be included, studies had to meet the following eligibility criteria: (1) observational studies or randomized clinical trials including women treated with opioids by any route of administration for relief of labor pain or post-cesarean pain; (2) studies evaluating the association of any gene polymorphism with at least one of the following outcomes: (a) pain score after opioid administration based on any patient-reported scale; (b) total opioid consumption; (c) 50% effective opioid dose (ED50); (d) analgesic satisfaction based on any patient-reported scale; (3) studies with sufficient data to calculate the above-mentioned outcomes (pain score, total opioid consumption, ED50, and analgesic satisfaction) as mean ± standard deviation; (4) incidence of any specific adverse effect of opioid therapy. The following studies were excluded from systematic review: (1) not human studies; (2) studies not related to the research topics; (3) reports, case series, meeting abstract, editorials, letters to the editor, review articles, and meta-analyses; (4) studies not evaluating the association of gene polymorphisms with at least one of the outcomes of interest; (5) non-English publications, due to limited translation resources.

All potentially relevant studies identified in the first screening step were then read in full to check whether they were eligible for inclusion. A manual review of primary and review article references was also performed to identify additional relevant studies that had been overlooked in the initial electronic search. In cases where data for a given clinical outcome could not be extracted from an eligible study, the missing data were requested by email to the corresponding author of the study. The study was excluded from the systematic review or meta-analysis if the corresponding author did not respond to the email or did not provide the data requested for the effect size calculation. Two investigators (M.G. and S.C) independently screened the papers to minimize the risk of excluding relevant records and a third investigator (S.T.) resolved any discrepancies or conflicts. The citations located and those excluded, including justification, have been listed in an Excel file, which is available upon request.

Data extraction

The following information was recorded for each included study: first author's last name, year of publication, study location, patient ethnicity, type of pain (i.e., labor pain or post-cesarean pain), time of pain assessment, opioid administered and route of administration, total number of opioid-treated patients, reported outcome of interest, scale used for pain score assessment, gene variant investigated, and the genotyping method used. As for OPRM1 rs1799971, which was found the most investigated SNP, the minor allele

frequency (MAF) and the *P*-value of Hardy Weinberg Equilibrium (HWE) test were also calculated from each study when genotype distribution was reported as three separate groups (AA, AG, GG), by an online HWE calculator (https://www.had2know.org/academics/hardy-weinberg-equilibrium-calculator-2-alleles.html). Means and standard deviations for continuous outcomes (pain score, total opioid consumption, ED50, and analgesic satisfaction), as well as incidence of adverse events following opioid therapy were extracted (or calculated) from each study for the three genotypes, when available as separate groups (homozygous major allele, heterozygous, and homozygous minor allele) or for combined groups as reported in the primary study. For continuous outcomes, regrouping heterozygous data to either homozygous group was calculated by combining means and standard deviations from each group, using an online tool available at https://www.statstodo.com/CombineMeansSDs.php. When data were reported as means with confidence intervals the standard deviation for each group was calculated by dividing the length of the confidence interval by 3.92 and then multiplying by the square root of the sample size, as reported by the Cochrane Handbook for Systematic Reviews of Interventions (https://training.cochrane.org/handbook/current/chapter-06#section-6-5-2-2). If the interquartile range (IQR, i.e., the difference between the third and first quartile values) was available, rather than standard deviation (SD), the standard deviation for each group was estimated with the formula proposed by the Cochrane handbook: SD = IQR/1.35 (https://training.cochrane.org/handbook/current/chapter-06#section-6-5-2–5). When median and range (minimum and maximum) or median, the first and the third quartile values were reported, the mean ± SD was estimated using an online tool available at https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html, which was also used to verify lack of data skewness. If the data were not skewed, mean and SD were used for calculation of the pooled estimate. In two cases [17, 24], the freely available software WebPlotDigitizer (version 4.6, https://automeris.io/WebPlotDigitizer/) was used to extract data from graphs. The data were independently extracted from eligible papers by two researchers (M.G. and S.T.), who subsequently cross-checked the data and resolved discrepancies.

Assessment of study quality

Two reviewers (M.G. and S.C.) independently assessed the quality of the included studies using the Q-Genie tool and any disagreement was resolved by consensus or by a third reviewer (S.T.). The Q-Genie tool has been validated for assessing the quality of genetic association studies and is a Likert-type scale consisting of eleven questions (item 1, rationale for study; item 2, selection and definition of outcome of interest; item 3, selection and comparability of comparison groups; item 4, technical classification of the exposure; item 5, non-technical classification of the exposure; item 6, other sources of bias; item 7, sample size and power; item 8, a priori planning of analyses; item 9, statistical methods and control for confounding; item 10, testing of assumptions and inferences for genetic analyses; and item 11, appropriateness of inferences drawn from results), with a maximum score of 7 and a minimum score of 1 for each question [25]. For studies with a control group, a score < 35 indicates poor quality, 35–45 moderate quality, and > 45 good quality. For studies without a control group, a score < 32 indicates low quality, 32–40 moderate quality, and > 40 good quality.

Statistical analysis

The mean difference (MD) and its 95% confidence intervals were used as summary statistics in meta-analyses of continuous variables if the outcome measures were on the same scale in all studies, otherwise the standard mean difference (SMD) and its 95% confidence intervals were derived for each study and used for pooling the results. If repeated time observations were reported in a single study, data with a normal distribution at the longest time point were used to determine the effect size of each study. With regard to the pooled risk of a given adverse effect, the odds ratio (OR) with 95% confidence intervals was calculated for each study and used as the summary effect size. Studies, irrespectively from the effect size, were pooled with the random-effect model, which assumes that the true effect size may differ from study to study due to differences (heterogeneity) among studies [26]. The inverse variance weighted average statistical method was used for all comparisons of MD or SMD, while the Mantel–Haenszel statistical method was used for pooling ORs. Heterogeneity between studies was estimated using the chi-squared-based Cochran's *Q* test and its statistical significance was set at $P < 0.10$. Between-study heterogeneity was also estimated by the I^2 statistic, with an I^2 value ranging from 0 to 25% indicating insignificant heterogeneity, 26–50% implying low heterogeneity, 51–75% representing medium heterogeneity, and 76–100% indicating high heterogeneity. Meta-analyses were performed for each gene polymorphism and outcome of interest when data were available from at least three studies, and subgroup analyses were performed based on the type of pain (i.e., labor pain or post-cesarean pain). In addition, leave-one-out sensitive meta- analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual results one at a time and recalculating the pooled OR estimates for the remaining results. All meta-analyses were conducted using the Review Manager (RevMan) 5.4.1 software and the statistically significant threshold for pooled analyses was set at $P < 0.05$. The presence of publication bias was

