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ORIGINAL RESEARCH

Assessing the Impact of Morphine on Adverse Outcomes in ACS Patients Treated with P2Y12 Inhibitors: Insights from Multiple Real-World Evidence

Chenxi Ouyang[1,2], Changjiang Meng[3], Fei Li[3], Shanshan Nie[3], Liying Gong[4], Yu Cao[5], Hong Yuan[3,5], Zeying Feng[6]

[1]School of Pharmacology, University of South China, Hengyang, Hunan, People's Republic of China; [2]The Affiliated Nanhua Hospital, Department of Pharmacy, Hengyang Medical School University of South China, Hengyang, Hunan, People's Republic of China; [3]Center of Clinical Pharmacology, The Third Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China; [4]Department of Critical Care Medicine, The Third Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China; [5]Department of Cardiology, The Third Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China; [6]Clinical Trial Institution Office, Liuzhou Hospital of Guangzhou Women and Children's Medical Center, Liuzhou, Guangxi, People's Republic of China

Correspondence: Zeying Feng, Clinical Trial Institution Office, Liuzhou Hospital of Guangzhou Women and Children's Medical Center, No. 50 Boyuan Avenue, Liuzhou, Guangxi, 545000, People's Republic of China, Email fengzeying@foxmail.com

Purpose: Mechanistic studies showed that morphine may impair the antiplatelet effect of P2Y12 inhibitors. However, Several clinical studies with cardiovascular events as an outcome are contradictory, and the broader impact of this drug interaction on additional organ systems remains uncertain. With multisource data, this study sought to determine the effects of morphine interaction with P2Y12 inhibitors on major adverse outcomes comprehensively, and identify the warning indicators.

Patients and Methods: Interaction signals were sought in 187,919 safety reports from the FDA Adverse Event Reporting System (FAERS) database, utilizing reporting odds ratios (repOR). In a cohort of 5240 acute coronary syndrome patients, the analyses were validated, and the biological effects of warning indicators were further studied with Mendelian randomization and mediation analysis.

Results: Potential risk of renal system adverse events in patients cotreated with morphine is significantly higher in FAERS (repOR 4.83, 95% CI 4.42–5.28, false discovery rate adjusted-P =3.55*10^{-209}). The analysis of in-house patient cohorts validated these results with an increased risk of acute kidney injury (adjusted OR: 1.65; 95% CI: 1.20 to 2.26), and we also found a risk of myocardial infarction in patients treated with morphine (adjusted OR: 1.55; 95% CI: 1.14 to 2.11). The Morphine group exhibited diminished Plateletcrit (PCT) levels post-surgery and lower PCT levels were associated with an increased risk of AKI.

Conclusion: The administration of morphine in patients treated with P2Y12 receptor inhibitors should be carefully evaluated. PCT may serve as a potential warning indicator for morphine-related renal injury.

Keywords: P2Y12 receptor inhibitors, morphine, kidney injury, Mendelian randomization

Introduction

Annually, an estimated 7 million individuals are diagnosed with acute coronary syndrome (ACS) globally.[1] P2Y12 receptor inhibitors are integral to ACS management, significantly reducing thrombotic events and enhancing patient prognosis. Nonetheless, the effectiveness of these agents is influenced by a variety of factors, such as patient-specific attributes and concurrent drug use.[2,3] Morphine, commonly administered for pain relief in ACS cases, has come under scrutiny for its potential to impede the absorption of P2Y12 inhibitors, thereby weakening their antiplatelet effect. Evidence from clinical randomized controlled trials indicates that morphine coadministration may lead to increased platelet reactivity when used alongside P2Y12 inhibitors.[4,5] In response to these concerns, the US Food and Drug Administration (FDA) revised the labeling for certain P2Y12 inhibitors in 2018 to include cautions regarding opioid

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interactions. Given that morphine is coadministered with P2Y12 inhibitors in approximately 10% to 30% of ACS patients, understanding the real-world implications of this drug interaction is critical.[6,7] However, there are few clinical studies about this interaction, and their findings are conflicting. Moreover, previous studies focused only on cardiovascular and death outcomes, the effect of this interaction on other organs is unclear.

