

Clinical pharmacology and safety of parenteral non-opioid analgesics after cardiothoracic surgery: An exploratory study integrating molecular docking and network-based analysis

● Lütfi Çağatay Onar¹, ● Ersin Güner², ● İbrahim Yılmaz³

¹Clinic of Cardiovascular Surgery, Dr. İsmail Fehmi Cumalıoğlu City Hospital, Tekirdağ, Türkiye

²Clinic of Pharmacy, Konya Numune Hospital, Konya, Türkiye

³Unit of Pharmacovigilance, Dr. İsmail Fehmi Cumalıoğlu City Hospital, Tekirdağ, Türkiye

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ABSTRACT

Objectives: Parenteral non-opioid analgesics are widely incorporated into multimodal pain protocols after cardiothoracic surgery, yet comparative early postoperative safety data remain limited in high-risk populations. This study evaluated the early postoperative safety profile of commonly used parenteral analgesics after cardiothoracic surgery and explored whether molecular and network-based analyses supported biological plausibility.

Patients and methods: This retrospective observational study included 721 consecutive adults undergoing cardiothoracic surgery through median sternotomy or thoracotomy between December 2018 and January 2026 at two tertiary referral centers. Patients received postoperative parenteral ketoprofen, diclofenac, tenoxicam, etofenamate, or metamizole according to institutional practice. Early adverse events included bleeding-related complications, renal dysfunction, gastrointestinal complications, hemodynamic instability, and rhythm-related concerns. Multivariable logistic regression used a composite adverse event endpoint. Pain control was assessed by serial numeric rating scale measurements. Exploratory molecular docking, protein-protein interaction (PPI) network construction, hub gene analysis, and functional enrichment analyses complemented the clinical analysis.

Results: Severe analgesic-related complications were infrequent. Increased surgical bleeding occurred in 1.9%, oliguria in 2.6%, acute kidney injury in 1.2%, and gastrointestinal bleeding in 0.6% of patients. Dyspeptic symptoms were the most common adverse event (6.0%). Postoperative pain scores improved across all groups, with adequate analgesic control in 87.8% of patients. In multivariable-adjusted analyses, increasing age (odds ratio [OR] 1.18, 95% confidence interval [CI] 1.02-1.36), NYHA class III-IV status (OR 1.42, 95% CI 1.03-1.96), reduced baseline renal function (OR 1.71, 95% CI 1.18-2.47), prolonged operative duration (OR 1.22, 95% CI 1.04-1.43), anticoagulant therapy (OR 1.56, 95% CI 1.11-2.19), and ketoprofen exposure (OR 1.39, 95% CI 1.01-1.91) were associated with increased complication risk. *In silico* analyses showed convergence of selected targets within inflammatory signaling, vascular regulation, platelet activation, and coagulation pathways. Interleukin-6 emerged as the principal hub gene in the constructed PPI network.

Conclusion: Parenteral non-opioid analgesics were associated with low severe early postoperative adverse event rates after cardiothoracic surgery while providing adequate analgesia under routine clinical conditions. Inter-agent variability should be interpreted cautiously given the exploratory retrospective design. Molecular and network analyses demonstrated biologically coherent pathway associations but did not establish mechanistic causality. These findings are hypothesis-generating and may inform prospective, experimentally validated investigations.

Keywords: Cardiothoracic surgery, analgesics, non-narcotic, anti-inflammatory agents, non-steroidal, postoperative complications, molecular docking simulation, drug-related side effects and adverse reactions.

Address for Correspondence: Assoc. Prof. Ph.D., İbrahim Yılmaz, Unit of Pharmacovigilance, Dr. İsmail Fehmi Cumalıoğlu City Hospital, Tekirdağ, Türkiye

E-mail: dryilmazi@yahoo.com **ORCID ID:** orcid.org/0000-0003-2003-6337

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Postoperative pain control in cardiothoracic surgery is not merely a matter of patient comfort but a determinant of early clinical recovery, with direct implications for respiratory mechanics, mobilization, and perioperative morbidity.^[1] In this setting, the analgesic strategy must be effective yet physiologically tolerable and safe in terms of adverse effects, particularly in patients frequently characterized by advanced age, cardiovascular comorbidity, and limited physiological reserve.^[2]

Although opioid based analgesic regimens have traditionally represented the cornerstone of postoperative pain management, growing recognition of their clinically significant adverse effects, particularly respiratory depression, excessive sedation, postoperative ileus, and gastrointestinal dysfunction, has accelerated the transition toward multimodal and opioid-sparing analgesic strategies.^[3,4] Consequently, parenteral non-opioid analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs) and related agents, have become integral components of contemporary early postoperative pain management protocols.^[5,6] Their analgesic efficacy, primarily mediated through cyclooxygenase inhibition and downstream modulation of inflammatory pathways, is well established.^[7] However, their safety profile in the cardiothoracic surgical context remains less clearly defined.^[6,8]

This uncertainty is clinically consequential. The early postoperative period following cardiothoracic surgery is characterized by dynamic hemodynamic conditions, perioperative fluid shifts, and frequent exposure to anticoagulant and vasoactive therapies.^[9,10] Within this milieu, non-opioid analgesics may plausibly influence renal perfusion, platelet function, and vascular tone through cyclooxygenase-dependent mechanisms.^[11] While such effects are pharmacologically anticipated, their translation into clinically observable adverse outcomes is neither uniform nor sufficiently characterized across different agents.^[12]

Despite their routine use, comparative data addressing the safety of individual parenteral non-opioid analgesics in this setting remain limited and methodologically heterogeneous.^[6,13] Existing studies have predominantly emphasized analgesic efficacy rather than safety-oriented endpoints, whereas real-world analyses reflecting early postoperative adverse events under routine clinical conditions remain relatively scarce.^[13,14] Consequently, selection of a specific agent in routine practice is frequently influenced more by institutional protocols and clinician experience than by robust comparative evidence.^[12,14]

Moreover, although the molecular pharmacology of these agents has been extensively characterized, its relationship to observed clinical safety patterns in complex surgical populations remains incompletely understood.^[15,16] Interactions involving inflammatory signaling, endothelial regulation, and coagulation pathways are likely to contribute to perioperative adverse event profiles, yet these mechanisms are rarely evaluated within an integrated framework linking molecular targets with clinical observations.^[16]

Accordingly, the present study was undertaken to evaluate the early postoperative clinical safety profile of commonly used parenteral non-opioid analgesics in patients undergoing cardiothoracic surgery. By adopting a retrospective observational design, the study aims to capture real-world safety outcomes within the context of routine clinical practice, with particular attention to adverse events of immediate postoperative relevance.

To complement the clinical observations and to provide a systems-level biological context, an exploratory *in silico* framework was incorporated, including molecular docking and network-based analyses. These approaches were not intended to establish mechanistic causality, but rather to identify plausible molecular interactions and functional relationships that may be consistent with the observed clinical patterns. In this context, protein–protein interaction (PPI) network construction and subsequent functional enrichment analyses were employed to examine whether the selected targets converge on biologically coherent pathways related to inflammation, vascular regulation, and coagulation.

Collectively, this combined clinical and computational strategy is intended to provide a structured, hypothesis-generating perspective on the safety profile of parenteral non-opioid analgesics in the cardiothoracic surgical setting, while maintaining a cautious interpretative framework consistent with the exploratory nature of the analyses.

PATIENTS AND METHODS

Study Design and Reporting Standards

This retrospective observational study was conducted to evaluate the clinical reliability profile of parenteral non-opioid analgesics administered in the early postoperative period following cardiothoracic surgery. The study design, data collection, and reporting followed the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies.^[17] Adult patients who underwent cardiothoracic surgical procedures via median sternotomy or thoracotomy between December 2018 and January 2026 at two tertiary referral centers located within the same province were retrospectively screened. During the study period, 3,156 patients underwent cardiothoracic surgery, and patients receiving postoperative parenteral non-opioid analgesic therapy at clinically effective doses during the early postoperative period were considered eligible. After application of eligibility criteria, 721 consecutive adult patients constituted the final study cohort.

Patient Selection

Patients were included if they had complete documentation available for assessment of baseline characteristics and early postoperative adverse events. Patients were excluded if the route or timing of analgesic administration was not clearly documented, if perioperative renal function data were unavailable, if documentation of early postoperative adverse events was insufficient for reliable evaluation, or if analgesic administration occurred outside the predefined early postoperative protocol window.

During the study period, 3,156 patients who underwent cardiothoracic surgery were screened for eligibility. Of these, 1,284 patients were excluded because they did not receive parenteral non-opioid analgesic therapy within the predefined early postoperative protocol window and 512 because postoperative analgesic management was based primarily on oral or opioid-dominant regimens. Additional exclusions included unclear documentation regarding the route or timing of analgesic administration (n=286), unavailable perioperative renal function data (n=213), and insufficient documentation of early postoperative adverse events for reliable evaluation (n=140). After application of the predefined eligibility criteria, 721 consecutive eligible patients constituted the final study cohort.

The study protocol was also approved by the Ethics Committee of Dr. İsmail Fehmi Cumalioğlu City Hospital (decision no: AN-261203-15, date: 12 March 2026), The study was conducted in accordance with the Declaration of Helsinki.

Analgesic Exposure

All evaluated medications were administered exclusively through intravenous or intramuscular routes during the immediate postoperative period in accordance with institutional multimodal analgesia protocols. This approach reflected routine clinical practice in the early recovery phase, when rapid onset of analgesia is required and gastrointestinal absorption may be unpredictable. The analgesic agents evaluated in this study included ketoprofen, diclofenac, tenoxicam, etofenamate, and metamizole. Selection of the analgesic agent and route of administration was determined by the attending surgical and anesthesia teams according to clinical condition, hemodynamic status, renal function, and institutional practice patterns. To minimize polypharmacy-related confounding, a single parenteral non-opioid analgesic agent was preferred for each patient during the early postoperative period. In the uncommon situations where more than one parenteral non-opioid analgesic was administered, those patients were excluded from the final study cohort. Intravenous paracetamol was routinely administered during the early postoperative period across all analgesic groups as part of the institutional multimodal analgesia protocol. Since paracetamol does not belong to the non-steroidal anti-inflammatory drug class and its administration frequency was comparable among groups, with no statistically significant differences observed, it was not incorporated as a primary analytical variable.