assessed graphically by drawing funnel plots and statistically by the Egger's test if at least ten studies were present in the pooled analysis. If there was statistical evidence of asymmetry in the funnel plot (Egger's P-value < 0.10), the "trim-and-fill" method was used to adjust the overall effect estimate. The ProMeta version 2 software (INTERNOVI di Scarpellini Daniele s.a.s., Cesena FO, Italy) was used for performing leave-one-out meta-analyses and assessment of publication bias and trim-and-fill analysis.

Results

Literature search

A total of 1198 studies were identified from databases (PubMed, $n = 558$; Web of Knowledge, $n = 499$; Cochrane Library, $n = 139$; OpenGray, $n = 0$) and manual literature search ($n = 2$). After removing 202 duplicates and 969 reports not fulfilling inclusion and exclusion criteria, 27 studies, all observational studies in study design, published between 2008 and 2024 were finally included in the systematic review [17–24, 27–45]. A detailed flowchart of the study selection process is shown in Fig. 1.

General characteristics and quality of included studies

The summarized characteristics of the included studies are shown in Table 1. Twelve studies included Asian patients from China and Singapore [17, 18, 20, 24, 28, 29, 37, 39, 41–45]; 9 studies enrolled multi-ethnic patients from the USA, Canada, Switzerland, Israel, and Singapore [19, 21–23, 27, 31, 33, 34, 36]; 4 studies included Caucasian patients from Europe [30, 32, 35, 38]; and 1 study enrolled patients from the Middle East [40]. Seventeen studies recruited patients with post-cesarean pain [18–20, 22–24, 28–31, 35–39, 41, 42], 9 studies enrolled patients with labor pain [17, 27, 32–34, 40, 43–45], and 1 study included patients with both types of pain [21]. In terms of prescribed opioids, morphine was administered in 7 studies [18, 19, 28, 29, 35, 38, 41], sufentanil in 8 studies [17, 24, 30, 32, 37, 43–45], fentanyl in 6 [20, 27, 33, 34, 39, 40], codeine in 2 [23, 31], hydrocodone and hydromorphone in 2 [22, 36], fentanyl with morphine in 1 [21], and sufentanil with tramadol in 1 study [42]. Overall, a total of 12 candidate polymorphic genes were analyzed (*OPRM1*, *COMT*, *CYP2D6*, *CYP3A4*, *ABCB1*, *ABCC3*, *UGT2B7*, *CGRP*, *OPRK1*, *OPRD1*, *KCNJ6*, *KCNJ9*), among which *OPRM1* rs1799971 was investigated in 17 studies [17–23, 27, 29, 30, 32–34, 37, 38, 40, 42]. As for the outcome investigated, the majority of the included studies assessed pain score after opioid administration ($n = 20$), followed by total opioid consumption ($n = 15$), analgesic satisfaction ($n = 4$), and half-maximal effective opioid concentration (EC50, $n = 2$). In addition, pruritus, nausea, and vomiting were the most frequent types of adverse effects investigated. The Q-Genie tool indicated that 22 studies were of good quality, 4 were of moderate quality, and 1 study was of low quality, indicating an overall good methodological quality of the considered studies. The results of the quality assessment for each study are presented in Supplementary Table 2. Meta-analyses with at least three studies were conducted for OPRM1 rs1799971, ABCB1 rs1128503, COMT rs4680, CYP3A4 rs2242480, and genetically predicted CYP2D6 phenotype. Results of quantitative data synthesis for OPRM1 rs1799971 are presented below, while results for the other genetic variants are described and presented in the Supplementary Material.

Association of *OPRM1* rs1799971 with pain score after opioid treatment

Thirteen cohorts from 12 studies, enrolling a total of 3320 patients, were available for the meta-analysis of the dominant model of *OPRM1* rs1799971 (GG or AG vs AA) and association with pain score after opioid treatment [18–23, 27, 30, 34, 37, 40, 42]. The pooled results showed no association with pain score under the dominant model of rs1799971 (Fig. 2A), both in the overall analysis, as well as in the subgroup of subjects with pain after cesarean section or patients with labor pain. In the overall analysis, a significant funnel plot asymmetry was detected according to the Egger's test ($P = 0.001$) and the subsequent trim-and-fill analysis identified six missing studies on the right side of the funnel plot (Supplementary Fig. 1). The adjusted trim-and-fill effect size was significant (SMD = 0.18, 95% CI 0.08–0.28. $P = 0.001$), indicating that the observed effect size was influenced by missing studies.

Six studies, including a total of 2344 patients, were available for the meta-analysis between the recessive model of *OPRM1* rs1799971(GG vs AG or AA) and pain score after opioid treatment [18–20, 23, 37, 42]. The Cochran's Q test revealed absence of between-study heterogeneity under the recessive model ($I^2 = 0\%$, $P = 0.72$). A significant difference of pain score was detected in the pooled analysis (Fig. 2B), which included patients with post-cesarean pain only (MD: 0.06; 95% CI: 0.00–0.12; $P = 0.04$).

