ORIGINAL CLINICAL RESEARCH REPORT

CME

Multimodal Analgesia and Enhanced Recovery Outcomes in Cardiac Surgical Patients: An Observational Cohort Study

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See Article, page 215

BACKGROUND: Multimodal analgesia, the use of more than 1 pharmacologic agent targeting different receptors, is a cornerstone of enhanced recovery after cardiac surgery (ERACS), but there are limited studies to support its efficacy. We aimed to explore associations between multimodal analgesia and enhanced recovery outcomes after cardiac surgery.

METHODS: We performed a retrospective cohort study using data from the Society of Thoracic Surgeons database from 2020 to 2023. Adults undergoing elective coronary artery bypass grafting (CABG), valve, or combined CABG-valve surgery were included. Our primary hypothesis was that multimodal analgesia would be associated with a lower maximum postoperative pain score on postoperative day 3 (POD3). Secondarily, we hypothesized that multimodal analgesia would be associated with reduced mechanical ventilation hours, intensive care unit stay, delirium, pneumonia, and reintubation. Linear mixed-effects regression models and generalized linear mixed-effects regression models were used to examine the extent the use of multimodal analgesia was associated with study outcomes after controlling for confounders.

RESULTS: Over the 4-year study period, there were 17,371 eligible cardiac surgical cases and 15,515 patients (89.3%) received multimodal analgesia. There was no association between multimodal analgesia use and maximum postoperative pain score on POD3 (b = −0.07, 95% confidence interval [CI], −0.32 to 0.18, P = .57), after adjusting for confounders. There was an association between multimodal analgesia use and initial mechanical ventilation hours (b = 0.45 hours, 95% CI, 0.04–0.86, P = .03). Compared to patients who received multimodal analgesia, those who did not receive multimodal analgesia had approximately 30 minutes longer of initial mechanical ventilation time on average. Initial mechanical ventilation time decreased as the number of multimodal analgesic increased (b= −0.33 hours, 95% CI, −76 to −0.10, P = .14) for 1 multimodal analgesic; Est = −1.98 hours, 95% CI, −3.79 to −0.18, P = .03 for 5 multimodal analgesics). Acetaminophen use was associated with a reduced likelihood of delirium (odds ratio [OR] = 0.75, 95% CI, 0.57–0.94, P = .02), while use of a regional nerve block was associated with increased likelihood of unplanned reintubation (OR = 1.59, 95% CI, 1.12–2.27, P = .01).

CONCLUSIONS: In this retrospective study, multimodal analgesia was not associated with the primary outcome of reduction in maximum pain score but was associated with more rapid extubation. Larger prospective observational and randomized controlled trials of individual analgesic drugs are needed to optimize ERACS protocols. (Anesth Analg 2026;142:220–230)

KEY POINTS

- **Question:** Does multi-modal analgesia enhance recovery after elective cardiac surgery by reducing pain and facilitating timely extubation and intensive care unit discharge?
- **Findings:** In a cohort of elective cardiac surgical patients, use of multimodal analgesia was not associated with a lower maximum postoperative pain score 3 days after cardiac surgery but was associated with fewer initial mechanical ventilation hours after surgery.
- **Meaning:** Multimodal analgesia may be associated with earlier extubation after cardiac surgery; however, more data are needed in regards to its impact on postoperative pain and which analgesics are most likely to be beneficial with the fewest side-effects.

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Accepted for publication April 14, 2025.

DOI: 10.1213/ANE.0000000000007612

Conflicts of Interest, Funding: Please see DISCLOSURES at the end of this article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

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In recent years, there has been increased popularity and adoption of Enhanced Recovery After Surgery (ERAS) protocols worldwide in nearly all surgery types including Enhanced Recovery after Cardiac Surgery (ERACS).[1–3] ERAS protocols include a multifaceted, protocolized approach to lessen surgical insult, promote recovery, and improve postoperative clinical outcomes. ERAS protocols are associated with reduced length of stay and fewer complications.[4] A core tenet of ERAS protocols is the use of multimodal analgesia, even though the evidence to support its use is somewhat limited.[5] Despite limited evidence, the use of multimodal analgesia has been selected by the Centers for Medicare and Medicaid Services (CMS) as a Merit-Based Incentive Payment System (MIPS) quality measure (Quality ID #477).[6]