Data Collection and Clinical Variables

Clinical data were retrieved from electronic medical records. Recorded variables included demographic characteristics such as age and sex, anthropometric measurements including body mass index, and operative characteristics defined by surgical access type categorized as median sternotomy or thoracotomy. For patients undergoing cardiac procedures requiring cardiopulmonary bypass, operative variables, including cardiopulmonary bypass duration and aortic cross-clamp time, were additionally recorded when applicable. Functional cardiovascular status was assessed using the New York Heart Association (NYHA) functional classification, and baseline cardiac performance was characterized by left ventricular ejection fraction (LVEF) measurements. Baseline renal function was evaluated using estimated glomerular filtration rate values obtained from preoperative laboratory data. Comorbid conditions included hypertension, diabetes mellitus, and chronic obstructive pulmonary disease, together with prior cardiovascular history such as previous myocardial infarction or cerebrovascular events. Perioperative medication exposure, including anticoagulants, diuretics, renin-angiotensin system inhibitors, beta-blockers, and antiarrhythmic therapy, was also documented. Particular attention was given to early postoperative adverse clinical events temporally associated with analgesic exposure, including bleeding tendency, renal function deterioration, gastrointestinal intolerance, hemodynamic instability, and rhythm-related clinical concerns.

Pain Assessment

Postoperative pain intensity was systematically monitored using the numeric rating scale (NRS), a validated 11-point scale ranging from 0 (no pain) to 10 (worst imaginable pain).^[18] Pain scores were recorded

routinely for four consecutive postoperative days as part of standard nursing documentation. For the purposes of the present study, the term “early postoperative period” referred to postoperative days 1-4, corresponding to the institutional monitoring interval used for postoperative analgesic administration, pain assessment, and adverse event surveillance. The institutional postoperative pain management protocol targeted an NRS value of ≤ 3 at rest, which was considered to represent adequate analgesic control. These standardized records allowed confirmation that the administered analgesic regimens achieved clinically effective pain relief and ensured that observed adverse clinical patterns were not attributable to subtherapeutic dosing or inadequate analgesic exposure.

Outcomes

The primary objective of the clinical component of the study was to evaluate the reliability profile of parenteral non-opioid analgesics rather than to determine superiority in analgesic efficacy. Outcomes of interest included dyspeptic symptoms or upper gastrointestinal intolerance, evidence of renal stress or early deterioration in renal function, clinically relevant bleeding tendency, episodes of hemodynamic instability temporally associated with analgesic administration, and rhythm-related clinical concerns observed in patients receiving antiarrhythmic therapy. Acute kidney injury was defined according to kidney disease: Improving global outcomes criteria.^[19] For multivariable regression analyses, a composite binary endpoint termed “postoperative adverse event evaluated in relation to analgesic exposure” was constructed. Patients were classified as having experienced an adverse event if at least one of the predefined clinically relevant postoperative complications occurred during the early postoperative period, including increased surgical bleeding, oliguria, acute kidney injury, gastrointestinal bleeding, dyspeptic symptoms, transient hypotension, or rhythm-related clinical concern. Increased surgical bleeding was operationally defined as cumulative chest drain output exceeding 450 mL within the first 24 hours postoperatively.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics for Windows, version 30 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range according to distributional properties, whereas categorical variables were presented as counts and percentages. Normality of continuous data was assessed using histogram inspection together with the Shapiro-Wilk test. Between-group comparisons for continuous variables were performed using the independent samples t-test when normality assumptions were met and the Mann-Whitney U test otherwise. Comparisons among more than two analgesic subgroups were performed using One-Way Analysis of Variance or the Kruskal-Wallis test as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. For the purpose of multivariable logistic regression analysis, a binary composite outcome variable was defined. Patients were classified as having experienced a postoperative adverse event if at least one of the following clinically relevant complications was documented during the early postoperative period: Increased surgical site bleeding within the first 24 hours, oliguria, acute kidney injury, gastrointestinal bleeding, dyspeptic symptoms, transient hypotension, or rhythm-related clinical concern. These events were evaluated in relation to analgesic exposure within the broader perioperative and surgical context. This composite approach was adopted to preserve

adequate statistical power given the relatively low individual incidence rates of each endpoint. Univariable logistic regression analyses were initially performed for clinically relevant perioperative variables potentially associated with postoperative adverse events. Variables considered clinically important and/or demonstrating potential association in univariable analyses were subsequently incorporated into the multivariable logistic regression model based on clinical relevance and previously established perioperative risk factors. Model covariates were selected based on clinical relevance and previously established perioperative risk factors. Multivariable logistic regression models were constructed to explore associations between analgesic exposure and adverse postoperative outcomes while adjusting for clinically relevant covariates. Results of both univariable and multivariable logistic regression analyses are presented in order to improve transparency regarding covariate evaluation and the potential influence of confounding. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Repeated postoperative pain measurements were analyzed using repeated-measures analysis of variance or linear mixed-effects modeling depending on distributional assumptions.

Given the exploratory observational design and the relatively limited number of adverse outcome events, multivariable adjustment was preferred over propensity score matching in order to preserve statistical power and cohort representativeness. No formal *a priori* sample size calculation was performed because of the retrospective and exploratory design of the study. All eligible patients meeting the predefined inclusion criteria during the study period were included in the final analysis. Post hoc power analysis was performed as described in the Supplementary Materials.

Sample Size Consideration

As this study was retrospective and exploratory in design, no formal *a priori* sample size calculation was performed before patient inclusion. Instead, all consecutive eligible patients meeting the predefined inclusion criteria during the predefined study period were included in the final cohort in order to maximize representativeness and statistical precision. The final cohort comprised 721 patients, which was considered adequate to provide a clinically meaningful descriptive assessment of early postoperative adverse events and to support exploratory regression analyses. Given the low incidence of several individual complications, the regression analyses were interpreted cautiously and were intended to identify potential associations rather than to establish definitive predictive or causal relationships. In addition, post hoc power analysis was performed and is provided in the Supplementary Materials.

In silico Analyses

Molecular Docking

To explore the putative structural basis underlying the pharmacological activity profile of the candidate compounds, an exploratory molecular docking analysis was performed against six therapeutically relevant target proteins implicated in inflammatory signalling, vascular regulation, and the renin-angiotensin-aldosterone system (RAAS). These targets were selected *a priori* based on their established roles in mediating cyclooxygenase activity, endothelial function, cytokine signalling, and vasomotor control. The docking-derived targets were subsequently used as seed proteins for PPI network construction and functional enrichment analyses.

It should be emphasised that the findings derived from the present docking analysis are inherently hypothesis-generating and should not be interpreted as direct evidence of biological activity. Rather, the results provide a structural and computational framework for identifying plausible ligand–target interactions and for prioritising candidate proteins for downstream network-based and functional analyses. In addition, no redocking validation was performed to assess the reproducibility of the docking protocol, and therefore the predicted binding modes should be interpreted with appropriate caution.

Target Selection and Structural Basis

Target proteins were selected based on their well-established roles in prostaglandin (PG) biosynthesis, nitric oxide-mediated vasomotor regulation, and angiotensin-dependent haemodynamic control. Three-dimensional crystal structures were retrieved from the protein data bank (PDB): (cyclooxygenase-1 [COX-1]; PDB ID: 5WBE),^[20] (cyclooxygenase-2 [COX-2]; PDB ID: 5IKR),^[21] endothelial nitric oxide synthase (eNOS/ nitric oxide synthase 3 [NOS3]; PDB ID: 5UO8),^[22] (angiotensin-converting enzyme [ACE]; PDB ID: 9SSA),^[23] (interleukin-6 receptor alpha [IL-6R α]; PDB ID: 1P9M),^[24] and (type-1 angiotensin II receptor [AGTR1]; PDB ID: 4ZUD).^[25] For IL-6R α , given that the deposited structure represents a hexameric signalling complex rather than a classical enzyme active site, docking was conducted using an interface-directed approach targeting the PPI surface, in line with emerging strategies for modulating cytokine receptor signalling.

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Computational Protocol

Ligand two-dimensional structures were constructed in ChemDraw Ultra 12.0, and three-dimensional conformations were subsequently generated and energy-minimised using the Merck Molecular Force Field (MMFF94) implemented in ChemBio3D Ultra 13.0. The lowest-energy conformers were exported in PDB format and converted to PDBQT format using Open Babel (v3.1.1), with Gasteiger partial charges assigned and rotatable bonds identified automatically. Detailed software versions and computational tools are provided in Supplementary Materials, Table S1.^[26–28]

Receptor structures were prepared using AutoDockTools (MGLTools v1.5.6) by removal of crystallographic water molecules and co-crystallised ligands, addition of polar hydrogen atoms, and assignment of Kollman united-atom charges. All structures were exported in PDBQT format. Grid boxes were defined to encompass experimentally characterised binding sites, with centre coordinates and dimensions specified individually for each target (see Supplementary Materials, Table S2).

Docking simulations were performed using AutoDock 4.2.6 with the Lamarckian Genetic Algorithm (LGA), with twenty independent runs executed per ligand-protein pair. Resultant conformations were ranked according to estimated binding free energy (ΔG , kcal/mol) and root-mean-square deviation ($\text{RMSD} \leq 2.0 \text{ \AA}$ threshold). The lowest-energy pose within the most populated cluster was selected as the representative binding mode for each complex.

Protein-ligand interaction analyses were conducted using BIOVIA Discovery Studio Visualizer (2025 Client). Conventional hydrogen bonds, π - π stacking, π -alkyl, alkyl-alkyl, and π -sulfur interactions were systematically characterised. Two-dimensional interaction diagrams and three-dimensional binding conformations were generated to illustrate non-covalent stabilisation patterns and ligand orientation within the respective binding cavities.

PPI Network Construction

Network and enrichment analyses were conducted to explore potential functional relationships among docking-derived targets within a systems biology framework. PPI networks were constructed using the STRING database (*Homo sapiens*, confidence score ≥ 0.700). The selected targets were imported into the STRING database (version 12.0; <https://string-db.org>) to construct a PPI network using *Homo sapiens* as the organism and a minimum required interaction score of 0.700. STRING integrates known and predicted protein associations derived from experimental data, curated databases, co-expression, and computational predictions.^[26] The resulting interaction network was exported and visualized using Cytoscape software (version 3.10.4), a platform for complex network analysis and visualization.^[27] Topological parameters including degree, betweenness centrality, and closeness centrality were calculated using the NetworkAnalyzer tool implemented in Cytoscape.

Hub Gene Identification

Hub genes were identified using the CytoHubba plugin in Cytoscape. The maximal clique centrality (MCC) algorithm was applied to rank nodes based on their topological importance within the network. CytoHubba enables identification of key regulatory nodes in biological networks.^[28]

Network Clustering Analysis

Network modularity and functional grouping of nodes were explored using the Markov Cluster Algorithm (MCL) implemented in STRING. This clustering approach allows visualization of functional modules within the PPI network.

Functional Enrichment Analysis

Functional enrichment analysis was performed using STRING. Gene ontology (GO) enrichment analysis, including biological process (BP), cellular component (CC), and molecular function (MF), was conducted based on the GO database.^[29]

Pathway enrichment analysis was also performed using the Kyoto encyclopedia of genes and genomes (KEGG) database^[30] and Reactome pathway database. The false discovery rate (FDR) was applied for multiple testing correction, and significantly enriched terms were ranked according to FDR values.