Association of *OPRM1* rs1799971 with total opioid consumption

Ten cohorts from 9 studies [17–23, 37, 42] were included in the meta-analysis of the dominant model of *OPRM1* rs1799971 and association with total opioid consumption. In the overall analysis (Fig. 3A), the pooled results indicated that individuals carrying the G allele (AG or GG) of

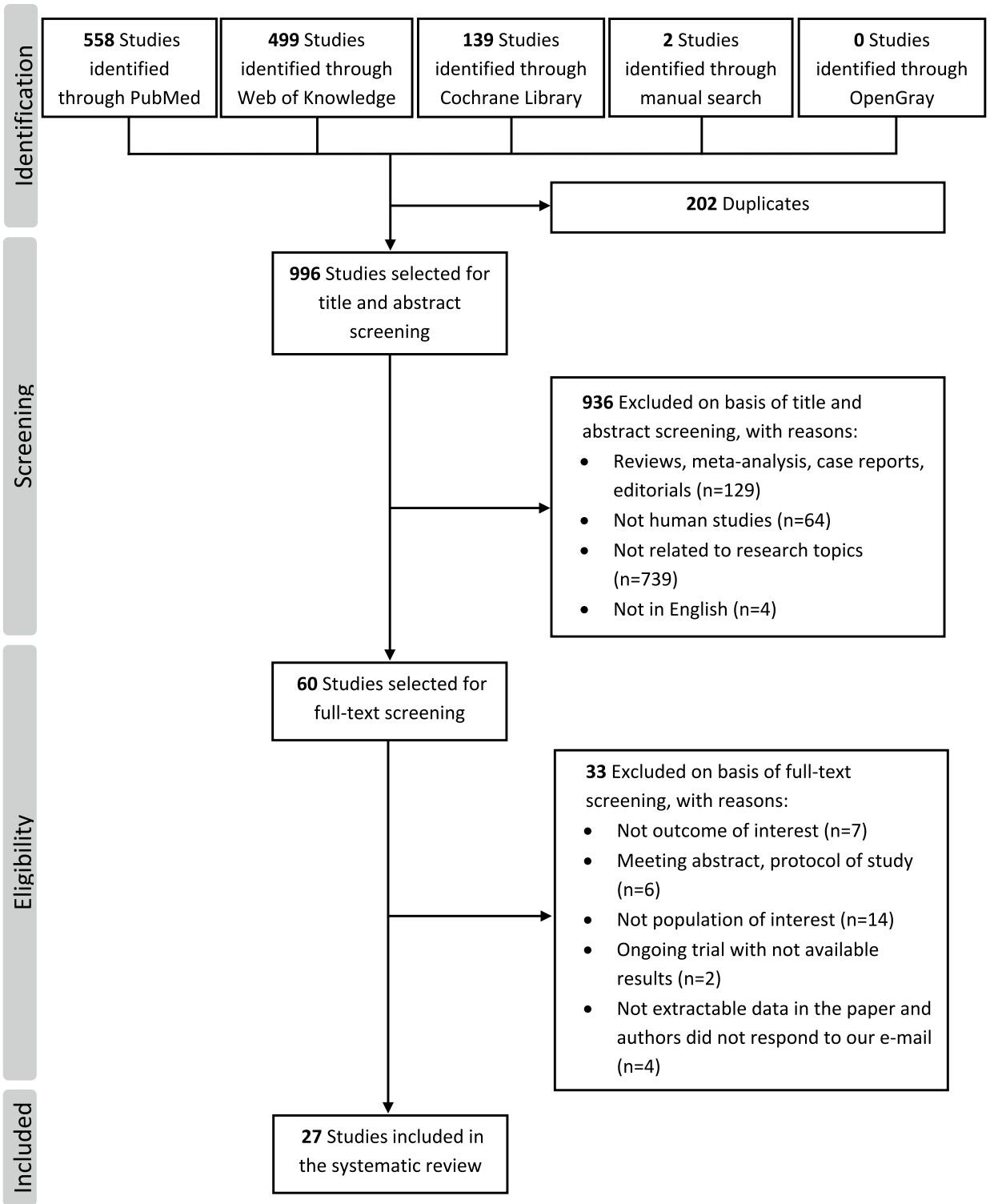

Fig. 1 Flowchart of literature search and selection process of eligible studies

rs1799971 required higher opioid doses for pain management compared to AA homozygous subjects (SMD: 0.26; 95% CI: 0.09–0.44; $P = 0.003$). The results were stable in sensitivity analysis (Supplementary Fig. 2A) with pooled SMD values ranging between 0.26 (95%CI: 0.09–0.44, $P = 0.003$) and 0.46 (95%CI: 0.26–0.67, $P < 0.0001$), and no publication bias was detected in the funnel plot (Egger's test P-value = 0.431, Supplementary Fig. 3). In addition

Table 1 Main characteristics of studies included in the systematic review

Author, year [Ref]	Country (ethnicity)	Type of pain	Opioid (adm. route)	Total N subjects (N genotyped)	Gene variant (MAF of rs1799971/P_{HWE}) (genotyping method)	Analgesic outcome of interest	Side effects	*Time of outcomes assessment*
Landau R, 2008 [27]	Switzerland (Mixed)	L	Fentanyl (intrathecal)	224 (158)	*OPRM1* rs1799971 (0.18/0.10) (pyrosequencing)	① (VRS) ③ (μg)	-	Over first 60 min after opioid administration
Sia AT, 2008 [18]	Singapore (Chinese)	P	Morphine (intravenous)	631 (588)	*OPRM1* rs1799971 (0.34/0.007) (TaqMan real-time PCR)	① (VAS) ② (mg)	Vomit, nausea, pruritus	Over first 24 h post-surgery
Tan E, 2009 [19]	Singapore (Mixed)	P	Morphine (intravenous)	1066 (994)	*OPRM1* rs1799971 (0.39/0.012) (TaqMan real-time PCR)	① (VAS) ② (mg)	-	Over first 24 h post-surgery
Sia AT, 2010 [28]	Singapore (Chinese)	P	Morphine (intravenous)	631 (620)	*ABCB1* rs1128503, rs2032582, rs1045642 (PCR–RFLP)	① (VAS) ② (mg)	CPSP	① and ② over first 24 h post-surgery; side effect at 3 months post-surgery
Tsai FF, 2010 [29]	China (Chinese)	P	Morphine (epidural)	217 (212)	*OPRM1* rs1799971 (0.33/0.43) (light cycler real-time PCR)	-	Pruritus	At 24 h post-surgery
Wong CA, 2010 [21]	USA (Mixed)	L /P	Fentanyl and morphine (intrathecal)	L: 210 (190) P: 105 (103)	*OPRM1* rs1799971 (L: 0.15/ < 0.001; P: 0.14/0.36) (pyrosequencing)	① (VAS) ② (μg/mg) ④ (VAS)	Vomit, nausea, pruritus	During labor: ① at 1st analgesia request, 10 min after opioid administration and at 2nd analgesia request; ② during labor; ④ at 1 h after delivery; side effects at 2nd request for analgesia Post-operative period: ① at 1st rescue analgesia request; ② over 72 h post-surgery; ④ at 24 h post-surgery; side effects over first 24 h post-surgery
De Capraris A, 2011 [30]	Italy (Caucasian)	P	Sufentanil (epidural)	80 (22)	*OPRM1* rs1799971 (0.11/0.55) (Sanger sequencing)	① (VAS)	-	At 6, 24, 48 h post-surgery