A primary aim of multimodal analgesia is to reduce postoperative pain and opioid usage during the perioperative period. Multimodal analgesia may also reduce opioid-related risks, including persistent opioid use, which occurs in approximately 10% to 15% of patients after cardiac surgery.[7–9] Other potential benefits of multimodal analgesia during the perioperative period include facilitation of enhanced surgical recovery by reducing mechanical ventilation hours and intensive care unit (ICU) length of stay, delirium, and facilitating earlier hospital discharge.[4,10]

Several consensus guidelines have been published outlining important principles of ERACS for cardiac surgical patients during the preoperative, intraoperative, and postoperative periods with recommendations for the use of multimodal, opioid-sparing analgesia.[2,11] Recently, the ERAS Cardiac Society, ERAS International Society, and The Society of Thoracic Surgeons (STS) released a joint consensus statement of best practices for the management of the adult patient undergoing cardiac surgery.[12] They reported with a moderate level of evidence that a "multimodal approach reduces reliance on opioid-based analgesia and optimizes perioperative pain management."[12] Unfortunately, these consensus guidelines offer limited guidance on which specific agents are most effective in terms of enhancing recovery.

Unlike other components of ERACS protocols, few studies have explored whether multimodal analgesia reduces pain or improves recovery in cardiac surgical patients. Several studies in noncardiac surgical patients have failed to demonstrate a benefit with multimodal analgesia.[10,13] Likewise, the use of multimodal analgesic agents is not without potential side effects.[14] For these reasons, it is important to explore whether the use of multimodal analgesia is associated with improvements in clinically meaningful, patient-centered outcomes. The aim of our study was to explore whether multimodal analgesia was associated with reduced pain and enhanced recovery after elective cardiac surgery in a large national cohort of cardiac surgical patients. Our primary study hypothesis was that the use of multimodal analgesia would be associated with lower maximum postoperative pain scores after cardiac surgery. Secondarily, we hypothesized that multimodal analgesia would be associated with fewer mechanical ventilation hours, reduced ICU length of stay, and less delirium, pneumonia, and reintubation.

METHODS

Patients and Data

The University of Virginia School of Medicine Institutional Review Board exempted the study and waived the requirement for written informed consent. A multicenter retrospective cohort study was conducted utilizing the national STS Adult Cardiac Surgery Database version 4.20.2. Patients were included in the study if they were at least 18 years of age at the time of surgery, had surgery between 2020 and 2023 and underwent one of the following elective procedures at an STS site: Isolated coronary artery bypass grafting (CABG) surgery, Isolated valve repair/replacement, combined CABG + valve repair/replacement.

Exclusion criteria were age less than 18 years or older than 90 years, emergency surgery, American Society of Anesthesiologists (ASA) physical status classification 5 or 6, postcardiopulmonary bypass (CPB) support with a ventricular assist device or extracorporeal membrane oxygenation, occurrence of operative mortality or missing data on operative mortality, and mechanical ventilation time greater than 72 hours.

For all patients, we collected demographics, comorbidities, STS calculated risk scores for postoperative complications, preoperative medications, laboratory values, intraoperative data, and postoperative outcomes. Definitions for all variables were based on STS database version 4.20.2 definitions (https://www.sts.org/sts-national-database).

Exposure of Interest

The anesthesiology module of the STS database (starting version 4.20.2) collects information on multimodal analgesia, which is defined in the database as receipt of at least 1 nonopioid analgesic medication from 2 hours before operating room exit up to 24 hours after surgery. Information on specific drugs is also collected and includes ketamine, dexmedetomidine, local anesthetic injection/regional anesthesia, intravenous lidocaine, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs included ketorolac, ibuprofen, naproxen, and celecoxib.

Study Outcomes

The study's primary outcome was the highest numeric postoperative pain score on postoperative day (POD) 3 after surgery. This is the only postoperative pain score data that is collected in the STS database anesthesiology module. Maximum pain score on POD3 was selected as our primary outcome because it is patient-centered and improved pain control is one of the primary objectives of multimodal analgesia. Although maximum pain score on POD3 occurs after the acute effects of early multimodal analgesia, it allows for exploring differences in pain score trajectory after cardiac surgery and prior studies have suggested that early multimodal analgesia can alter pain score trajectory.(PMIDs 35155466, 26730224) Secondary outcomes were initial mechanical ventilation hours after surgery, initial intensive care unit hours after surgery, postoperative delirium, postoperative pneumonia, and unplanned postoperative reintubation.