RESULTS

Baseline Demographic and Clinical Characteristics

A total of 721 patients who underwent cardiothoracic surgery were included in the analysis. Among these patients, 546 underwent procedures via median sternotomy, whereas 175 underwent thoracic procedures via thoracotomy. Baseline demographic and clinical characteristics of the study population are summarized in Table 1.

Patients in the sternotomy group were older than those in the thoracotomy group (63.8 ± 8.4 vs. 57.2 ± 10.5 years, $p < 0.001$) and demonstrated a higher prevalence of advanced heart failure, reflected by a greater proportion of NYHA class III-IV patients (61.5% vs. 15.4%, $p < 0.001$). LVEF and baseline glomerular filtration rate were lower in the sternotomy cohort ($47.1 \pm 8.6\%$ vs. $55.4 \pm 7.9\%$, $p < 0.001$ and 74.2 ± 12.5 vs. $88.6 \pm 14.2 \text{ mL/min/1.73 m}^2$, $p < 0.001$, respectively). Cardiometabolic comorbidities including diabetes mellitus and hypertension were more frequent in patients undergoing sternotomy. Chronic obstructive pulmonary disease was more prevalent in the thoracotomy group (25.1% vs. 16.7%, $p = 0.01$). Operative duration was longer in the sternotomy cohort (214 ± 52 vs. 168 ± 47 minutes, $p < 0.001$).

Distribution of Postoperative Analgesic Exposure

The distribution of parenteral non-opioid analgesics administered during the early postoperative period is shown in Table 2.

Ketoprofen was administered to 162 patients (22.5%), diclofenac to 148 patients (20.5%), tenoxicam to 132 patients (18.3%), etofenamate to 119 patients (16.5%), and metamizole to 160 patients (22.2%). The distribution of analgesic exposure was relatively balanced across all five agents, and all medications were administered via intravenous or intramuscular routes according to institutional multimodal analgesia protocols.

Postoperative adverse events evaluated in relation to analgesic exposure clinically relevant postoperative adverse events evaluated in relation to analgesic exposure during the early postoperative period are summarized in Table 3.

Increased surgical site bleeding within the first 24 postoperative hours was observed in 14 patients (1.9%). Oliguria occurred in 19 patients (2.6%), while acute kidney injury was documented in 9 patients (1.2%). Gastrointestinal bleeding was observed in 4 patients (0.6%). Dyspeptic symptoms were more frequent and occurred in 43 patients (6.0%). Less common events included transient hypotension in 6 patients (0.8%) and rhythm-related clinical concern in 5 patients (0.7%).

Non-analgesic Postoperative Complications

Postoperative complications not directly attributed to analgesic exposure are presented in Table 4.

Postoperative atrial fibrillation was the most frequent complication and occurred in 118 patients (16.4%). Atelectasis requiring physiotherapy was observed in 96 patients (13.3%), while pneumonia occurred in 28 patients (3.9%). Prolonged mechanical ventilation exceeding 24 hours was documented in 41 patients (5.7%). Stroke or transient ischemic attack occurred in 11 patients (1.5%). Surgical site infection was

Table 1. Baseline demographic and clinical characteristics of the study population

Variable	Sternotomy (n=546)	Thoracotomy (n=175)	p-value
Age (years)	63.8±8.4	57.2±10.5	<0.001
Male sex	392 (71.8%)	112 (64.0%)	0.04
BMI (kg/m ²)	29.3±4.6	27.8±4.2	0.01
NYHA class III-IV	336 (61.5%)	27 (15.4%)	<0.001
LVEF (%)	47.1±8.6	55.4±7.9	<0.001
Baseline GFR (mL/min/1.73 m ²)	74.2±12.5	88.6±14.2	<0.001
Diabetes mellitus	246 (45.1%)	49 (28.0%)	<0.001
HbA1C (%)	7.3±1.1	6.7±0.9	<0.001
Hypertension	312 (57.1%)	62 (35.4%)	<0.001
COPD	91 (16.7%)	44 (25.1%)	0.01
FEV1/FVC ratio	69.2±7.8	65.4±8.1	0.002
Previous ICU	208 (38.1%)	19 (10.9%)	<0.001
Previous TIA	42 (7.7%)	6 (3.4%)	0.04
Previous malignancy	31 (5.7%)	12 (6.9%)	0.52
Type of operation			
CABG	476 (87.2%)	-	-
Valve surgery	46 (8.4%)	-	-
Combined cardiac procedures	24 (4.4%)	-	-
Pulmonary/thoracic procedures	-	175 (100%)	-
Operation duration (minutes)	214±52	168±47	<0.001
Cardiopulmonary bypass duration, min	94.6±31.8	41.8±24.6	<0.001
Aortic cross-clamp time, min	63.7±21.4	28.9±17.8	<0.001
Analgesic use within 72 h before surgery	74 (13.6%)	21 (12.0%)	0.61

Sternotomy (n=546) and thoracotomy (n=175), total cohort n=721. Cardiopulmonary bypass duration and aortic cross-clamp time were recorded when applicable. Lower mean values in the thoracotomy group reflect the inclusion of procedures with limited or no extracorporeal circulation requirements rather than the absence of cardiac surgical procedures within this subgroup. Continuous variables were compared using the independent Samples t-test or Mann-Whitney U test according to the distributional properties. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. BMI: Body mass index; NYHA: New York Heart Association; LVEF: Left ventricular systolic function; GFR: Glomerular filtration rate; COPD: Chronic obstructive pulmonary disease; CABG: Coronary artery bypass graft surgery; ICU: Intensive care unit; TIA: Transient ischemic attack.

Table 2. Distribution of postoperative parenteral non-opioid analgesic exposure

Analgesic agent	Number of patients (n)	Percentage (%)
Ketoprofen	162	22.5
Diclofenac	148	20.5
Tenoxicam	132	18.3
Etofenamate	119	16.5
Metamizole	160	22.2
Total	721	100

Values are presented as number and percentage. No statistical comparison was performed for this descriptive table.

observed in 18 patients (2.5%), re-exploration for bleeding in 8 patients (1.1%), and intensive care unit (ICU) readmission in 15 patients (2.1%). In-hospital mortality was 1.8% (13 patients).

Postoperative Analgesic Effectiveness

Postoperative pain scores and adequacy of analgesic control during the early postoperative period are presented in Table 5. Postoperative pain scores decreased progressively from postoperative day (POD) 1 to POD 4 across all analgesic groups. Mean NRS values remained within or close to

Table 3. Postoperative adverse events evaluated in relation to analgesic exposure

Complication	Number of patients (n)	Percentage (%)
Increased surgical site bleeding (first 24 h)	14	1.9
Oliguria	19	2.6
Acute kidney injury	9	1.2
Gastrointestinal bleeding	4	0.6
Dyspeptic symptoms	43	6.0
Transient hypotension	6	0.8
Rhythm-related clinical concern	5	0.7

Values are presented as number and percentage. No statistical comparison was performed for this descriptive table.

the predefined clinically acceptable range throughout the observation period, with overall adequate analgesia achieved in 87.8% of patients. Although numerically higher adequate analgesia rates were observed in the metamizole and etofenamate groups, between-agent differences did not reach statistical significance. These findings indicate that all evaluated parenteral non-opioid analgesics provided clinically effective early postoperative pain control under routine practice conditions.

Table 4. Non-analgesic postoperative complications observed during the early postoperative period

Complication	Number of patients (n)	Percentage (%)
Postoperative atrial fibrillation	118	16.4
Atelectasis requiring physiotherapy	96	13.3
Pneumonia	28	3.9
Prolonged mechanical ventilation (>24 h)	41	5.7
Stroke/TIA	11	1.5
Surgical site infection	18	2.5
Re-exploration for bleeding	8	1.1
ICU readmission	15	2.1
In-hospital mortality	13	1.8

Values are presented as number and percentage. No statistical comparison was performed for this descriptive table. ICU: Intensive care unit; TIA: Transient ischemic attack.

Values are presented as mean $\pm$ standard deviation or number and percentage. NRS denotes NRS; POD, postoperative day. Adequate analgesia was defined as an NRS score ≤ 3 at rest. Between-group comparisons of daily NRS scores were performed using one-way analysis of variance or Kruskal-Wallis test, as appropriate. Adequate analgesia rates were compared using the chi-square test. The overall p-value reflects between-agent comparison across repeated postoperative pain measurements. Overall, postoperative pain control remained within the predefined clinically acceptable range during the observation period, confirming that the administered parenteral non-opioid analgesics provided effective analgesia under routine clinical conditions.

Distribution of Complications According to Analgesic Class

The distribution of analgesic-related adverse clinical events according to the primary analgesic agent administered during the early postoperative period is presented in Table 6. Rates of increased surgical bleeding within the first 24 postoperative hours were 3.1% in patients receiving ketoprofen, 2.7% with diclofenac, 2.3% with tenoxicam, 0.8% with etofenamate, and 0.6% with metamizole ($p=0.08$). Oliguria was observed in 3.7%, 3.4%, 3.0%, 1.7%, and 1.2% of patients, respectively ($p=0.12$). Acute kidney injury occurred in 1.9% of patients receiving ketoprofen, 2.0% with diclofenac, 1.5% with tenoxicam, 0.8% with etofenamate, and was not observed in patients receiving metamizole ($p=0.09$).

Gastrointestinal bleeding was infrequent and distributed similarly across treatment groups ($p=0.94$). Dyspeptic symptoms were observed more frequently in patients receiving ketoprofen (8.6%), diclofenac (6.8%), and tenoxicam (6.8%) compared with etofenamate (3.4%) and metamizole (3.8%), reaching statistical significance ($p=0.03$). Transient hypotension and rhythm-related clinical concerns were rare and showed no significant differences between analgesic groups ($p=0.91$ and $p=0.99$, respectively) (Table 6).

Multiple comparisons were not formally adjusted because the analyses were exploratory and intended to describe potential safety signals rather than to confirm definitive between-agent differences. Therefore, p-values should be interpreted as nominal, and findings with borderline statistical significance should be considered hypothesis-generating.