The aim of this study is to comprehensively understand the impact of the interaction between morphine and P2Y12 receptor inhibitors using various analytical methods applied to multiple data sources. Initially, signal mining was conducted utilizing data from the Food and Drug Administration Adverse Event Reporting System (FAERS) database. The analysis revealed a significant signal associated with renal impairment-related events. Subsequently, this signal was validated among 5240 ACS patients. Furthermore, we endeavored to identify potential early warning indicators associated with renal injury and employed Mendelian randomization (MR) analysis utilizing genomic data to ascertain the causal relationship between the early warning indicators and renal injury.

Materials and Methods

Pharmacovigilance Data Analysis

Open Vigil FDA v1.0.2, an open-access tool available at http://openvigil.sourceforge.net/, was employed to clean and normalize pharmacovigilance data retrieved from the FAERS database.[8] We collected reports related to ticagrelor and clopidogrel between the first quarter of 2014 and the fourth quarter of 2021 suspected of causing adverse events (AEs). The potential risk associated with these reports was quantified using reporting odds ratios (repOR). Moreover, the interactive effects of morphine with either clopidogrel or ticagrelor were assessed through the interaction_perc_diff metric. Adverse drug reactions (ADRs) were categorized and detailed following the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1, employing the preferred term (PT) and system organ class (SOC) classifications. Detailed methods are in Supplementary Method S1.

Cohort Analysis of ACS Patients

We performed a cohort analysis of patients diagnosed with ACS and treated with percutaneous coronary intervention (PCI) from June 1, 2007, to November 30, 2021, at the Third Xiangya Hospital of Central South University. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of The Third Xiangya Hospital of Central South University (approval number R18030). Patients treated with P2Y12 inhibitors prior to PCI were eligible for inclusion. As prasugrel is still not available in the Chinese market, the study only included patients who were taking clopidogrel or ticagrelor. The exclusion criteria were (1) patients under 18 years of age; (2) patients on dialysis; (3) patients without preprocedure and postprocedure in-hospital serum creatinine values; and (4) patients who experienced hypotension during PCI. If a patient had multiple eligible PCI procedures on record, only the patient's first PCI procedure on record was included.(5) Patients who were treated sequentially with two different P2Y12 inhibitors during their current hospitalization. Patient clinical information was obtained from the electronic medical record system and included age, sex, admission diagnosis, discharge diagnosis, treatment and medication records, and laboratory test results. Postoperative acute kidney injury (AKI), myocardial infarction (MI), postoperative all-cause death, and cardiovascular death were included as study endpoints. Patients who used morphine intravenously before PCI treatment during hospitalization were defined as the morphine exposure group. AKI is defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria,[9] MI was defined according to the fourth edition of the Uniform Definition of Myocardial Infarction (UDMI).[10] The date and cause of death were obtained through linkage to the death dataset in the Chinese National Death Surveillance by matching the resident ID card numbers of each patient.[11] We used multivariable regression and IPTW to balance potential confounding factors, Detailed methods are in Supplementary Method S2.

Screening for Warning Indicators Correlated with Renal Injury of Morphine

Initially, we employed multiple regression analysis to assess the association between platelet indices—mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), and platelet count (PLT)—and the risk of acute kidney injury

(AKI) within a cohort divided into morphine and non-morphine groups, exploring the potential impact of these indices and their variations on AKI risk. Subsequently, we identified genetic variants related to these platelet traits from a meta-analysis of genome-wide association studies (GWAS) conducted on data from the UK Biobank and INTERVAL studies, encompassing a total of 166,066 individuals. We further analyzed summary data on MI from an extensive GWAS that included 7018 cases of MI and 361,194 controls. In addition, we performed two-sample Mendelian randomization (MR) to investigate the causal relationships between the platelet traits and MI, and to explore the potential mediating role of serum creatinine levels in this association. For a comprehensive description of our methods, please refer to Supplementary Method S3.