Statistical Analysis

The study was conducted in accordance with all applicable Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Descriptive statistics were presented as means, standard deviations, medians, interquartile ranges (IQR) for continuous variables where appropriate, and frequencies and proportions for categorical variables.

We used 3 sets of linear mixed-effects regression models to examine the extent to which the use of multimodal analgesia was associated with maximum postoperative pain score on POD3. In Model 1, use of multimodal analgesia (yes versus no) was included as a fixed effect. Use of any multimodal analgesia was modeled as the reference group, given the larger proportion of patients who received multimodal analgesia. In Model 2, the total number of nonopioid analgesics (reference: zero) was included as a fixed effect. This variable was modeled as a categorical variable with the intention of detecting a potential nonlinear association between the count of nonopioid analgesics used and the maximum pain score. A single case in which 6 nonopioid analgesics were administered was excluded from Model 2 to prevent extreme estimated coefficients. In Model 3, each of the 6 nonopioid analgesics (ketamine, dexmedetomidine, regional nerve block, acetaminophen, lidocaine, NSAIDs; reference: no) were included as individual fixed effects.

Similar sets of linear mixed-effects regression models were specified to evaluate the extent to which the use of multimodal analgesia was associated with initial mechanical ventilation hours (capped at 48 hours) after surgery and initial ICU hours after surgery. Although the distribution of initial mechanical ventilation hours after surgery was right-skewed, the distribution of residuals did not violate the assumptions of heteroscedasticity; therefore, the original raw values of mechanical ventilation hours were used in the models. However, initial ICU time was log-transformed.

In all models, both site ID and surgeon ID were included as random intercepts, with surgeons nested within sites, to account for within-site and within-surgeon correlations. In the postoperative day 3 pain score models, patient's pain score at baseline, age, gender, race/ethnicity, body mass index (BMI), history of diabetes, drug use, active smoking, cancer, and intraoperative dosage of medication (fentanyl, sufentanil, and midazolam) were included as control variables. In the initial mechanical ventilation time and initial ICU hour models, patients' age, gender, race/ethnicity, BMI, history of diabetes, hypertension, chronic lung disease, dialysis, active smoking, left ventricular ejection fraction (LVEF), CPB time in hours, intraoperative dosages of medications, and total crystalloid volume (liters) were included as control variables. Control variables were selected a priori based on which variables were most likely to be confounders (association with exposure and outcome). Marginal effect estimates, representing average effects across the population, were calculated for the various models and displayed on forest plots to summarize results.

To examine the extent to which the use of multimodal analgesia was associated with postoperative delirium, postoperative pneumonia, and unplanned postoperative reintubation, generalized linear mixed-effects regression models with a binomial link were used. The 3 sets of generalized linear mixed-effects regression models were similarly parameterized as described above, except that patients with 4 or more nonopioid-analgesics used were combined into 1 category in Model 2. As the proportion of negative postoperative outcomes were low, we only controlled for predicted morbidity/mortality to allow models to converge and reduce unstable estimates. Predicted morbidity/mortality was rescaled into 0 to 100 to allow variables to be on similar scales.

RESULTS

There were 17,809 elective adult cardiac surgical cases from 51 sites between 2020 and 2023 that underwent CABG, valve, or combined CABG-valve surgery. Of these, 193 cases had initial mechanical ventilation time ≥72 hours, and 298 cases had operative mortality coded as "1" (mortality) or "99" (missing). Both sets were excluded from the analysis. The final analyzed cohort consisted of 17,371 elective cardiac surgical cases of whom 15,515 (89.3%) received multimodal analgesia. Descriptive statistics for the analytic cohort are presented in Table 1.