Table 1 (continued)

Author, year [Ref]	Country (ethnicity)	Type of pain	Opioid (adm. route)	Total N subjects (N genotyped)	Gene variant (MAF of rs1799971/P_{HWE}) (genotyping method)	Analgesic outcome of interest	Side effects	*Time of outcomes assessment*
VanderVaarrt S, 2011 [31]	Canada (Mixed)	P	Codeine (oral)	80 (45)	*CYP2D6* *2, *3, *4, *5, *6, *7, *8, *9, *10, *12, *14, *17, *29, *41, *XN (multiplexed microarray assay)	① (VAS) ② (mg/kg)	-	At day 2 and 3 post-surgery
Camorcia M, 2012 [32]	Italy (Caucasian)	L	Sufentanil (epidural)	77 (57)	*OPRM1* rs1799971 (0.22/0.18) (pyrosequencing)	③ (μg)	-	Over first 30 min after opioid administration
Landau R, 2013 [33]	USA (Mixed)	L	Fentanyl (intravenous)	OPRM1: 106 (98) COMT: 106 (100)	*OPRM1* rs1799971 (0.22/0.97), *COMT* rs4680 (pyrosequencing)	④ (NVPS)	-	At 15 min after opioid administration
Boswell MV, 2013 [22]	USA (Mixed)	P	Hydrocodone and hydromorphone (oral)	158 (158)	*OPRM1* rs1799971 (0.10/0.01) (bead-based multiplex assay)	① (VAS) ② (mg)	Vomit, nausea, pruritus, confusion, weakness, constipation, dizziness, dry mouth, loss of appetite, respiratory depression, sleep disturbance, sonnolence, sweating,	At 72 h post-surgery
Ginosar Y, 2013 [34]	USA/Israel (Mixed)	L	Fentanyl (epidural)	125 (125)	*OPRM1* rs1799971 (0.15/0.85) (PCR–RFLP)	① (VAPS)	-	At request for analgesia
Quinta R, 2014 [35]	Portugal (Caucasian)	P	Morphine (NR)	55 (55)	*CYP2D6* rs1135840, rs35742686, rs3892097, rs5030655 (TaqMan real-time PCR)	-	Pruritus	Over first 12 h post-surgery
Stauble ME, 2014 [36]	USA (Mixed)	P	Hydrocodone and hydromorphone (oral)	156 (156)	*CYP2D6* rsIDs NR (xTAG Mutation Detection assay)	① (VAS) ② (mg)	-	At day 3 after surgery

Table 1 (continued)

Author, year [Ref]	Country (ethnicity)	Type of pain	Opioid (adm. route)	Total N subjects (N genotyped)	Gene variant (MAF of rs1799971/P_{HWE}) (genotyping method)	Analgesic outcome of interest	Side effects	*Time of outcomes assessment*
Baber M, 2015 [23]	Canada (Mixed)	P	Codeine (oral)	255 (98)	*OPRM1* rs1799971 (0.21/0.13), *COMT* rs4633, rs4818, rs4680, *CYP2D6* rsIDs NR, *ABCB1* rs1128503, rs2032582, rs1045642, *UGT2B7* rs7439366 (TaqMan real-time PCR)	① (VAS) ② (mg/kg)	-	Over first 48 h post-surgery
Xu GH, 2015 [37]	China (Chinese)	P	Sufentanil (epidural)	180 (161)	*OPRM1* rs1799971 (0.36/0.22) (Sanger sequencing)	① (VAS) ② (mL) ④ (VRS)	Nausea, pruritus	① at 6, 12, 24 h post-surgery; ② ④ and side effects over first 24 h post-surgery
Pettini E, 2018 [38]	Italy (Caucasian)	P	Morphine (intrathecal)	63 (63)	*OPRM1* rs1799971 (0.15/0.67) (TaqMan real-time PCR)	-	Pruritus, PONV	At 24 h and 48 h post-surgery
Xie W, 2018 [39]	China (Chinese)	P	Fentanyl (epidural)	548 (521)	*CGRP* 4218 T/C (PCR–RFLP)	① (VAS) ② (μg/kg)	Vomit, nausea, pruritus	Over first 24 h post-surgery
Lv J, 2018 [24]	China (Chinese)	P	Sufentanil (intravenous)	208 (208)	*CYP3A4* rs2242480 (PCR–RFLP)	① (NRS) ② (μg)	-	At 8 h, 24 h, and 48 h post-surgery
Zhang J, 2018 [20]	China (Chinese)	P	Fentanyl (epidural)	240 (240)	*OPRM1* rs1799971 (0.35/0.72), *ABCB1* rs1128503, *CYP3A4* rs2242480 (Sanger sequencing)	① (VAS) ② (μg/kg)	Vomit, nausea, dizziness	① at 12 h and 24 h post-surgery; ② at 24 h and 48 h post-surgery; side effects at a not specified time
Zgheib NK, 2018 [40]	Lebanon (Middle Eastern)	L	Fentanyl (epidural)	250 (220)	*OPRM1* rs1799971 (0.12/0.06), *OPRM1* rs9479757 *OPRM1* rs2075572 (TaqMan real-time PCR)	① (VAS) ④ (VAS)	Vomit, nausea, pruritus	① at 1st request for analgesia, at 10, 20, and 30 min after opioid administration and at the 2nd request for analgesia; ④ over 1st 2 h after delivery; side effects at a not specified time