Statistical Analysis

In the internal cohort study, continuous variables were presented as mean ± standard deviation (SD) and compared using the Mann–Whitney *U*-test. Categorical variables were expressed as counts and percentages and evaluated using the Chi-square test or Fisher's exact test when expected frequencies were less than five. At baseline, missing data were infrequent (less than 4% for the majority of variables), and missing values were replaced with the average of non-missing items. We defined AKI and MI events as binary endpoints and calculated odds ratios (OR) with 95% confidence intervals with logistic regression models. Hazard ratios (HR) of mortality were computed using a Cox proportional hazards regression model. The adjusted covariates included age, sex, BMI, Killip class, classification of ACS, heart rate, complicating disease, number of vascular lesions, blood pressure, BNP, creatinine, glucose, intra-aortic balloon pump (IABP) or not, type of contrast agent and type of P2Y12 inhibitor.

MR analyses were performed with the TwoSampleMR R package. All reported P values are 2-sided; P values of multiple comparisons in the FAERS analysis were Benjamini–Hochberg adjusted, and a false discovery rate (FDR) and/or P value less than 0.05 was considered statistically significant. The statistical programs used for the analysis were Stata® 14.0 package (Stata Corp LP, College Station, TX, United States) and R, version 4.0.4 (R Core Team, Vienna, Austria).

Sensitivity Analyses

In the internal cohort study, we performed some sensitivity analyses. First, inverse probability of treatment weighting (IPTW) was used to balance the baseline characteristics between cohorts. With the IPTW approach, propensity score (PS) was calculated with a logistic regression model that predicted the probability of receiving morphine for each individual. Each individual is then weighted according to the PS. The standardized mean difference (SMD) before and after adjustment for IPTW was examined graphically. SMD<0.1 was considered acceptable for morphine use to measure the balance of baseline characteristics. Logistic regression and Cox regression were used again to calculate the OR and HR after weighting to compare the consistency of the results before and after weighting. Second, we limited the analysis to participants without cardiogenic shock or intraoperative hypotension. Third, we performed stratified analyses based on the classification of acute coronary syndrome (ACS), delineating between non-ST-elevation ACS (NSTEACS) and ST-elevation myocardial infarction (STEMI). Fourth, we also performed a propensity score–matching(PSM) analysis to test the robustness of the results. Briefly, multivariate logistic regression, including age, sex, BMI, smoking status, heart rate, blood glucose, BNP, white blood cells, high-density lipoprotein, triglycerides and cholesterol at admission, concurrent diagnosis of diabetes, chronic kidney disease (CKD), hypertension and hyperlipidemia, perioperative administration of angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers and calcium channel blockers, type of contrast agent, type of P2Y12 inhibitor, number of vascular lesions, Killip class, and classification of ACS, was performed to estimate the propensity score. The morphine users and nonusers were matched by propensity scores with a 1:2 nearest neighbor caliper matching method without replacement. We set a caliper of 0.02 SDs of the logit of the propensity score. After matching, we fitted a Logistic regression model to quantify ORs and 95% Cis.

Results

Associations Between Morphine Use and Adverse Outcomes in ACS Patients Receiving p2y12 Inhibitor Based on Pharmacovigilance Data