Predictors of Postoperative Adverse Events Evaluated in Relation to Analgesic Exposure

Results of univariable and multivariable logistic regression analyses evaluating factors associated with postoperative adverse events evaluated in relation to analgesic exposure are presented in Table 7. In univariable analyses, increasing age (OR: 1.24 per 10 year increase, 95% CI: 1.11 to 1.39, $p<0.001$), advanced heart failure status defined as NYHA class III to IV (OR: 1.67, 95% CI: 1.23 to 2.28, $p=0.001$), reduced left ventricular systolic function (LVEF $<45\%$; OR: 1.51, 95% CI: 1.11 to 2.06, $p=0.009$), impaired baseline renal function (glomerular filtration rate [GFR] <60 mL/min; OR: 1.94, 95% CI: 1.41 to 2.67, $p<0.001$), longer operative duration (OR: 1.29 per 60 minute increase, 95% CI: 1.11 to 1.50, $p=0.001$), concomitant anticoagulant therapy (OR: 1.71, 95% CI: 1.23 to 2.37, $p=0.001$), loop diuretic use (OR: 1.61, 95% CI: 1.16 to 2.24, $p=0.004$), and ketoprofen exposure (OR: 1.54, 95% CI: 1.12 to 2.12, $p=0.008$) were associated with an increased likelihood of postoperative adverse events. Diabetes mellitus, previous myocardial infarction, ACE inhibitor therapy, and diclofenac exposure also demonstrated nominal associations in univariable analyses, whereas male sex, hypertension, chronic obstructive pulmonary disease (COPD), and amiodarone therapy were not significantly associated with adverse outcomes.

Following multivariable adjustment for clinically relevant perioperative covariates, increasing age remained independently associated with postoperative adverse events (adjusted OR: 1.18 per 10 year increase, 95% CI: 1.02 to 1.36, $p=0.02$). Advanced functional heart failure status (NYHA class III to IV; adjusted OR: 1.42, 95% CI: 1.03 to 1.96, $p=0.03$), reduced baseline renal function (GFR <60 mL/min; adjusted OR: 1.71, 95% CI: 1.18 to 2.47, $p=0.004$), and prolonged operative duration (adjusted OR: 1.22 per 60 minute increase, 95% CI: 1.04 to 1.43, $p=0.01$) also remained independently associated with increased complication risk. Among perioperative medication-related variables, concomitant anticoagulant therapy (adjusted OR: 1.56, 95% CI: 1.11 to 2.19, $p=0.01$) and loop diuretic use (adjusted OR: 1.48, 95% CI: 1.05 to 2.08, $p=0.02$) remained significant predictors in adjusted analyses. Among analgesic exposures, ketoprofen remained independently associated with a higher risk of postoperative adverse events (adjusted OR: 1.39, 95% CI: 1.01 to 1.91, $p=0.04$). Diclofenac and tenoxicam demonstrated non-significant trends toward increased risk, whereas etofenamate and metamizole were not associated with increased risk following multivariable adjustment.

In silico Results

Molecular Docking Results

The estimated binding energies and residue-level interaction profiles for all ligand-protein pairs are summarised in Supplementary Table S3, which provides a comprehensive overview of the comparative docking performance across all targets. Across all six targets, tenoxicam consistently exhibited the most favourable binding energies, ranging from -8.74 kcal/mol at IL-6R α to -11.71 kcal/mol at COX-2. This pattern may suggest a relatively broad interaction profile; however, such observations should be interpreted within the exploratory scope of the present analysis and viewed as hypothesis-generating. Three-dimensional binding conformations and representative two-dimensional interaction diagrams are presented in Figures 1-3, respectively. The chemical structures of the investigated compounds are provided in Supplementary Figure S1.

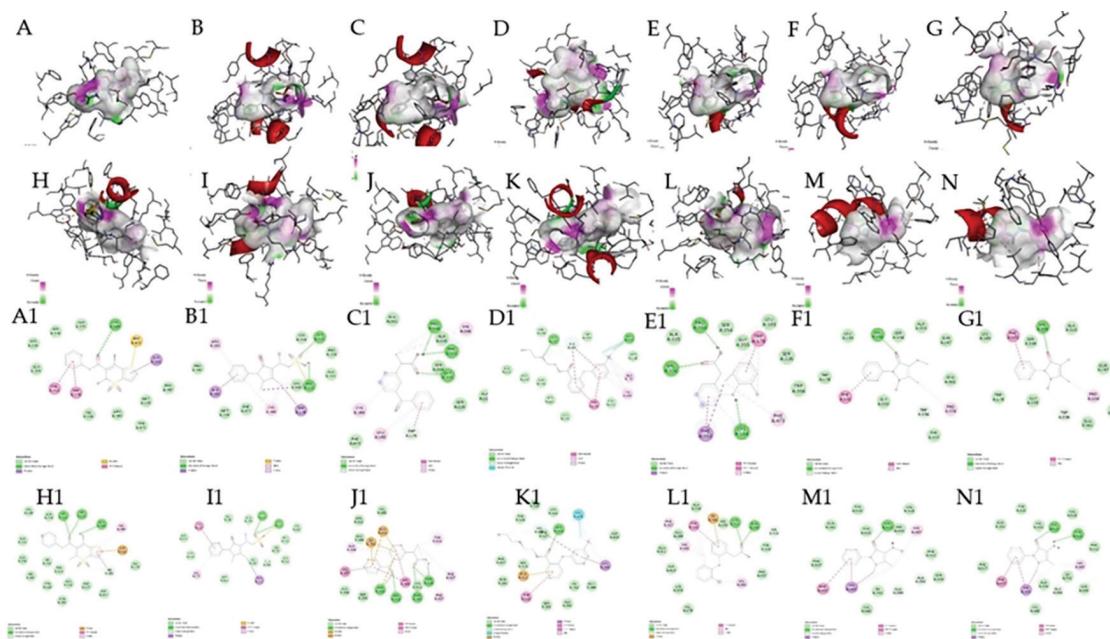


Figure 1. 3D binding conformations and corresponding 2D interaction diagrams of the ligands within the active sites of cyclooxygenase isoforms, visualised using BIOVIA Discovery Studio Visualizer (2025 Client). Ligands are shown in stick representation, whereas proteins are depicted using a combination of cartoon and surface models to illustrate binding pocket topology and ligand accommodation. The upper panels (A-N) represent 3D binding conformations, arranged in two rows (COX-1: A-G; COX-2: H-N). The lower panels (A1-N1) display the corresponding 2D residue-level interaction diagrams for each ligand-protein complex. (A-G) Tenoxicam-COX-1, metamizole-COX-1, ketoprofen-COX-1, etofenamate-COX-1, diclofenac-COX-1, 4-methylaminoantipyrine (4-MAA)-COX-1, and 4-aminoantipyrine (4-AA)-COX-1; (H-N) tenoxicam-COX-2, metamizole-COX-2, ketoprofen-COX-2, etofenamate-COX-2, diclofenac-COX-2, 4-methylaminoantipyrine (4-MAA)-COX-2, and 4-aminoantipyrine (4-AA)-COX-2. (A1-N1) Corresponding 2D interaction diagrams for each ligand-protein complex. In the 2D interaction diagrams, conventional hydrogen bonds are indicated by green dashed lines; π - π stacking interactions by purple lines; π -alkyl and alkyl interactions by light pink lines; and π -sulfur interactions by yellow dashed lines. Residues involved in interactions are shown as coloured circles.

COX: Cyclooxygenase.

COX-1 and COX-2

At the cyclooxygenase active sites, the canonical Arg120-Tyr355 anchoring dyad and the hydrophobic channel formed by Leu352, Leu359, Val349, and Phe518 dominated the binding landscape. Tenoxicam demonstrated the highest estimated affinity at COX-1 ($\Delta G = -11.23$ kcal/mol) and COX-2 ($\Delta G = -11.71$ kcal/mol), as detailed in Supplementary Table S3, engaging Ser530 and Tyr385—residues of established mechanistic relevance to cyclooxygenase inhibition—through conventional hydrogen bonding, while achieving extensive hydrophobic stabilisation via Met522.

Metamizole and its principal metabolites, 4-methylaminoantipyrine (4-MAA) and 4-aminoantipyrine (4-AA), displayed comparatively modest binding energies (COX-1: -10.52, -8.31, -8.21 kcal/mol; COX-2: -9.86, -8.73, -8.65 kcal/mol), consistent with their known profile of weak and reversible cyclooxygenase interaction. The observed binding geometries are broadly congruent with those reported for classical non-steroidal anti-inflammatory agents and may offer a structural rationale for differential COX selectivity; however, this interpretation remains provisional pending experimental validation.

Endothelial Nitric Oxide Synthase (NOS3/eNOS)

Docking at the eNOS active site yielded binding energies in the range of -7.54 to -9.97 kcal/mol (Supplementary Table S3). Tenoxicam ($\Delta G = -9.97$

kcal/mol) and diclofenac ($\Delta G = -9.78$ kcal/mol) demonstrated comparatively favourable estimated affinities, engaging the haem-proximal Cys184 residue—a structurally critical determinant of NOS active site geometry—predominantly through hydrophobic contacts. Additional π -sulfur stabilisation was observed for tenoxicam via Phe473.

Metamizole and ketoprofen engaged the conserved Gly355-Phe353 region through hydrogen bonding, supplemented by π -stacking and alkyl interactions. Notably, the majority of compounds exhibited non-classical binding orientations at eNOS relative to their behaviour at cyclooxygenase sites, which may reflect the distinct electrostatic and structural environment of the haem-containing active site. These findings remain exploratory and do not permit inference regarding functional NOS modulation in the absence of biochemical corroboration.

Angiotensin-Converting Enzyme (ACE)

The ACE active site is characterised by a zinc-coordinating histidine cluster (His353, His383, His387, His513) and hydrophobic subsites (Phe457, Phe527, Tyr520, Tyr523). Tenoxicam again exhibited the highest estimated affinity ($\Delta G = -10.86$ kcal/mol; Supplementary Table S3), forming hydrogen bonds with Glu384, His353, and His513, alongside hydrophobic contacts with Val380—a contact pattern broadly analogous to that observed for established ACE inhibitor scaffolds engaging the S1 and S2 subsites.