Table 1 (continued)

Author, year [Ref]	Country (ethnicity)	Type of pain	Opioid (adm. route)	Total N subjects (N genotyped)	Gene variant (MAF of rs1799971/P_{HWE}) (genotyping method)	Analgesic outcome of interest	Side effects	*Time of outcomes assessment*
Kung CC, 2018 [41]	China (Chinese)	P	Morphine (epidural)	217 (217)	*CYP3A4* rs2242480, rs28371759, *CYP2D6* rs3892097, rs28365063, *UGT2B7* rs7439366, rs7439152, *ABCB1* rs1045642, *ABCC3* rs2277624, *OPRK1* rs1051660, *OPRD1* rs1042114, *KCNJ6* rs2070995, *KCNJ9* rs2737703 (TaqMan real-time PCR)	-	Pruritus	Over first 24 h post-surgery
Wang L, 2019 [42]	China (Chinese)	P	Sufentanil and tramadol (intravenous)	830 (266)	*OPRM1* rs1799971 (0.30/0.020), *COMT* rs4680 (TaqMan real-time PCR)	① (VAS) ② (mL)	CPSP	① at 24 h and 48 h post-surgery; ② at 12 h, 24 h and 48 h post-surgery; side effect at 3 months post-surgery
Xiaohong Y, 2020 [43]	China (Chinese)	L	Sufentanil (epidural)	97 (97)	*COMT* rs4680 (light cycler real-time PCR)	② (mL)	-	NR
Chen Y, 2023 [17]	China (Chinese)	L	Sufentanil (epidural)	356 (240)	*OPRM1* rs1799971 (0.36/0.87), *COMT* rs4680 (Sanger sequencing)	② (μg)	PONV, pruritus, urine retention, fever, tachycardia, hypotension, respiratory inhibition,	② during labor; side effects over first 20 min after opioid administration
Shu X, 2024 [44]	China (Chinese)	L	Sufentanil (epidural)	600 (573)	*CYP3A4* rs2242480 (TaqMan real-time PCR)	① (VAS) ② (mg)	Nausea, vomit, pruritus, hypotension, dizziness, uroschesis	② during labor; ① and side effects at 1 h and 3 h after opioid administration
Li W, 2024 [45]	China (Chinese)	L	Sufentanil (epidural)	239 (239)	*ABCB1* rs1128503, *ABCB1* rs1045642 (PCR–RFLP)	① (VAS)	Dizziness, nausea, urinary retention, constipation, pruritus	① at 1 h and 2 h after opioid administration; side effects after opioid administration

①, pain score after opioid administration based on any patient-reported scale; ②, total opioid consumption; ③, 50% effective opioid dose (ED50); ④, analgesic satisfaction based on any patient reported scale; pain scale or unit of measure used is indicated in the brackets. Abbreviations: *Adm*., administration; *CPSP*, chronic postsurgical pain; *L*, labor pain; *MAF*, minor allele frequency; *NR*, not reported; *NRS*, Numerical Rating Scale; *NVPS*, Numerical Verbal Pain score; *P*, post-cesarean pain; P_{HWE}, P-value of Hardy Weinberg Equilibrium; *PONV*, postoperative nausea and vomiting; *RFLP*, restriction fragment length polymorphism; *USA*, United States of America; *VAS*, Visual Analog Score; *VAPS*, Visual Analogue Pain scale; *VRS*, Verbal Rating Scale