From the FAERS database, we extracted 187,919 reports, including 165,487 of clopidogrel, 22,432 of ticagrelor, and 2504 with concurrent morphine and P2Y12 inhibitor use (Supplementary Figure S1). As the most concerning outcome in

the past, morphine users had a higher risk of cardiac and vascular AEs when compared with non-morphine users in the FAERS (repOR 1.76, 95% CI 1.60 to 1.94, FDR adjusted -P=6.36×10^{-6}). Remarkably, Patients treated with morphine reported the highest proportion of renal system AEs (repOR 4.83, 95% CI 4.42 to 5.28, FDR adjusted -P=3.62×10^{-209} (Figure 1). In terms of PT statistics, renal failure, chronic kidney disease, and acute kidney injury were in the 1st, 2nd, and 4th places in the ranking of increased risk of adverse events from morphine (Supplementary Figure S2). Separate calculations for clopidogrel and ticagrelor also yielded essentially the same conclusion(Supplementary Figures S3 and S4). The interaction_perc_diff value also showed a higher additive interaction between morphine and P2Y12 inhibitors for kidney-related AEs (Supplementary Tables S1 and S2).

Retrospective Analysis Validated the Associations Between Morphine Use and Renal Dysfunction in ACS Patients Receiving p2y12 Inhibitors

A total of 5240 patients met the inclusion criteria during 7409 hospitalizations between June 2007 and November 2021 (Supplementary Figure S1), and 857 (16.4%) were treated with morphine preoperatively (Supplementary Table S3). In the multivariate logistic regression models, the risks of AKI and MI were higher among patients using morphine (adjusted OR: 1.79; 95% CI: 1.29 to 2.45 and adjusted OR: 1.57; 95% CI: 1.15 to 2.12)(Figure 2A). There was a trend toward an increased risk of postoperative all-cause mortality and cardiovascular mortality with morphine use, although the difference was not statistically significant. The adjusted HRs of all-cause mortality and cardiovascular mortality for ACS patients treated with morphine compared with nonusers were 1.40 (95% CI: 0.90–2.19) and 1.38 (95% CI: 0.85–2.24) within 1 year, and 1.64 (95% CI: 0.92–2.92) and 1.53 (95% CI: 0.82–2.83) within 3 months (Figure 2B and C). The primary results were robust in sensitivity analyses. After IPTW adjustment, both groups were well balanced in terms of baseline characteristics, with no SMD above 0.1 for any of those parameters (Supplementary Figure S5). The weighted calculated results are consistent with the logistic regression results (Supplementary Table S4 and Figure S6). After excluding patients with cardiogenic shock or intraoperative hypotension, the risk of MI and AKI of morphine users remained (Supplementary Table S5). Our analyses for individual types of ACS generally showed a positive association with the risk of AKI and MI, with significant effects observed for NSTEACS (Supplementary Table S6). After propensity score matching of 1:2 (Supplementary Table S7), morphine use was also associated with increased risk of AKI (OR, 1.56; 95% CI, 1.09–2.22) and MI(OR, 1.50; 95% CI, 1.07–2.10) (Supplementary Table S8). Additionally, there was an observable trend suggesting a higher predisposition to postoperative overall mortality and cardiovascular-related mortality in patients who received morphine, although this association did not reach statistical significance, as indicated in Supplementary Figure S7.

AE SOC	Log2 (OR95%CI)	OR(95%CI)	Total	With P2Y12 receptor inhibitors		With P2Y12 receptor inhibitors +morphine		FDR-adjusted p
				Total	AE	Total	AE	
Renal and urinary		4.83(4.42-5.28)	187919	185415	14411	2504	725	3.55*10^{-209}
Immune System		2.91(1.67-5.08)	187919	185415	331	2504	13	8.75*10^{-5}
Psychiatric		2.82(2.56-3.11)	187919	185415	16303	2504	536	6.05*10^{-6}
Infections and Infestations		2.82(2.11-3.76)	187919	185415	1303	2504	49	2.54*10^{-13}
Gastrointestinal		2.11(1.93-2.31)	187919	185415	26685	2504	657	4.67*10^{-62}
General and Administration Site		2.01(1.78-2.28)	187919	185415	49071	2504	1046	1.13*10^{-65}
Metabolism and Nutrition		1.99(1.84-2.16)	187919	185415	7363	2504	184	2.16*10^{-11}
Musculoskeletal and Connective Tissue		1.91(1.64-2.23)	187919	185415	8507	2504	206	1.58*10^{-17}
Cardiac and Vascular		1.76(1.60-1.94)	187919	185415	24090	2504	522	6.36*10^{-6}
Respiratory, Thoracic, and Mediastinal		1.71(1.54-1.91)	187919	185415	18365	2504	398	7.13*10^{-23}
Skin and Subcutaneous Tissue		1.33(1.12-1.58)	187919	185415	8154	2504	145	1.08*10^{-3}
Nervous System		1.32(1.19-1.49)	187919	185415	28427	2504	483	6.97*10^{-8}
Blood and Lymphatic		1.28(1.08-1.52)	187919	185415	8463	2504	145	4.00*10^{-3}