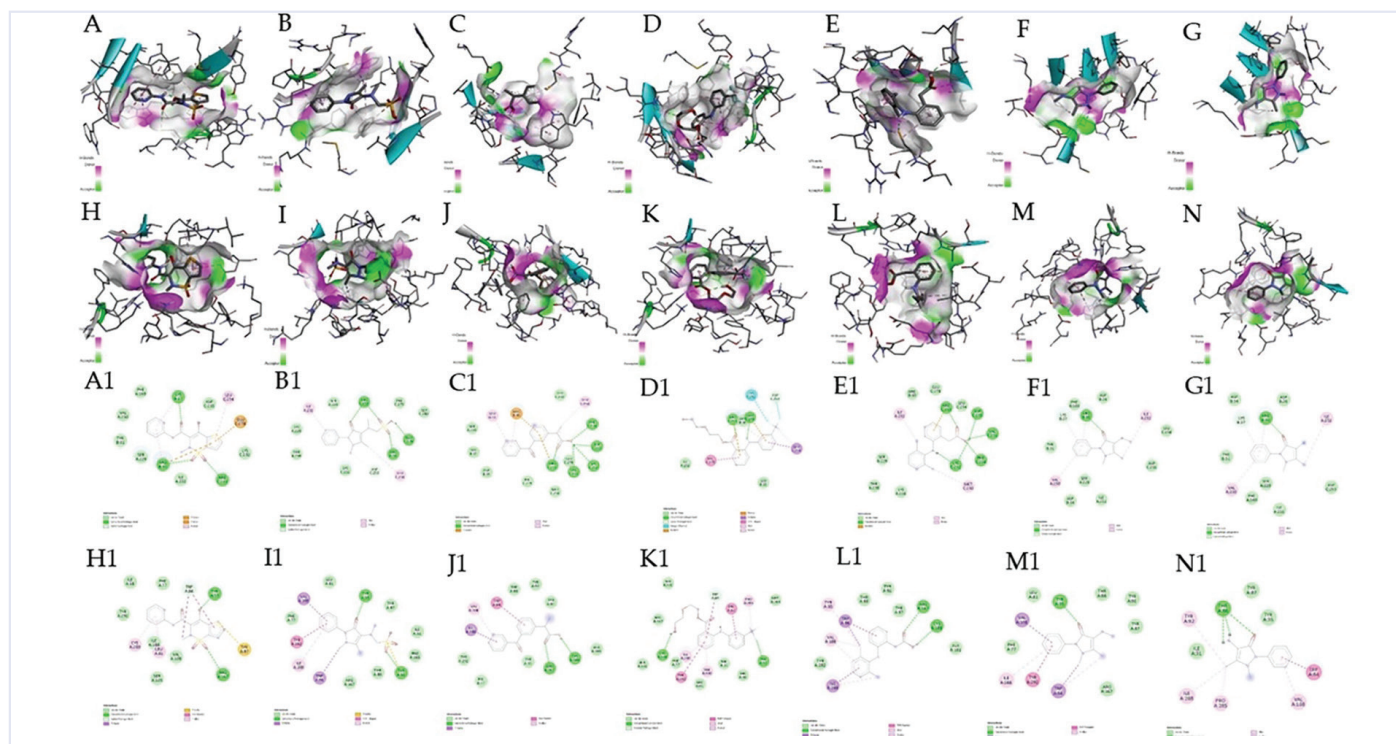


Figure 2. 3D binding conformations and corresponding 2D interaction diagrams of the ligands within the active sites of endothelial nitric oxide synthase (NOS3) and angiotensin-converting enzyme (ACE), visualised using BIOVIA Discovery Studio Visualizer (2025 Client). Ligands are shown in stick representation, whereas proteins are depicted using a combination of cartoon and surface models to illustrate binding pocket topology and ligand accommodation. The upper panels (A-N) represent 3D binding conformations, arranged in two rows (NOS3: A-G; ACE: H-N). The lower panels (A1-N1) display the corresponding 2D residue-level interaction diagrams for each ligand-protein complex. (A-G) Tenoxicam-NOS3, metamizole-NOS3, ketoprofen-NOS3, etofenamate-NOS3, diclofenac-NOS3, 4-methylaminoantipyrine (4-MAA)-NOS3, and 4-aminoantipyrine (4-AA)-NOS3; (H-N) tenoxicam-ACE, metamizole-ACE, ketoprofen-ACE, etofenamate-ACE, diclofenac-ACE, 4-methylaminoantipyrine (4-MAA)-ACE, and 4-aminoantipyrine (4-AA)-ACE. (A1-N1) Corresponding 2D interaction diagrams for each ligand-protein complex. In the 2D interaction diagrams, conventional hydrogen bonds are indicated by green dashed lines; π - π stacking interactions by purple lines; π -alkyl and alkyl interactions by light pink lines; and π -sulfur interactions by yellow dashed lines. Residues involved in interactions are shown as coloured circles.

Ketoprofen ($\Delta G = -8.92$ kcal/mol) and metamizole ($\Delta G = -8.70$ kcal/mol) demonstrated intermediate affinities with engagement of the zinc-coordinating histidine residues, whereas the aminoantipyrine metabolites showed comparatively lower estimated energies (4-MAA: -7.40 ; 4-AA: -6.92 kcal/mol). These observations may tentatively suggest that certain non-steroidal agents could warrant further investigation for potential off-target ACE-related vascular effects, although this remains a hypothesis requiring prospective experimental validation.

IL-6R α

Given the atypical nature of the IL-6R α binding interface—a broad and relatively shallow PPI surface rather than a discrete enzymatic cavity—binding energies were, as expected, lower (range: -6.58 to -8.74 kcal/mol; Supplementary Table S3) and should be interpreted with particular caution. Tenoxicam ($\Delta G = -8.74$ kcal/mol) engaged Lys27, Arg30, and Arg233 through hydrogen bonding, whereas ketoprofen and diclofenac formed hydrogen bonds with Arg233 and adjacent interface residues including Val251, Lys252, Phe234, and Asp253.

These preliminary observations raise the speculative possibility that certain anti-inflammatory compounds may interact with the IL-6 signalling axis via a receptor-interface mechanism. However, such an interpretation remains strictly hypothesis-generating and requires rigorous biochemical and cellular validation.

AGTR1

At AGTR1, a G protein-coupled receptor with an architecturally distinct orthosteric binding pocket, tenoxicam demonstrated the highest estimated affinity ($\Delta G = -9.99$ kcal/mol; Supplementary Table S3), forming hydrogen bonds with Tyr35 and π -sulfur stabilisation via Tyr87, alongside hydrophobic contacts with Leu81 and Cys289.

Metamizole ($\Delta G = -9.54$ kcal/mol) similarly engaged Tyr35 and Tyr92, with π -interactions involving Tyr292. Etofenamate ($\Delta G = -8.51$ kcal/mol) exhibited a comparatively dense interaction network involving Cys180, Tyr92, and multiple aromatic residues (Tyr87, Trp84, Tyr292), whereas the aminoantipyrine derivatives showed binding energies in the range of -7.21 to -7.56 kcal/mol.

These exploratory findings provide structural hypotheses for potential RAAS-modulating properties of these agents; however, the biological significance of these interactions remains to be established.

PPI Network Results

To characterise the functional landscape of the docking-derived targets, a PPI network was first constructed using the STRING database, followed by integrated enrichment analyses. The overall interaction architecture is presented in Figure 4, whereas subsequent Cytoscape-based refinement and visualisation of network topology are shown in

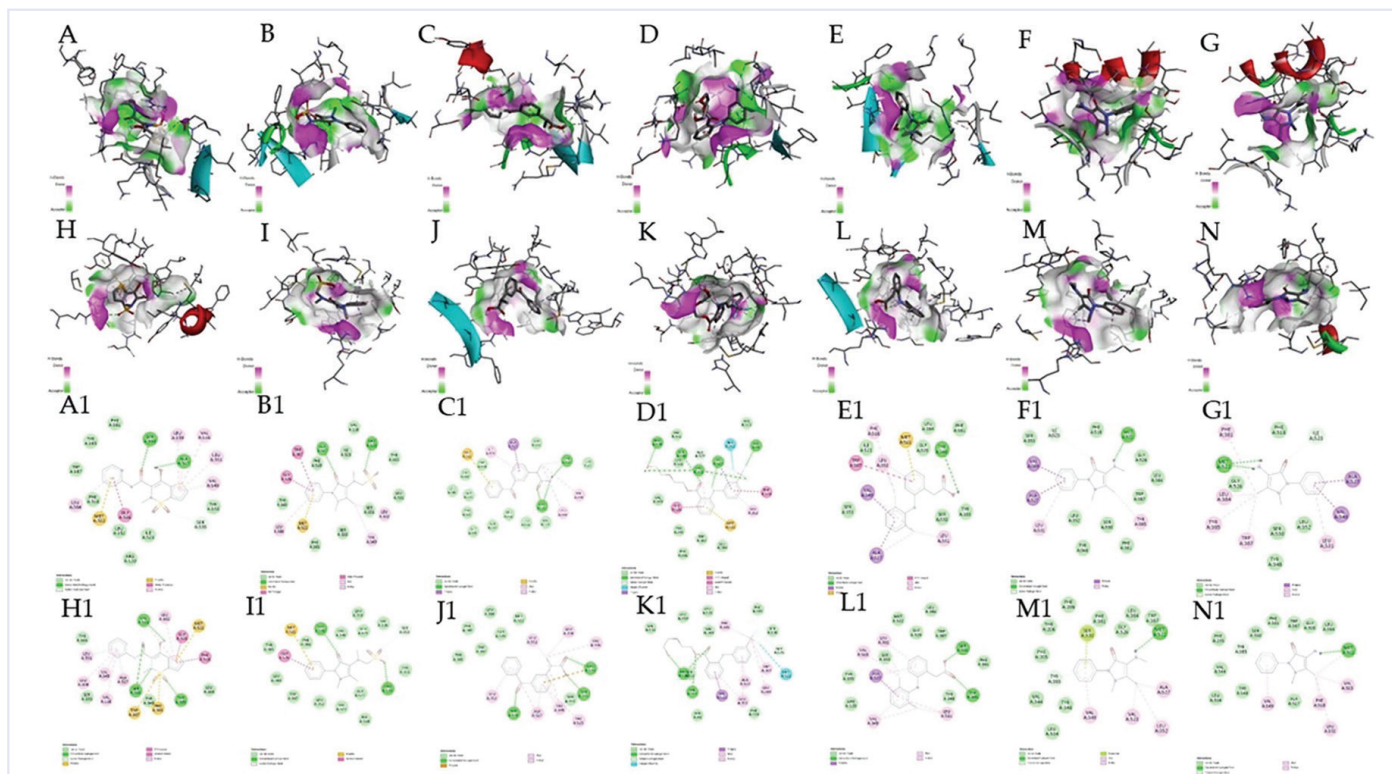


Figure 3. 3D binding conformations and corresponding 2D interaction diagrams of the ligands within the binding interface of interleukin-6 receptor alpha (IL-6R α) and the active site of type-1 angiotensin II receptor (AGTR1), visualised using BIOVIA Discovery Studio Visualizer (2025 Client). Ligands are shown in stick representation, whereas proteins are depicted using a combination of cartoon and surface models to illustrate binding topology and ligand accommodation. The upper panels (A-N) represent 3D binding conformations, arranged in two rows (IL-6R α : A-G; AGTR1: H-N). The lower panels (A1-N1) display the corresponding 2D residue-level interaction diagrams for each ligand-protein complex. (A-G) Tenoxicam-IL-6R α , metamizole-IL-6R α , ketoprofen-IL-6R α , etofenamate-IL-6R α , diclofenac-IL-6R α , 4-methylaminoantipyrine (4-MAA)-IL-6R α , and 4-aminoantipyrine (4-AA)-IL-6R α ; (H-N) Tenoxicam-AGTR1, metamizole-AGTR1, ketoprofen-AGTR1, etofenamate-AGTR1, diclofenac-AGTR1, 4-methylaminoantipyrine (4-MAA)-AGTR1, and 4-aminoantipyrine (4-AA)-AGTR1. (A1-N1) Corresponding 2D interaction diagrams for each ligand-protein complex. In the 2D interaction diagrams, conventional hydrogen bonds are indicated by green dashed lines; π - π stacking interactions by purple lines; π -alkyl and alkyl interactions by light pink lines; and π -sulfur interactions by yellow dashed lines. Residues involved in interactions are shown as coloured circles.