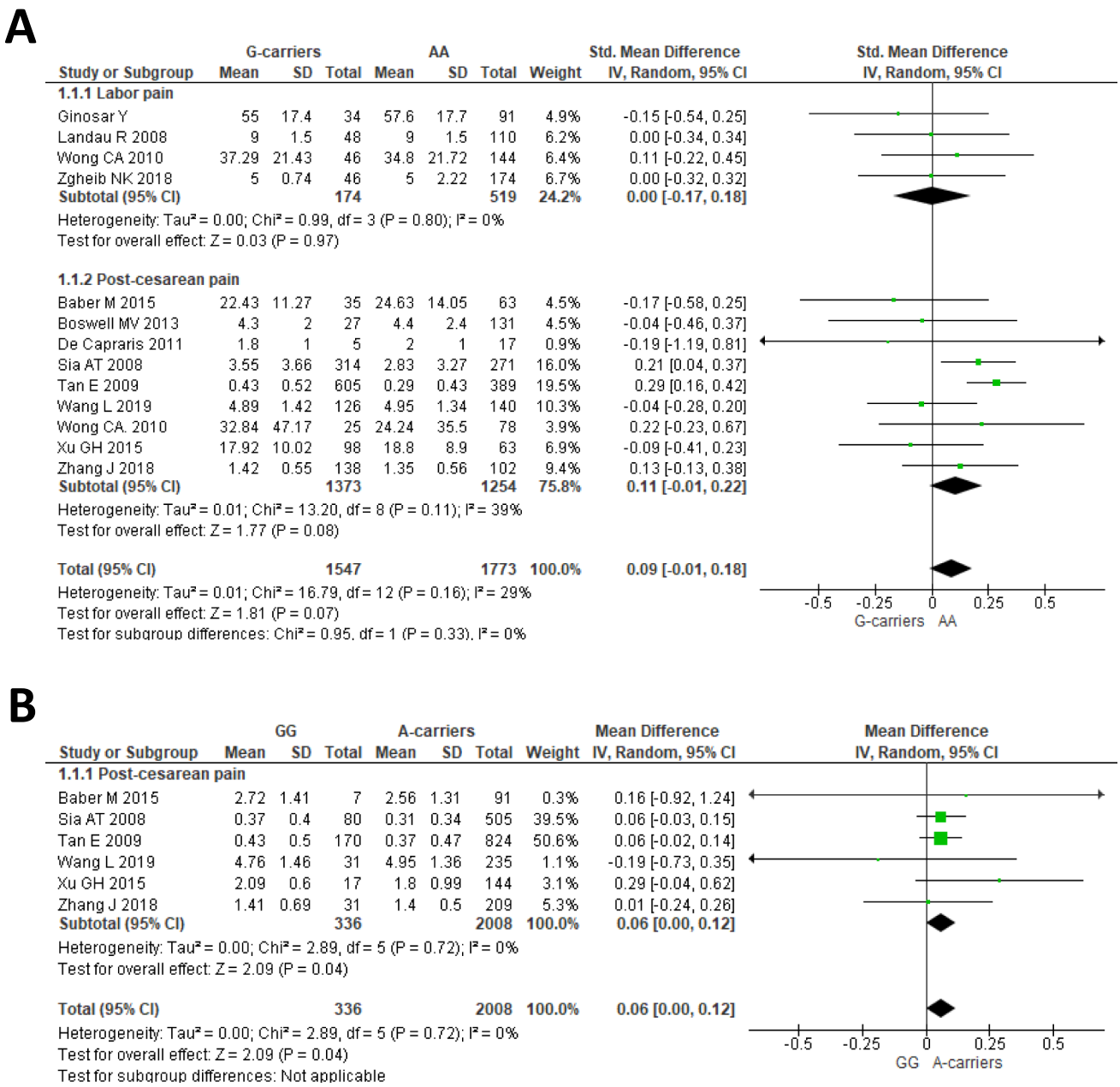

Fig. 2 Forest plots of the standardized mean differences of pain score after opioid treatment for relief of labor pain and post-cesarean pain, for the dominant model (GG or AG vs AA) (**A**) or for the recessive model (GG vs AG or AA) (**B**) of *OPRM1* rs1799971. Note that the diamond symbol in B is shown twice to emphasize the lack of studies for the subgroup of patients with labor pain

(Fig. 3A), a significant effect of the dominant model of rs1799971 on total opioid consumption was detected also in the subgroups of subjects with labor pain (SMD: 0.25; 95% CI: 0.05–0.44; $P=0.01$) and post-cesarean pain (SMD: 0.27; 95% CI: 0.05–0.48; $P=0.01$).

Six studies including patients with post-cesarean pain only [18–20, 23, 37, 42] were available for the association between the recessive model of *OPRM1* rs1799971 and total opioid consumption (Fig. 3B). A significant difference was observed among carriers of rs1799971 GG genotype in comparison to carriers of the A-allele in terms of opioid dose requirement for pain management of post-cesarean pain (SMD: 0.59; 95% CI: 0.17–1.02; $P=0.006$, Fig. 3B). The results were stable in sensitivity analysis (Supplementary Fig. 2B), with pooled SMD values ranging between 0.41 (95%CI: 0.09–0.72, $P=0.011$) and 0.67 (95%CI: 0.20–1.14, $P=0.005$).

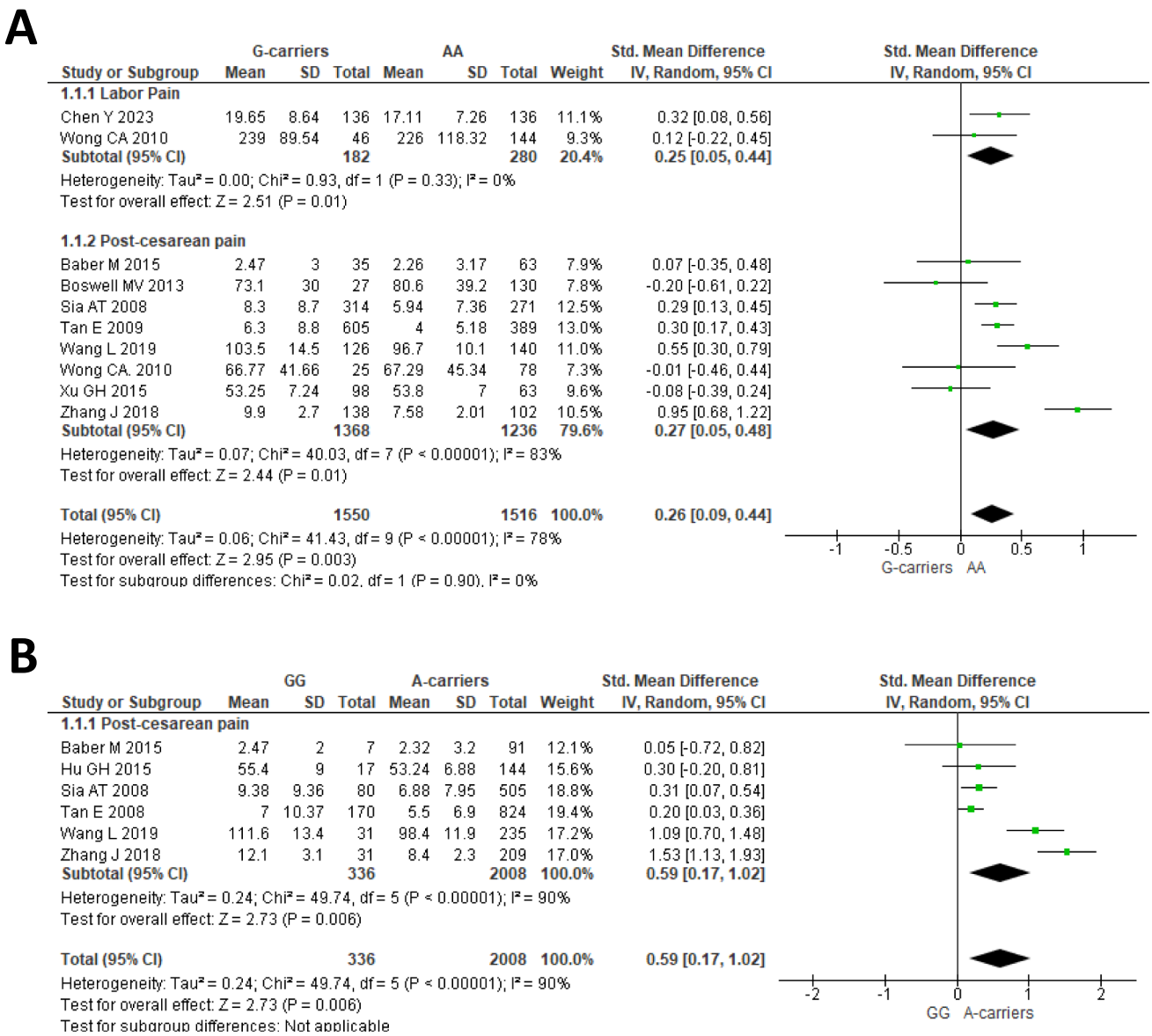

Fig. 3 Forest plots of the standardized mean differences of total opioid consumption after opioid treatment for relief of labor pain and post-cesarean pain, for the dominant model (GG or AG vs AA) (**A**) or for the recessive model (GG vs AG or AA) (**B**) of *OPRM1* rs1799971. Note that the diamond symbol in B is shown twice to emphasize the lack of studies for the subgroup of patients with labor pain