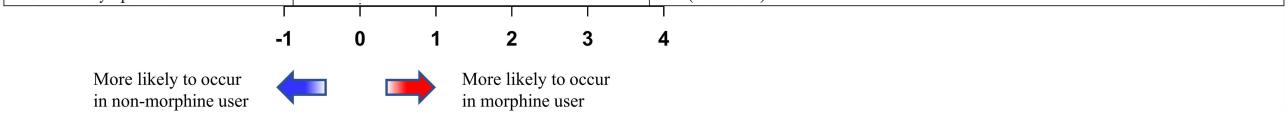
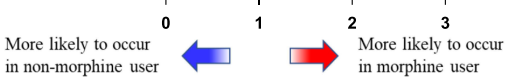


Figure 1 Analysis of AEs in different organs/systems in morphine and non-morphine users among patients with Clopidogrel/Ticagrelor based on the FAERS. AE= adverse event; FDR= false discovery rate; FAERS = Food and Drug Administration Adverse Event Reporting System; OR = odds ratio; SOC= system organ class.

A

Outcome	Adj OR95%CI	Adj OR(95%CI)	Total	With P2Y12 receptor inhibitors		With P2Y12 receptor inhibitors + morphine		adjusted p
				Total	AE	Total	AE	
myocardial infarction		1.57(1.15-2.12)	5240	4383	166	857	82	0.004
acute kidney injury		1.79(1.29-2.45)	5240	4383	140	857	82	0.003



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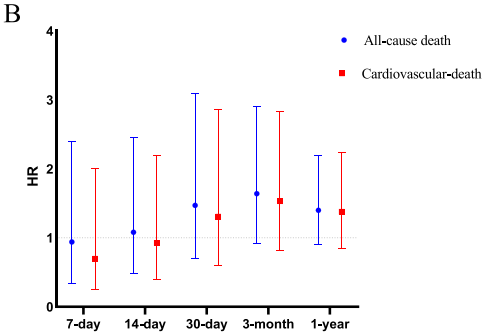

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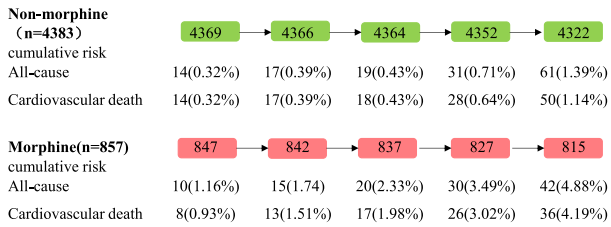


Figure 2 Retrospective Analysis for Patients cohorts. (**A**) Displays the adjusted odds ratios (Adj OR) and their respective 95% confidence intervals (CI) for myocardial infarction and acute kidney injury in morphine users. (**B**).The hazard ratio for all-cause death and cardiovascular death after co-administration of morphine at various time points (7-day, 14-day, 30-day, 3-month, and 1-year), blue dots represent all-cause death, while red dots represent cardiovascular death. (**C**) The cumulative risk of all-cause death and cardiovascular death between non-morphine and morphine treated patients, The numbers in green boxes indicate the number of patients remaining at each time interval for both groups.Percentages below these numbers represent the cumulative risk for each type of death in each group.