Table 1. Demographic and Clinical Characteristics of Patients in Cohort

Variable	Value	Multimodal analgesia: Yes		Multimodal analgesia: No	
		n	%	n	%
Gender	Male	11,297	72.8	1246	67.2
	Female	4218	27.2	607	32.8
Age (y)	<45	603	3.9	82	4.4
	45–54	1567	10.1	177	9.6
	55–64	4352	28.0	509	27.5
	65–74	6159	39.7	711	38.4
	≥75	2837	18.3	374	20.2
Race/ethnicity	Non-Hispanic white	11,476	77.4	1405	78
	Non-Hispanic black	789	5.3	185	10.3
	Non-Hispanic other	1425	9.6	92	5.1
	Hispanic	1148	7.7	120	6.6
Body mass index	Underweight/healthy weight	3534	22.8	376	20.3
	Overweight	5622	36.2	682	36.9
	Obesity	6351	41	791	42.8
Drug use within 1 y		275	1.8	29	1.6
Cancer within 5 y		874	5.6	76	4.1
Diabetes		6149	39.6	786	42.4
Hypertension		13,094	84.4	1653	89.2
Dialysis		448	2.9	59	3.2
Active smoking		2052	13.2	312	16.8
Nonopioid analgesic used	Dexmedetomidine	11,759	75.8	-	-
	Ketamine	4387	28.3	-	-
	Lidocaine	1370	8.8	-	-
	Regional nerve block	2010	13	-	-
	NSAIDs	1805	11.6	-	-
	Acetaminophen	11,789	76	-	-
Number of multimodal analgesics used	1	4277	27.6		
	2	5982	38.6	-	-
	3	4085	26.4	-	-
	4	1097	7.1	-	-
	5	46	.3	-	-
	6	1	0	-	-
		Mean	SD	Mean	SD
Baseline numeric pain score		2.3	4.3	2.0	4.1
CPB time (h)		119.0	50.8	119.4	53.5
LVEF (%)		56.1	10.5	53.5	11.3
Maximum numeric pain score POD 3		5.1	3.2	6.2	3.5
Initial mechanical ventilation hours		6.3	6.6	7.8	8.4
Initial ICU hours		62.5	61.2	75.3	82.5
		n	%	n	%
Postoperative delirium		509	3.3	55	3.0
Postoperative pneumonia		192	1.2	23	1.2
Unplanned reintubation		104	0.7	4	0.2

Abbreviations: CPB, cardiopulmonary bypass time; ICU, intensive care unit; LVEF, left ventricular ejection fraction; NSAIDs, nonsteroidal anti-inflammatory drugs; POD, postoperative day; SD, standard deviation.

Association Between the Use of Multimodal Analgesia and Maximum Postoperative Pain Score on Postoperative Day 3

The adjusted associations between multimodal analgesia use and maximum postoperative pain score on POD3 are shown in Table 2. Model 1 showed no association between multimodal analgesia use and maximum postoperative pain score on POD3 (b= −0.07, 95% confidence interval [CI], −0.32 to 0.18, P = .57), after adjusting for confounding variables. Similarly, Model 2 showed no association between the number of multimodal analgesics used and maximum postoperative pain score on POD3. When individual nonopioid-analgesics were included in Model 3, there was an association between NSAID use and maximum postoperative pain score on POD3 (b= 0.36, 95% CI, 0.10–0.63, P = .007). Patients who received NSAIDs reported a slightly higher maximum pain score on POD3, as compared to those who did not receive any NSAIDs, after controlling for the use of other nonopioid-analgesics, baseline pain score, and other confounding variables. There was no association between the other 5 nonopioid analgesics and maximum postoperative pain score on POD3. Figure 1 shows marginal estimates for predicted maximum pain score on POD3 from Model 3 with variables that had a significant association shown in the figure. Importantly, the association persisted when excluding dexmedetomidine (Supplemental Digital Content 1, Supplemental Table 1, https://links.lww.com/AA/F352) as well as intraoperative opioids and benzodiazepines (Supplemental Digital

Table 2. Linear Mixed-Effects Regression Models Estimating the Association Between Multimodal Analgesia and Maximum Postoperative Pain Score on Postoperative Day 3