Association of *OPRM1* rs1799971 with patient's analgesic satisfaction and risk of opioid side effects

Four studies [21, 27, 37, 40] involving 669 subjects were available for the effect of the dominant model of *OPRM1* rs1799971 (GG or AG vs AA) on patient's analgesic satisfaction (Fig. 4). No significant differences were detected in the pooled results between carriers of the rs1799971 G allele in comparison to carriers of the rs1799971 AA genotype, in both the overall and subgroup analyses (Fig. 4). As regard to the association of *OPRM1* rs1799971 with the risk of opioid side effects, meta-analyses with at least three studies were available for pruritus ($N_{studies} = 9$), nausea ($N_{studies} = 7$), and vomiting ($N_{studies} = 5$). No significant differences were found in the overall analyses or in the subgroups of patients under either the dominant or the recessive genetic model of rs1799971 (Supplementary Figs. 4, 5 and 6).

Discussion

In the present study we conducted a systematic review and meta-analysis of the association between genetic polymorphisms and efficacy and safety of opioids administered

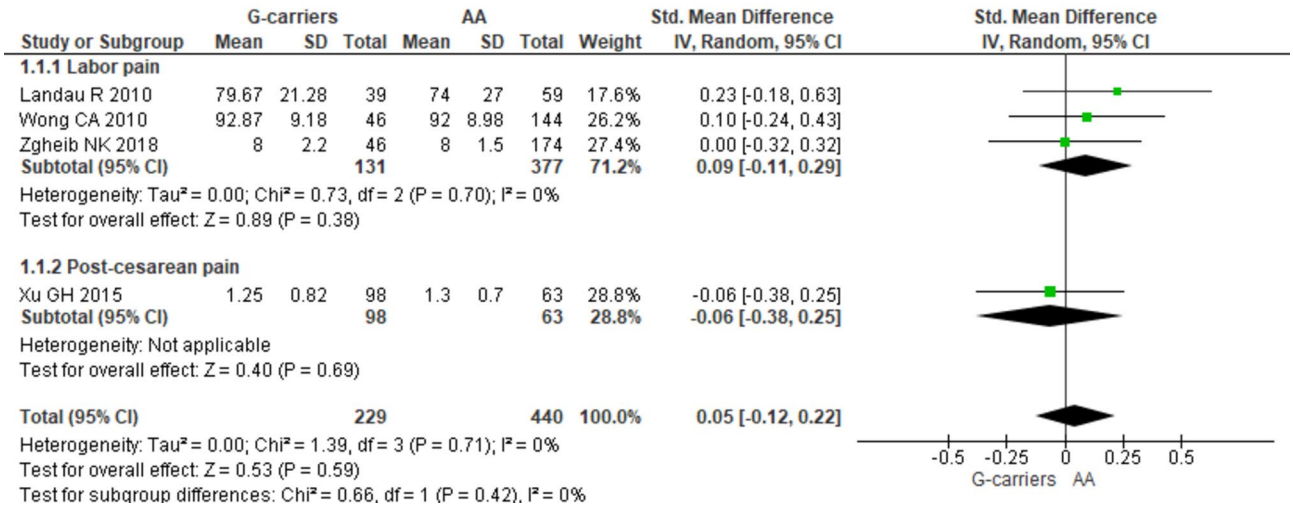

Fig. 4 Forest plot of the standardized mean difference of patient's analgesic satisfaction after opioid treatment for relief of labor pain and post-cesarean pain, for the dominant model of *OPRM1* rs1799971 (GG or AG vs AA)

for pain relief during labor or after cesarean section. The pooled results of good/moderate quality of the included studies highlight *OPRM1* rs1799971 as a determinant of opioid consumption for labor and post-cesarean pain relief, with carriers of the variant G allele requiring higher opioid doses compared to AA subjects. The robustness of this finding was proven by sensitivity meta-analysis that showed stability of the pooled effect estimate. In addition, the recessive model of rs1799971 was found associated with pain scores and total opioid consumption of patients with post-cesarean pain. Conversely, all overall meta-analyses conducted for *ABCB1* rs1128503, *COMT* rs4680, *CYP3A4* rs2242480, and genetically predicted *CYP2D6* phenotype revealed no significant association with the clinical endpoint investigated, which included pain score, total opioid consumption, patient's analgesic satisfaction, and opioid side effects.

OPRM1 rs1799971 (118 A > G) is a functional variant that has long been considered as one of the most promising genetic candidates for pain sensitivity and opioid analgesia [46]. *OPRM1* rs1799971 leads to a non-synonymous A > G substitution at position 118 of *OPRM1*, which exchanges an Asn residue at amino acid position 40 of the N-terminal extracellular region of the receptor for an Asp. In wild-type receptors, the Asn residue serves as a site for N-glycosylation, which is completely removed by the amino acid exchange for Asp [47]. The first molecular consequence discovered for rs1799971 was an approximately three times higher affinity of beta-endorphin for the variant MORs compared to the most common allelic form of the receptor. However, such evidence was not confirmed for exogenous opioids, such as fentanyl and morphine, for which the binding affinity to MOR resulted unaltered [48]. Subsequently, rs1799971 was reported to reduce the signaling efficiency of MOR by more than a third when induced by exogenous opioids [49] and to a decrease of MOR expression, with carriers of the G allele showing halved *OPRM1* mRNA levels in the brain compared to wild-type A carriers [50]. Interestingly, rs1799971 appears to affect MOR expression in the brain via a genetic-epigenetic interaction conferred by the minor 118G allele: rs1799971 replaces the CA nucleotides at position 117/118 with CG, leading to the introduction of a new CpG site that confers a higher methylation degree, which in turn impedes MOR upregulation in brain tissues [51]. Since opioid-mediated analgesia mainly relies on MOR density, carriers of the variant G-allele have been postulated to exhibit poor response to opioids. Nevertheless, to date, no standardized genotype-to-phenotype groupings have been proposed for *OPRM1* and none of the current guidelines recommends the *OPRM1* genotype-guided dosing of opioids in any pain setting [52].