Taken together, the analyses based on in-house cohorts, consensually pinpointed that morphine users had higher renal dysfunction risk when compared with non-morphine users, in ACS patients receiving P2Y12 inhibitors, which is consistent with the findings from Real-World Pharmacovigilance Data.

Screening for Warning Indicators Correlated with Adverse Effects of Morphine

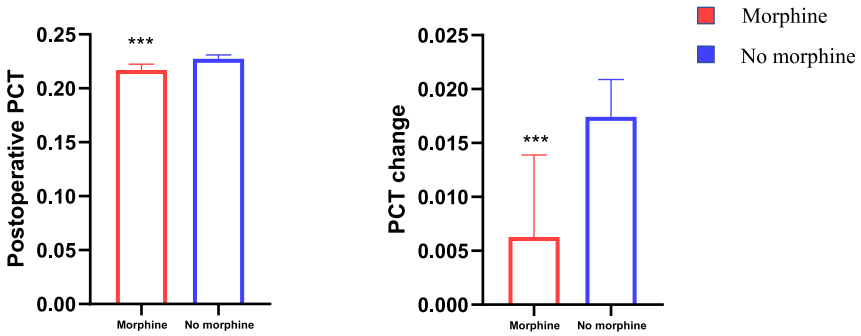
In the internal cohort study, we found that postoperative PCT and PLT were lower and had a decrease than the preoperative levels in the morphine group (Figure 3A), and the results remained significant after correction using multivariate logistic regression analysis (Supplementary Table S9), meanwhile, higher PCT levels and postoperative change values were found to be protective factors against the development of AKI (adjusted OR=0.039, *P*=0.04; adjusted OR=0.002, *P*=0.02) (Figure 3B).

To further clarify the causal relationship between PCT changes and the development of kidney damage, we performed a Mendelian randomization analysis with IVW (Inverse Variance Weighted) as the primary outcome. Out of the four platelet indices examined, only an increase in PCT levels demonstrated a significant association with lower blood creatinine levels, as indicated by a beta coefficient (B) of −0.08 and a *P* of 0.01, which is depicted in Figure 3C. Moreover, higher levels of blood creatinine were identified as a risk factor for the development of MI (B=0.02, *P*=0.03), as detailed in Supplementary Table S10. The results of the weighted median, MR–Egger, and maximum likelihood MR were in general agreement with IVW (Supplementary Table S10). Elevated PCT levels were shown to mediate a reduction in MI by lowering blood creatinine levels, and PCT did not directly affect MI (Figure 3D).

Discussion

Using multiple data sources, this study demonstrated the effects of morphine-P2Y12 inhibitor interactions on patients' primary organs. In the FAERS database analysis, coadministration of a P2Y12 antagonist with morphine was found to have the greatest increase in the rate of reported renal-related AEs and to exhibit an additive interaction. In the cohort studies, we consistently found an increased risk of AKI and MI in patients after the coadministration of morphine and

A



B

Platelet parameter	Adj OR 95%CI	Adj OR(95%CI)	P-value
Platelet count change		0.999(0.994-1.004)	0.60
Postoperative platelet count		0.999(0.996-1.001)	0.28
MPV change		0.947(0.670-1.324)	0.73
Postoperative MPV		0.991(0.856-1.147)	0.90
PDW change		1.074(0.946-1.219)	0.27
Postoperative PDW		1.114(1.016-1.221)	0.02
Plateletcrit change		0.002($1.5*10^{-5}$-0.317)	0.02
Postoperative plateletcrit		0.039(0.002-0.881)	0.04

C

Platelet parameters	Beta 95%CI	Beta(95%CI)	Inverse variance weighted p-value
Platelet distribution width		0.02(-0.05-0.10)	0.51
Platelet count		0.01(-0.07-0.08)	0.86
Mean platelet volume		0.02(-0.03-0.06)	0.44
Plateletcrit		-0.08(-0.15- -0.02)	0.01