Figure 5A. Associated functional enrichment profiling is summarised in Table 8.

Gene Ontology (GO) Biological Process Enrichment

GO biological process enrichment analysis showed that the selected targets were principally associated with inflammatory, hemodynamic, and thrombotic processes. The most significantly enriched term was neutrophil mediated immunity (gene count =4, strength =2.54, signal =2.90, FDR = 7.43×10^{-6}), followed by regulation of platelet activation (gene count =4, strength =2.22, signal =2.35, FDR = 4.81×10^{-5}), regulation of blood pressure (gene count =5, strength =1.76, signal =2.02, FDR = 4.81×10^{-5}), blood circulation (gene count =6, strength =1.51, signal =1.73, FDR = 4.81×10^{-5}), and response to fluid shear stress (gene count =3, strength =2.29, signal =1.90, FDR = 4.00×10^{-4}) (Figure 5B; Table 8).

This profile was not biologically diffuse; rather, the enriched terms converged on a coherent axis of vascular inflammatory signalling, platelet activation, and blood pressure regulation. This pattern is consistent with the integrated functional landscape of a target set comprising IL6, ACE/AGTR1, NOS3, and F2/F5, as also reflected in the PPI network shown in Figure 4.

GO CC Enrichment

GO cellular component enrichment pointed to three significant compartments: interleukin-6 receptor complex (gene count =2, strength =3.16, signal =1.43, FDR =0.0038), endoplasmic reticulum lumen (gene count =4, strength =1.45, signal =0.99, FDR =0.0078), and serine-type endopeptidase complex (gene count =2, strength =2.23, signal =0.77, FDR =0.0475) (Figure 5C; Table 8). These results were entirely consistent with the biological composition of the network, including cytokine receptor signalling for IL6/IL6R, secretory and luminal processing for PTGS2/IL6/F2/F5, and protease-related coagulation biology for F2/F5.

GO MF Enrichment

Only two GO molecular function terms reached significance, but both were mechanistically informative. Prostaglandin-endoperoxide synthase activity was enriched through PTGS1 and PTGS2 (COX-2) (gene count =2, strength =3.34, signal =1.34, FDR =0.0055), whereas bradykinin receptor binding was enriched through ACE and AGTR1 (gene count =2, strength =3.34, signal =1.34, FDR =0.0055) (Figure S2A; Table 8). This represents a concise but pharmacologically meaningful pattern: one branch reflects cyclooxygenase-driven eicosanoid biology, whereas the other corresponds to the renin-angiotensin-bradykinin axis.

Reactome Pathway Enrichment

Reactome analysis reinforced the same mechanistic interpretation. The enriched pathways included Interleukin-6 signalling (gene count=2, strength=2.60, signal=0.96, FDR=0.0232), MAPK3 (ERK1) activation (gene count=2, strength=2.64, signal=0.96, FDR=0.0232), MAPK1 (ERK2) activation (gene count=2, strength=2.69, signal=0.96, FDR=0.0232), common pathway of fibrin clot formation (gene count=2, strength=2.30, signal=0.95, FDR=0.0232), and synthesis of PG and thromboxanes (gene count=2, strength=2.47, signal=0.95, FDR=0.0232) (Figure S2B; Table 8).

This enrichment profile directly links the inflammatory core (IL6/IL6R), the cyclooxygenase branch (PTGS1/PTGS2), and the coagulation branch (F2/F5) within a common signalling framework.

KEGG Pathway Enrichment

KEGG pathway analysis identified enrichment in several pathways relevant to inflammation, endothelial biology, and thrombosis. The most relevant selected pathways were AGE-RAGE signalling pathway in diabetic complications (gene count=3, strength=1.84, signal=1.44, FDR=0.0017), HIF-1 signalling pathway (gene count=3, strength=1.81, signal=1.43, FDR=0.0017), platelet activation (gene count=3, strength=1.73, signal=1.39, FDR=0.0017), renin-angiotensin system (gene count=2, strength=2.28, signal=1.38, FDR=0.0037), arachidonic acid metabolism (gene count=2, strength=1.86, signal=1.02, FDR=0.0135), and VEGF signalling pathway (gene count=2, strength=1.89, signal=1.02, FDR=0.0135) (Figure S2C; Table 8).

Taken together, the enrichment analyses across GO (BP, CC, and MF), KEGG, and reactome delineate an integrated mechanism involving hypoxic-inflammatory signalling, platelet reactivity, vascular regulation, and cyclooxygenase-linked lipid mediator biology.

Cytoscape-based Hub Gene Analysis

Topological analysis in Cytoscape identified IL6 as the dominant hub within the exploratory PPI network. IL6 exhibited the highest degree (6), closeness centrality (0.80000), betweenness centrality (0.67857), and MCC score (6.00000), suggesting a comparatively central position in network connectivity and shortest-path communication (Tables 9 and 10). ACE and NOS3 demonstrated similar topological profiles, each showing degree values of 3, closeness centrality values of 0.57143, betweenness centrality values of 0.04762, and MCC scores of 4.00000. F2 and AGTR1 also occupied relatively central positions within the network, whereas F5 and IL6R appeared comparatively peripheral, with degree values of 1 and betweenness centrality values of 0.00000 (Table 10).

Taken together, these findings may suggest a network organisation centred predominantly on IL6-associated inflammatory signalling, accompanied by secondary contributions from vascular regulatory and coagulation-related nodes. However, these observations should be interpreted as exploratory and hypothesis-generating topological associations rather than mechanistic evidence of causal biological interactions.

Table 5. Postoperative pain scores and adequacy of analgesic control

Analgesic agent	n	POD 1 NRS	POD 2 NRS	POD 3 NRS	POD 4 NRS	POD 1	POD 4	Overall	p-value
Ketoprofen	162	3.1±0.8	2.6±0.7	2.2±0.6	1.8±0.5	126 (77.8%)	155 (95.7%)	140 (86.4%)	0.18
Diclofenac	148	3.0±0.7	2.5±0.7	2.1±0.6	1.7±0.5	118 (79.7%)	143 (96.6%)	129 (87.2%)	0.22
Tenoxicam	132	3.2±0.8	2.7±0.7	2.3±0.6	1.9±0.5	99 (75.0%)	125 (94.7%)	112 (84.8%)	0.14
Etofenamate	119	3.0±0.7	2.4±0.6	2.0±0.5	1.7±0.5	96 (80.7%)	115 (96.6%)	106 (89.1%)	0.27
Metamizole	160	2.9±0.7	2.4±0.6	2.0±0.5	1.6±0.5	132 (82.5%)	156 (97.5%)	146 (91.3%)	0.09
Overall	721	3.0±0.8	2.5±0.7	2.1±0.6	1.7±0.5	571 (79.2%)	694 (96.3%)	633 (87.8%)	0.16

Between-group comparisons of daily NRS scores were performed using one-way analysis of variance or Kruskal-Wallis test according to distributional assumptions. Adequate analgesia rates were compared using the chi-square test. Values are presented as mean ± standard deviation or number (%). Adequate analgesia was defined as NRS ≤3 at rest
NRS: Numeric rating scale; POD: Postoperative day.

Table 6. Distribution of postoperative adverse events according to primary analgesic class

Complication	Ketoprofen (n=162)	Diclofenac (n=148)	Tenoxicam (n=132)	Etofenamate (n=119)	Metamizole (n=160)	p-value
Increased surgical bleeding (24 h)	5 (3.1%)	4 (2.7%)	3 (2.3%)	1 (0.8%)	1 (0.6%)	0.08
Oliguria	6 (3.7%)	5 (3.4%)	4 (3.0%)	2 (1.7%)	2 (1.2%)	0.12
Acute kidney injury	3 (1.9%)	3 (2.0%)	2 (1.5%)	1 (0.8%)	0 (0%)	0.09
Gastrointestinal bleeding	1 (0.6%)	1 (0.7%)	1 (0.8%)	0 (0%)	1 (0.6%)	0.94
Dyspeptic symptoms	14 (8.6%)	10 (6.8%)	9 (6.8%)	4 (3.4%)	6 (3.8%)	0.03
Transient hypotension	2 (1.2%)	1 (0.7%)	1 (0.8%)	1 (0.8%)	1 (0.6%)	0.91
Rhythm-related concern	1 (0.6%)	1 (0.7%)	1 (0.8%)	1 (0.8%)	1 (0.6%)	0.99

Values are presented as number and percentage. Between-group comparisons were performed using the chi-square test or Fisher's exact test, as appropriate. Given the exploratory nature of the subgroup analyses, p-values should be interpreted cautiously because of the potential risk of type I error inflation.

Table 7. Univariable and multivariable logistic regression analysis for postoperative adverse events evaluated in relation to analgesic exposure

Variable	Univariable OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age (per 10-year increase)	1.24	1.11-1.39	<0.001	1.18	1.02-1.36	0.02
Male sex	1.09	0.76-1.56	0.64	1.06	0.71-1.59	0.78
NYHA class III-IV	1.67	1.23-2.28	0.001	1.42	1.03-1.96	0.03
LVEF <45%	1.51	1.11-2.06	0.009	1.37	1.01-1.86	0.04
Baseline GFR <60 mL/min	1.94	1.41-2.67	<0.001	1.71	1.18-2.47	0.004
Diabetes mellitus	1.38	1.01-1.89	0.04	1.29	0.93-1.78	0.12
Hypertension	1.19	0.88-1.60	0.25	1.12	0.82-1.54	0.46
COPD	1.31	0.91-1.89	0.15	1.24	0.85-1.82	0.26
Previous myocardial infarction	1.44	1.05-1.97	0.02	1.31	0.94-1.83	0.11
Operation duration (per 60 min increase)	1.29	1.11-1.50	0.001	1.22	1.04-1.43	0.01
Concomitant anticoagulant therapy	1.71	1.23-2.37	0.001	1.56	1.11-2.19	0.01
Loop diuretic use	1.61	1.16-2.24	0.004	1.48	1.05-2.08	0.02
ACE inhibitor therapy	1.41	1.02-1.95	0.03	1.33	0.94-1.89	0.10
Amiodarone therapy	1.34	0.92-1.95	0.12	1.28	0.86-1.91	0.22
Ketoprofen exposure	1.54	1.12-2.12	0.008	1.39	1.01-1.91	0.04
Diclofenac exposure	1.41	1.03-1.94	0.03	1.32	0.96-1.81	0.08
Tenoxicam exposure	1.36	0.98-1.89	0.06	1.27	0.91-1.78	0.12
Etofenamate exposure	0.95	0.66-1.36	0.77	0.92	0.63-1.34	0.66
Metamizole exposure	0.74	0.52-1.06	0.09	0.79	0.54-1.15	0.21

Odds ratios (ORs) are presented with 95% confidence intervals (CI). The outcome variable represents the composite endpoint of postoperative adverse events evaluated in relation to analgesic exposure during the early postoperative period.