Variable	Value	Model 1		Model 2		Model 3	
		Est	95% CI	Est	95% CI	Est	95% CI
Multimodal analgesia	No	−.07	−.32 to −.18	-	-	-	-
Number of multimodal analgesics used	1	-	-	.05	−.21 to −.30	-	-
	2	-	-	.03	−.23 to −.30	-	-
	3	-	-	.23	−.05 to −.52	-	-
	4	-	-	.32	−.01 to −.66	-	-
	5	-	-	.64	−.34 to 1.62	-	-
Ketamine	Yes	-	-	-	-	.10	−.04 to −.24
Dexmedetomidine	Yes	-	-	-	-	.14	−.02 to −.30
Regional nerve block	Yes	-	-	-	-	.10	−.10 to −.30
Acetaminophen	Yes	-	-	-	-	−.07	−.23 to −.09
Lidocaine	Yes	-	-	-	-	.11	−.14 to −.37
NSAIDs	Yes	-	-	-	-	.36	.10 to −.63**
Numeric pain score	Baseline	.23	.19 to −.27***	.23	.19 to −.27***	.23	.19 to −.27***
Age (y)	45–54	−.31	−.61 to −.02*	−.31	−.61 to −.02*	−.31	−.61 to −.02*
	55–64	−.97	−1.23 to −.70***	−.97	−1.23 to −.70***	−.96	−1.23 to −.69***
	65–74	−1.45	−1.71 to −1.19***	−1.44	−1.71 to −1.18***	−1.44	−1.70 to −1.17***
	≥75	−2.08	−2.36 to −1.80***	−2.07	−2.35 to −1.79***	−2.06	−2.34 to −1.78***
Gender	Female	.37	.26 to −.49***	.38	.26 to −.49***	.38	.26 to −.49***
Race	Non-Hispanic Black	.16	−.06 to −.39	.16	−.06 to −.39	.17	−.06 to −.39
	Non-Hispanic other	−.07	−.26 to −.12	−.07	−.26 to −.12	−.07	−.26 to −.12
	Hispanic	.04	−.16 to −.23	.05	−.15 to −.24	.05	−.14 to −.24
Body mass index	Overweight	.14	0 to −.27*	.13	0 to −.26	.13	0 to −.26
	Obesity	.34	.21 to −.48***	.34	.20 to −.47***	.34	.20 to −.47***
Diabetes	Yes	.09	−.01 to −.20	.10	−.01 to −.20	.10	−.01 to −.20
Drug use	Yes	1.02	.65 to − 1.39***	1.01	.64 to 1.38***	1.01	.64 to 1.38***
Active smoking	Yes	−.15	−.25 to −.05**	−.15	−.25 to −.05**	−.15	−.26 to −.05**
Cancer	Yes	−.05	−.16 to −.26	.05	−.17 to −.26	.05	−.16 to −.26
Intraoperative fentanyl dose (μg)	-	0	0–0*	0	0–0*	0	0–0*
Intraoperative sufentanil dose (μg)	-	0	0–0	0	0–0	0	0–0
Intraoperative midazolam dose (mg)	-	.02	0 to −.04	.02	0 to −.04	.02	0 to −.04

Abbreviations: CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs.
*P <.05, **P <.01, and ***P <.001.

Content 2, Supplemental Table 2, https://links.lww.com/AA/F353).

Consistent across the 3 models, there was an association between baseline pain score and maximum postoperative pain score on POD3 (b= 0.23, 95% CI, 0.19–0.27, P < .001 for all models). Patients with higher pain scores at baseline were more likely to report higher maximum postoperative pain scores. Patients who were older, female, obese, had a history of drug use within 1 year, and history of active smoking were also more likely to report higher maximum postoperative pain scores than their counterparts. The use of intraoperative fentanyl was also associated with increased maximum postoperative pain score, though the effect was very small.

Association Between the Use of Multimodal Analgesia and Initial Mechanical Ventilation Hours After Surgery

As shown in Table 3, there was an association between multimodal analgesia and initial mechanical ventilation hours (Model 1: b= 0.45 hours, 95% CI, 0.04–0.86, P = .001). Compared to patients who received multimodal analgesia, those who did not receive any multimodal analgesia were likely to have ~30 minutes longer of initial mechanical ventilation time. Results were consistent when the number of multimodal analgesics was included in Model 2. The initial mechanical ventilation time decreased as the number of multimodal analgesic increased (b= −0.33 hours, 95% CI, −76 to −0.10, P = .14 for 1 multimodal analgesic; b= −1.98 hours, 95% CI, −3.79 to −0.18, p=.03 for 5 multimodal analgesics). When individual nonopioid-analgesics were included in Model 3, the use of dexmedetomidine was associated with increased initial mechanical ventilation time (b= 0.57 hours, 95% CI, 0.29–0.85, P < .001), whereas the use of acetaminophen (b= −0.93 hours, 95% CI, −1.20 to −0.65, P < .001) or NSAIDS (b= −1.44 hours, 95% CI, −1.91 to −0.97, P < .001) was associated with decreased initial mechanical ventilation time. Figure 2 shows marginal estimates for predicted initial mechanical ventilation hours from Model 3 with variables that had a significant association shown in the figure.