D

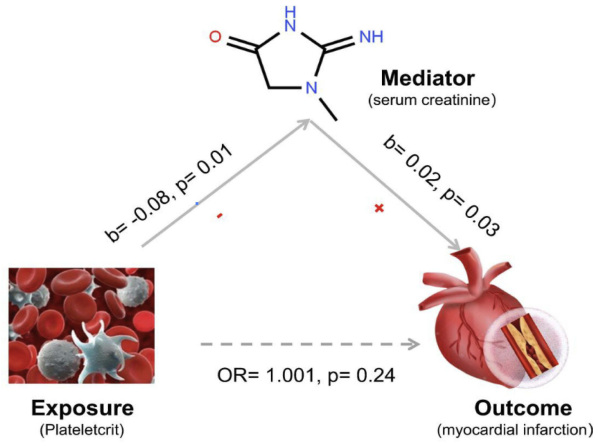


Figure 3 Screening and analysis of platelet indices for warning signs associated with morphine-induced renal injury.(**A**) Bars represent the mean and upper limits at a 95% confidence interval of postoperative PCT and PCT change than the preoperative levels in morphine group versus nonmorphine group. (**B**) Logistic regression analysis on in-house patient cohort data for association between platelet indices and AKI. (**C**) Mendelian randomization analysis for association between platelet indices and serum creatinine with Inverse variance weighted. (**D**) Decreased PCT levels were found to mediate an increased risk of MI through elevated blood creatinine levels, while PCT itself did not directly influence MI incidence. Triple asterisk indicates $p < 0.001$.

Abbreviation: AKI, acute kidney injury CI, confidence interval; MI, myocardial infarction; OR, odds ratio; PCT, plateletcrit.

a trend toward an increased risk of postoperative all-cause mortality and cardiovascular death. Based on Mendelian randomization analysis, we detected PCT as a potential warning indicator correlated with renal injury of morphine. Our findings alert physicians to the potential for renal impairment following morphine use.

The CRUSADE registry was one of the earliest to reveal that morphine administration within the first 24 hours of hospitalization was linked to an increased risk of death and MI in patients with NSTEACS.[6] Other researchers subsequently followed up on this issue. According to the post hoc subanalysis of the EARLY ACS trial, patients receiving clopidogrel and morphine had a significantly higher probability of ischemic events at 96 hours and a higher rate of mortality or myocardial infarction at 30 days.[7] The ATLANTIC trial showed pre-admission ticagrelor reduced MI occurrences in non-morphine patients, with no such effect in those given morphine.[12] However, the results of studies on the effects of morphine on cardiovascular events are inconsistent. In the FAST-MI registry and a subanalysis of the CIRCUS trial, morphine was not associated with a higher risk of clinical events, including death and MI.[13,14] In our cohort study, the risk of MI was higher after morphine use, and no significant risk of death was observed. Noticeably, we demonstrated for the first time an increased risk of AKI after the coadministration of morphine, which expands the study perspective to events beyond the cardiovascular system. AKI is a common and serious complication of PCI with an incidence of 3% to 19% and is associated with an increased risk of postprocedural MI, in-hospital bleeding, and death.[15] Additionally, our Mendelian randomization investigation demonstrated that increased creatinine levels influence the onset of MI, which is similar to the findings of Mendelian randomization by other researchers.[15,16] Therefore, more attention should be paid to renal injury caused by morphine co-administration. Meanwhile, our findings on renal adverse events help to explain the increased risk of MI from a new perspective.