NYHA: New York Heart Association; LVEF: Left ventricular systolic function; COPD: Chronic obstructive pulmonary disease; ACE: Angiotensin-converting enzyme.

DISCUSSION

The present study provides a clinically oriented evaluation of the early postoperative safety profile of parenteral non-opioid analgesics in patients undergoing cardiothoracic surgery, complemented by an exploratory *in silico* analysis designed to contextualize the observed clinical patterns within a systems-level biological framework. The principal findings suggest that, under routine clinical conditions, these agents are generally associated with a low incidence of severe adverse events, whereas more frequent but comparatively mild outcomes—most notably dyspeptic symptoms—demonstrate variability across analgesic classes. Among the evaluated agents, ketoprofen was associated with a modest increase in complication risk in multivariable-adjusted analyses; however, this observation should be interpreted with appropriate caution in light of the non-randomized design and the potential for residual confounding.

Interpretation of these findings requires careful consideration of the clinical context. Cardiothoracic surgical populations are inherently heterogeneous, with variability in age, cardiac function, renal reserve, and perioperative pharmacotherapy likely influencing both analgesic selection and susceptibility to adverse events. In routine practice, the choice of a specific analgesic agent reflects clinical judgement rather than random allocation, introducing an element of indication bias that cannot be fully accounted for despite multivariable adjustment.^[31] Within

the present cohort, patients perceived to have higher perioperative bleeding, renal, or hemodynamic risk profiles may have preferentially received certain analgesic agents according to clinician judgement and institutional practice patterns, which may have contributed to the observed differences in postoperative adverse event rates despite statistical adjustment. Accordingly, the associations identified in the present analysis should not be construed as causal, but rather as indicative of clinically relevant patterns emerging under real-world conditions. The marked baseline differences between sternotomy and thoracotomy populations should also be acknowledged as a potential source of residual confounding. Although multivariable adjustment was applied, propensity score matching or stratified sensitivity analyses were not performed, primarily to avoid further reduction in effective sample size given the relatively low number of adverse events. Accordingly, the adjusted associations reported in the present study should be interpreted cautiously.^[31,32] In addition, cardiopulmonary bypass duration and aortic cross-clamp time may represent clinically relevant contributors to postoperative bleeding and organ dysfunction, particularly in cardiac surgical populations. Although these variables were recorded for applicable procedures, they were not incorporated into the primary regression framework because they were not uniformly applicable across the heterogeneous sternotomy-thoracotomy cohort. Their potential confounding influence should therefore be acknowledged.

Table 8. Functional enrichment analysis of selected targets

Category	Term	Gene count	Strength	Signal	FDR	Matching genes
GO biological process	Neutrophil mediated immunity	4	2.54	2.90	7.43e-06	<i>ACE, F2, IL6R, IL6</i>
GO biological process	Regulation of platelet activation	4	2.22	2.35	4.81e-05	<i>NOS3, F2, IL6R, IL6</i>
GO biological process	Regulation of blood pressure	5	1.76	2.02	4.81e-05	<i>ACE, NOS3, PTGS1, PTGS2, AGTR1</i>
GO biological process	Blood circulation	6	1.51	1.73	4.81e-05	<i>ACE, NOS3, PTGS1, PTGS2, F5, AGTR1</i>
GO biological process	Response to fluid shear stress	3	2.29	1.90	4.00e-04	<i>ACE, NOS3, PTGS2</i>
GO cellular component	Interleukin-6 receptor complex	2	3.16	1.43	0.0038	<i>IL6R, IL6</i>
GO cellular component	Endoplasmic reticulum lumen	4	1.45	0.99	0.0078	<i>F2, PTGS2, F5, IL6</i>
GO cellular component	Serine-type endopeptidase complex	2	2.23	0.77	0.0475	<i>F2, F5</i>
GO molecular function	Prostaglandin-endoperoxide synthase activity	2	3.34	1.34	0.0055	<i>PTGS1, PTGS2</i>
GO molecular function	Bradykinin receptor binding	2	3.34	1.34	0.0055	<i>ACE, AGTR1</i>
KEGG	AGE-RAGE signaling pathway in diabetic complications	3	1.84	1.44	0.0017	<i>NOS3, IL6, AGTR1</i>
KEGG	HIF-1 signaling pathway	3	1.81	1.43	0.0017	<i>NOS3, IL6R, IL6</i>
KEGG	Platelet activation	3	1.73	1.39	0.0017	<i>NOS3, F2, PTGS1</i>
KEGG	Renin-angiotensin system	2	2.28	1.38	0.0037	<i>ACE, AGTR1</i>
KEGG	Arachidonic acid metabolism	2	1.86	1.02	0.0135	<i>PTGS1, PTGS2</i>
KEGG	VEGF signaling pathway	2	1.89	1.02	0.0135	<i>NOS3, PTGS2</i>
Reactome	Interleukin-6 signaling	2	2.60	0.96	0.0232	<i>IL6R, IL6</i>
Reactome	MAPK3 (ERK1) activation	2	2.64	0.96	0.0232	<i>IL6R, IL6</i>
Reactome	MAPK1 (ERK2) activation	2	2.69	0.96	0.0232	<i>IL6R, IL6</i>
Reactome	Common pathway of fibrin clot formation	2	2.30	0.95	0.0232	<i>F2, F5</i>
Reactome	Synthesis of PG and thromboxanes (TX)	2	2.47	0.95	0.0232	<i>PTGS1, PTGS2</i>

ACE: Angiotensin-converting enzyme; NOS3: Nitric oxide synthase; GO: Gene ontology; KEGG: Kyoto encyclopedia of genes and genomes; PG: Prostaglandins; VEGF: Vascular endothelial growth factor; FDR: False discovery rate.

Within this framework, the study is best understood as providing hypothesis-generating insights into the safety profile of commonly used parenteral non-opioid analgesics during the early postoperative period. While the overall incidence of serious complications was low, the observed variability across agents particularly with respect to gastrointestinal and renal-related endpoints may warrant further investigation in more controlled settings. Because multiple subgroup comparisons were performed across several analgesic categories in the setting of relatively low-frequency clinical events, nominal p values should be interpreted cautiously and considered exploratory in nature, with a potential risk of type I error inflation.^[36] Accordingly, the observed difference in dyspeptic symptoms was interpreted as a nominal and hypothesis-generating safety signal rather than as confirmatory evidence of a true between-agent difference.

The observed rates of bleeding-related events, renal dysfunction, and gastrointestinal complications in the present cohort should also be interpreted in relation to the recent clinical literature on postoperative NSAID and non-opioid analgesic use after cardiac and cardiothoracic surgery. In a large adult cardiac surgery cohort evaluating early ketorolac administration, Liu et al.^[37] reported hemorrhage or hematoma in 0.7% of patients and severe acute kidney injury in 3.8%, although the bleeding definition was broader than surgical-site bleeding and renal outcomes focused on severe AKI. In a randomized trial of perioperative ketorolac

in acute type A aortic dissection surgery, Lv et al.^[38] reported postoperative hemorrhage within 24 hours >1 L in 3.70% of ketorolac-treated patients and 9.09% of placebo-treated patients, renal failure in 1.85% and 0%, AKI stage II or III in 7.41% and 18.18%, respectively, and no gastrointestinal bleeding, ulceration, or perforation in either group. A recent meta-analysis of randomized trials evaluating NSAIDs as part of multimodal analgesia after cardiac surgery also addressed bleeding, acute kidney injury, and gastrointestinal bleeding as safety outcomes.^[38] Taken together, these studies suggest that severe bleeding, renal, and gastrointestinal events during short-term postoperative NSAID exposure are generally infrequent, although direct quantitative comparison with the present cohort remains limited by differences in patient populations, analgesic agents, outcome definitions, and perioperative management strategies.^[37,38]

To extend these clinically derived observations beyond descriptive analysis, an exploratory network-based approach was incorporated with the specific aim of examining whether the pharmacological targets engaged by these agents converge on biologically coherent functional domains relevant to the observed adverse event profile. This approach reflects the recognition that postoperative complications in cardiothoracic surgery often arise from the interplay of interconnected systems namely inflammatory signalling, endothelial regulation, and coagulation rather than from isolated molecular effects. Accordingly, the integration of molecular docking and PPI analysis was not intended

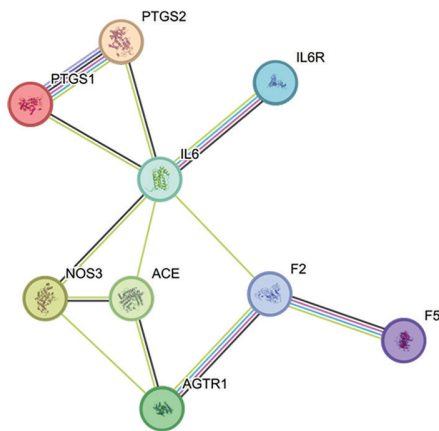


Figure 4. PPI network of docking-derived targets. The PPI network was generated using the STRING database (Homo sapiens; minimum required interaction score ≥ 0.700), illustrating known and predicted associations among the selected targets. Nodes represent proteins, and edges indicate functional associations derived from experimental data, curated databases, co-expression, and text mining. Edge thickness reflects the confidence of the interaction score.

ACE: Angiotensin-converting enzyme; NOS3: Nitric oxide synthase; PPI: Protein-protein interaction.

to establish direct mechanistic links between individual compounds and clinical outcomes, but rather to evaluate whether the target landscape exhibits structured connectivity within pathways plausibly related to these processes.

The network-based topological analysis conducted in the present study provides a preliminary framework for interpreting the functional relationships among the selected targets. In particular, IL6 emerged as a highly connected and topologically central node across multiple centrality metrics, a finding that may reflect its well-established role in inflammatory signalling cascades. However, it should be emphasised that such network-derived measures do not imply functional dominance or causal hierarchy, but rather indicate relative positioning within the constructed interaction map. The observed prominence of IL6, together with the intermediary positioning of F2 and the consistent involvement of ACE, NOS3, and AGTR1, may be indicative of a coordinated interface between inflammatory signalling, vascular regulation, and coagulation-related processes. These observations are therefore best interpreted as hypothesis-generating and exploratory, providing a systems-level perspective that may guide future experimental studies aimed at validating the biological relevance of these interactions under physiological and pathological conditions.