Consistent across the 3 models, patients who were older, nonwhite, female, obese, had a history of

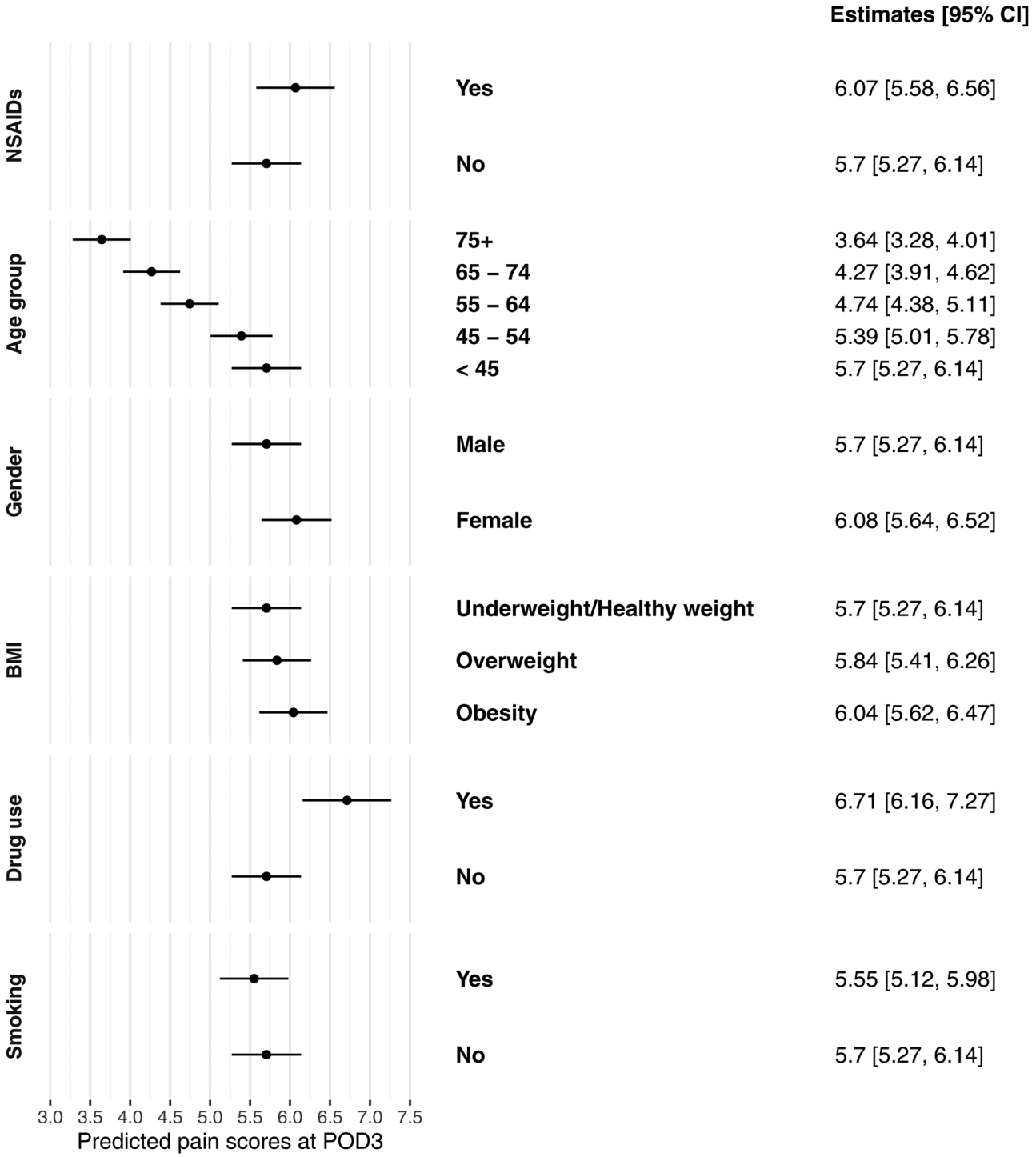

Figure 1. Forest plot showing marginal effect estimates for predicted maximum pain score on POD3 with variables that had a significant association shown in the figure. Marginal effect estimates represent the average effect of a variable across the studied population. POD3 indicates postoperative day 3.

diabetes, hypertension, chronic lung disease, dialysis, lower LVEF, and increased CPB time were also more likely to have longer initial mechanical ventilation time. The use of intraoperative midazolam and total crystalloid volume were also associated with increased postoperative ventilation time, though the effect was very small.