A growing number of studies have recently revealed that platelets play an important role in AKI and are critical acute modulators of inflammation and hemostatic processes.[17–20] Animal studies have highlighted that Clopidogrel can confer protection against cell apoptosis and oxidative damage in a mouse model of renal ischemia-reperfusion injury,[21] but multiple RCTs have shown morphine delays and weakens the exposure and action of P2Y12 receptor inhibitors.[4,5] Moreover, research has shown that the use of opioid drugs may lead to acute kidney injury through mechanisms involving hypotension and rhabdomyolysis.[22] Furthermore, in the study conducted by Mingjing Pi et al, an analysis of subtypes of opioid analgesics revealed that Compared to dezocine, exposure to morphine, but not the other 7 types of opioid analgesics, was significantly associated with an increased risk of hospital-acquired AKI (adjusted hazard ratio: 1.56, 95% Cl: 1.40–1.78).[23] The above content mechanistically explains the increased risk of kidney injury in PCI patients when administering morphine concurrently.

Considering the potential association of platelet indices with platelet reactivity, we mined potential warning indicators of morphine-associated kidney injury from commonly used platelet indices in the expectation of improving monitoring accessibility. PCT, which represents the proportion of platelet volume in relation to total blood volume, is calculated based on the PLT and MPV. In healthy individuals, PCT is primarily influenced by variations in PLT.[24] In the setting of AKI, the observed decrease in PLT and PCT can be attributed to the consumption and destruction of platelets,[25] providing a plausible biological explanation for the association between PCT levels and AKI. Although the connection between PCT and renal injury has not been extensively explored, some studies have reported associations between PLT and AKI as well as platelet reactivity. In the study conducted by Kertai MD et al, it was observed that for every 30×10^9/L decrease in the postoperative platelet count of patients undergoing arterial bypass surgery, there was a 14% increase in the risk of postoperative AKI.[26] Additional studies have found that lower platelet counts are associated with higher platelet reactivity in patients receiving chronic dual antiplatelet therapy (DAPT).[27,28] A decrease in platelet count after morphine use was also observed in our internal cohort study, which partly explains the effect of morphine on PCT.

Study Strengths and Limitations

Our study has some notable strengths. First, we combined the advantages of the three data sources from clinical, real-world pharmacovigilance, and GWAS. The multisource analysis provides much stronger confidence in the evidence than any single-source analysis. Second, MR mediation analysis was used employing genetic variation as an instrumental variable to discover and quantify causation, overcoming the impact of possible confounding and reverse causality. Third, the results of cohorts analysis remained consistent in 2 different adjusted models (IPTW and logistic regression), which

were used to adjust for imbalances between the 2 groups regarding baseline characteristics. In addition, to exclude possible false-positive results caused by morphine itself triggering hypotension, we excluded patients who developed intraoperative hypotension from the internal cohort study. However, we acknowledge that our study has several limitations. First, limited by the quality of the data from the in-house study, we were unable to find more direct evidence that morphine interacts with P2Y12 antagonists to increase the risk of AKI, and we did not establish a nonsurgical group or a group of patients not taking P2Y12 inhibitors as controls. Also, since the FAERS database contains medical record reports only of patients who experienced AEs, we could not obtain the incidence of AEs but only the potential risk by calculating the OR based on the proportion of reports in the database. Despite our attempts to make the results more robust with the analysis of data from multiple sources, the above limitations affect the reliability of the findings. Additionally, while our findings suggest PCT as a potential warning indicator, we must exercise caution in interpreting these results. Further research is needed to establish the predictive value of PCT and other platelet indices in the context of AKI.

Conclusion

Our comprehensive study, on a wide spectrum of patients with ACS treated by P2Y12 receptor inhibitors, suggests that the administration of morphine requires careful consideration due to the possible increase in the risk of renal damage, which mediates the development of MI. PCT is a potential warning indicator for morphine-related renal injury.

Acknowledgments

We extend our appreciation to the developers of the Open Vigil FDA tool for providing a valuable resource for cleaning and normalizing pharmacovigilance data.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of The Third Xiangya Hospital of Central South University (approval number R18030). Informed patient consent was not required by the ethics committee in view of the retrospective nature of the research and the anonymity of the study data.

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Disclosure

The authors have no conflicts of interest to disclose in this work.

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