Our pooled results showed that carriers of the variant rs1799971 G allele require higher opioid doses for achieving adequate pain relief compared to wild-type homozygous patients. These findings differ from a previous meta-analysis published in 2013 [53], which showed that women carrying the rs1799971 G allele require less fentanyl doses for labor pain compared with those with the AA genotype. However, such discrepant result can be ascribed to the smaller sample size of the previous meta-analysis ($N = 460$) compared to the one included in the present study ($N = 3066$). On the other hand, our results are in the same direction of association as compared to previous meta-analyses evaluating the relationship between rs1799971 and opioid consumption in patients with postsurgical pain [54, 55]. It is noteworthy that previous meta-analyses focusing on different types of postsurgical pain [54, 55] included very few studies on

post-cesarean pain, which in turn may differ from other types of post-operative pain [56]. In addition, our pooled results showed a statistically significant association between the recessive model of rs1799971 and pain score after opioid treatment in patients with post-cesarean pain, with carriers of rs1799971GG genotype showing higher pain scores compared to carriers of the A allele. On the other hand, the present meta-analysis revealed no significant association between the dominant model of rs1799971 and pain score after opioid treatment. Nevertheless, the trim-and-fill-adjusted result was significant, suggesting that the pooled effect size may be underestimated due to possible missing studies. This latter result is in line with results of the above-mentioned meta-analyses conducted on patients with post-surgical pain, which reported significant higher postoperative pain scores after opioid treatment among carriers of the G allele of rs1799971 when compared to AA individuals [54, 55]. As regard to the association of *OPRM1* rs1799971 with opioid side effects, no association was found in overall analyses, as well in the subgroups of patients with labor pain and post-cesarean pain. Although sparse evidence exists on the association of rs1799971 with nausea and vomiting induced by opioids when administered for postoperative pain [57, 58], our findings are consistent with the results of a recent meta-analysis that showed no impact of rs1799971 on the risk of nausea or vomiting after opioid administration in patients with postoperative pain [54].

We acknowledge some limitations of the present study that should be considered when interpreting the results. First, the sample size of our meta-analyses was relatively small, especially when meta-analyses were conducted in the subgroup of patients with labor pain or when the role of SNPs other than rs1799971 was investigated. In addition, Hardy–Weinberg imbalance was found in some of the included studies, so we cannot rule out population stratification or selection bias in these studies. Therefore, the results of the present meta-analysis should be interpreted with caution. Despite this, only 1 (4%) of the included studies was rated of poor quality, 4 studies (12%) were of moderate quality, and 22 studies (81%) of good quality, suggesting an overall good methodological quality of the considered studies. Second, we attempted to conduct a comprehensive systematic review of all available published reports; however, corresponding authors of some eligible studies were unable to provide the data requested for the effect size calculation or did not respond to our email. In addition, 4 non-English reports were identified and excluded from the systematic review due to limited translation resources. This may explain, at least in part, the asymmetry detected in the funnel plot for the association of rs1799971 with pain score. Nevertheless, the trim-and-fill-adjusted result was significant, suggesting that the pooled effect size may have been underestimated. Third, the studies included in the present systematic review differ with respect to the type of pain (i.e., labor pain or post-cesarean pain). However, for each gene polymorphism and outcome of interest, subgroup analyses were performed based on the type of pain. Moreover, the included studies differ with respect to some other characteristics, such as type of administered opioid, route of administration, patients' ethnicity, and genotyping method, which may have an impact on the effect size estimation. The opioids investigated in the studies included in this systematic review differ in their pharmacokinetic and pharmacodynamic properties. For example, morphine, codeine (which is converted to morphine), fentanyl, and sufentanil act as complete agonists with high selectivity for μ-opioid receptors (MORs), their primary site of action. Although hydrocodone has a relatively weak binding affinity for MORs, it is metabolized by CYP2D6 through demethylation at the 3-carbon position to hydromorphone, a metabolite with significantly higher MOR affinity. Tramadol, a 4-phenyl-piperidine derivative of codeine, also shows high selectivity for MORs, but acts as a partial agonist at these receptors. However, despite these differences all opioid analgesics share the common characteristic that they interact with opioid receptors to relieve pain and that they have certain side effects, although some of these are more common with one drug than another. Nevertheless, the limited number of studies included in each meta-analysis hampered the possibility to deeply investigate factors potentially causing between-study heterogeneity, which emerged in some of the meta-analyses conducted. Lastly, due to the lack of access to original data of primary studies, our meta-analyses are based on unadjusted estimates, so the pooled results might be confounded by relevant covariates, such as age, sex, comorbidities, and adjuvant multimodal analgesia administered to manage labor and post-cesarean pain. Therefore, a meta-analysis of individual participant data should be performed in the future to obtain pooled estimates for SNPs adjusted for confounding variables.

Conclusions

The present systematic review and meta-analysis reviewed the relationship between genetic variants and efficacy and safety of opioids for pain relief during labor or after cesarean section. The pooled results highlight *OPRM1* rs1799971 as a genetic factor with potential clinical utility in predicting opioid dose requirement in such pain settings. If further corroborated by larger studies, this pharmacogenetic factor could potentially assist clinicians in optimizing maternal pain management during labor and after cesarean section. However, given the insufficient evidence for other polymorphic variants, there remains a need to investigate the impact of genetic variability on the efficacy and safety of opioid

medications in the contexts of labor-and post-cesarean pain management.

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Data availability Data is provided within the manuscript or supplementary information files.

Declarations

Conflict of interest The authors declare no competing interests.

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