Notably, this integrative network perspective aligns with the enrichment patterns observed in the present analysis, which demonstrated convergence on pathways related to inflammatory signalling, endothelial function, and thrombosis. The concordance between

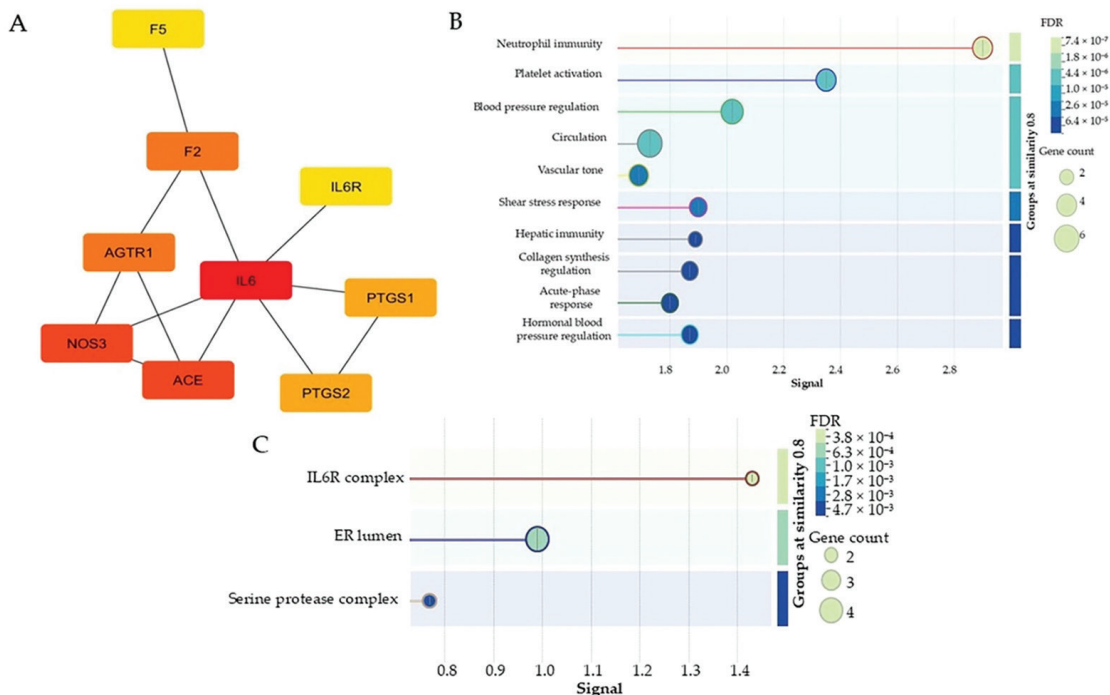


Figure 5. Cytoscape-based network topology and gene ontology enrichment analysis of the selected targets. (A) Refined protein-protein interaction network visualization generated in Cytoscape, demonstrating the topological relationships among the selected targets. Node color intensity reflects relative topological importance within the network. (B) Gene ontology biological process enrichment analysis showing predominant associations with inflammatory signaling, platelet activation, vascular regulation, and hemodynamic processes. (C) Gene ontology cellular component enrichment analysis demonstrating enrichment of the IL6 receptor complex, endoplasmic reticulum lumen, and serine protease-related complexes. Bubble size represents gene count, whereas color intensity reflects false discovery rate (FDR) significance.

ACE: Angiotensin-converting enzyme; NOS3: Nitric oxide synthase; AGTR1: Type-1 angiotensin II receptor.

Table 9. Hub gene ranking obtained using the MCC algorithm implemented in the CytoHubba plugin of Cytoscape. Higher MCC scores indicate greater topological importance within the PPI network

Rank	Gene	MCC score
1	<i>IL6</i>	6.00000
2	<i>ACE</i>	4.00000
3	<i>NOS3</i>	4.00000
4	<i>F2</i>	3.00000
5	<i>AGTR1</i>	3.00000
6	<i>PTGS1</i>	2.00000
7	<i>PTGS2</i>	2.00000
8	<i>F5</i>	1.00000
9	<i>IL6R</i>	1.00000

MCC: Maximal clique centrality; PPI: Protein-protein interaction.

Table 10. Network centrality measures derived from Cytoscape analysis, including degree, closeness centrality, and betweenness centrality values for each node within the PPI network

Gene	Degree	Closeness centrality	Betweenness centrality
<i>F5</i>	1	0.40000	0.00000
<i>IL6</i>	6	0.80000	0.67857
<i>IL6R</i>	1	0.47059	0.00000
<i>PTGS1</i>	2	0.50000	0.00000
<i>F2</i>	3	0.61538	0.29762
<i>ACE</i>	3	0.57143	0.04762
<i>NOS3</i>	3	0.57143	0.04762
<i>AGTR1</i>	3	0.50000	0.07143
<i>PTGS2</i>	2	0.50000	0.00000

PPI: Protein-protein interaction; ACE: Angiotensin-converting enzyme; NOS3: Nitric oxide synthase; AGTR1: Type-1 angiotensin II receptor.

network topology and functional enrichment supports the internal coherence of the analytical framework without implying mechanistic inference. In this context, the *in silico* component should be viewed as a structured means of contextualizing the clinical findings within a biologically plausible landscape, rather than as an explanatory model of causation.

The incorporation of *in silico* analyses in the present study was therefore intended to provide a complementary, hypothesis-generating perspective to the clinical findings, rather than to establish direct mechanistic inference. Importantly, this approach allows the identification of structured relationships within the target network that may not be readily apparent from clinical data alone, thereby offering a conceptual bridge between pharmacological target engagement and observed clinical variability.

Several limitations inherent to the clinical design of the present study should be acknowledged. The retrospective and observational nature of the analysis precludes causal inference and introduces the potential for residual confounding despite statistical adjustment. Analgesic selection was not randomized and likely reflects clinician preference and patient-specific factors, thereby introducing indication bias. In addition,

the number of covariates incorporated into the multivariable model relative to the total number of adverse events may have increased the risk of model overfitting. Accordingly, the regression findings should be interpreted as exploratory estimates rather than definitive effect measures. Furthermore, the study was conducted within a limited number of centers operating under similar institutional protocols, which may restrict the generalizability of the findings to other clinical settings. The analysis was also confined to early postoperative outcomes and does not capture longer-term safety profiles associated with these agents. Moreover, no experimental, biochemical, or patient-level mechanistic validation was performed to directly link the exploratory *in silico* findings with the observed clinical outcomes; therefore, the translational interpretation of these associations should be considered hypothesis-generating and interpreted cautiously. The concomitant administration of intravenous paracetamol across all study groups may represent a potential limitation with respect to complete isolation of the effects attributable to the index analgesic agents. Nevertheless, because paracetamol exposure was distributed comparably among groups and represents a pharmacologically distinct analgesic class, its potential impact on the comparative interpretation of the study findings was considered limited.

In parallel, the computational component of the study carries its own methodological constraints. Docking simulations were performed on static crystallographic structures and therefore do not capture the conformational dynamics including induced-fit phenomena and allosteric reorganization that characterize protein-ligand interactions under physiological conditions. The absence of molecular dynamics simulations further limits the ability to assess the temporal stability of predicted binding modes. In addition, empirical scoring functions provide only approximate estimates of binding affinity and may not fully account for entropic contributions or solvent effects, particularly in complex or flexible systems.

No formal redocking validation was undertaken to assess pose reproducibility, and implicit solvent conditions preclude explicit modelling of water-mediated interactions and pH-dependent protonation states. Interaction classifications derived from BIOVIA Discovery Studio are algorithmically defined and may differ from those generated by alternative platforms, particularly for weak or non-classical interactions. Accordingly, the docking results should be regarded as exploratory structural observations rather than definitive evidence of biological activity.

Taken together, both the clinical and computational findings presented in this study should be interpreted within a cautious, hypothesis-generating framework. The integrated approach adopted here is intended to inform, rather than to resolve, questions regarding the safety profile of parenteral non-opioid analgesics in the cardiothoracic surgical setting. Future studies incorporating prospective designs, standardized analgesic protocols, and experimental validation at the molecular and cellular levels will be required to further delineate the relationships suggested by the present analysis.

The present study provides a clinically grounded evaluation of the early postoperative safety profile of parenteral non-opioid analgesics in cardiothoracic surgical patients, complemented by an exploratory *in silico* analysis intended to contextualize these observations within a broader biological framework. Within the constraints of a retrospective, real-world design, the findings suggest that these agents

are generally associated with a low incidence of severe adverse events, while demonstrating agent-specific variability in more common, non-severe outcomes. Importantly, the observed associations should not be interpreted as evidence of causal relationships, but rather as indicative of patterns that may reflect the complex interaction between pharmacological effects and patient-specific clinical factors in the early postoperative setting. In this respect, the results are best viewed as hypothesis-generating and reflective of routine clinical practice rather than controlled experimental conditions. The incorporation of molecular docking and network-based analyses was undertaken to examine whether the pharmacological target space of these agents exhibits coherent organization within biological pathways plausibly relevant to the observed clinical outcomes. While no mechanistic inference can be drawn, the convergence of targets within domains related to inflammatory signalling, vascular regulation, and coagulation may offer a systems-level perspective that aligns with the clinical observations and supports the internal consistency of the analytical framework. Taken together, the integrated clinical and computational findings presented herein provide a structured, exploratory perspective on the safety profile of parenteral non-opioid analgesics in cardiothoracic surgery. These observations may inform the design of future investigations, including prospective clinical studies and experimental pharmacological analyses, aimed at clarifying the relationships suggested by the present work under more controlled and mechanistically resolved conditions.

Ethics

Ethics Committee Approval: The study protocol was also approved by the Ethics Committee of Dr. İsmail Fehmi Cümaloğlu City Hospital (decision no: AN-261203-15, date: 12 March 2026). The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was waived because of the retrospective observational design of the study.

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For transparency, the authors note that an artificial intelligence-assisted language model (ChatGPT, OpenAI) was utilized to support language correction. This assistance was limited to linguistic refinement; all scientific content, critical analysis, and final editorial decisions were made exclusively by the authors.

Footnotes

Authorship Contributions

Surgical and Medical Practices: L.Ç.O.; Concept: L.Ç.O., İ.Y.; Design: L.Ç.O., E.G., İ.Y.; Data Collection or Processing: L.Ç.O., E.G., Analysis or Interpretation: L.Ç.O., E.G., İ.Y.; Literature Search: İ.Y.; Writing: L.Ç.O., E.G., İ.Y.

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Supplementary Materials Links: <https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/c212079e-91cc-4404-8e29-4f7d12152cda.pdf>

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