Association Between the Use of Multimodal Analgesia and Initial Intensive Care Unit Hours After Surgery

Results in Supplemental Digital Content 3, Supplemental Table 3, https://links.lww.com/AA/F354 showed no association between multimodal analgesia and initial ICU hours, regardless of whether

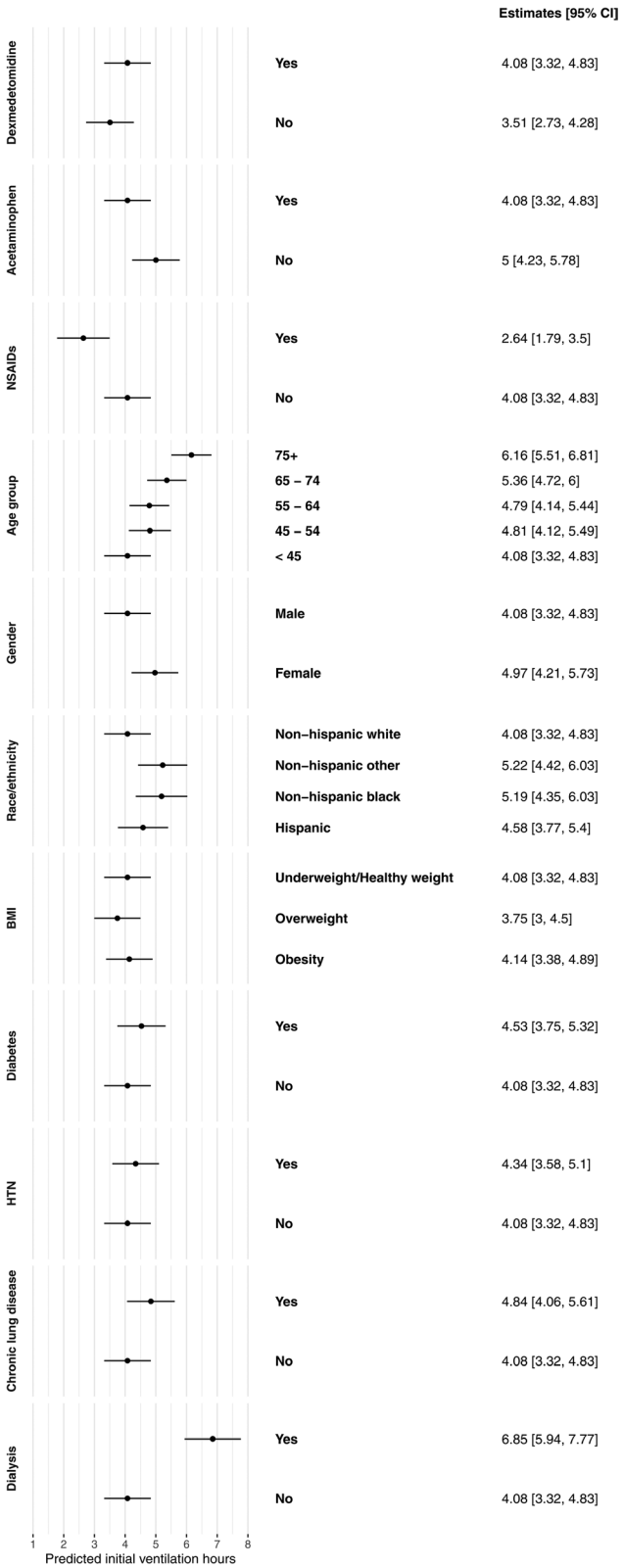

Figure 2. Forest plot showing marginal effect estimates for predicted postoperative mechanical ventilation hours with variables that had a significant association shown in the figure. Marginal effect estimates represent the average effect of a variable across the studied population.

use of multimodal analgesia was modeled as a dichotomous variable (Model 1), or as the total number of nonopioid-analgesics used (Model 2). When individual nonopioid analgesics were included in Model 3, results showed that the use of acetaminophen or NSAIDs was associated with reduced initial ICU hours (~4% and ~7% fewer hours in ICU, respectively). Figure 3 shows marginal estimates for predicted initial ICU hours after surgery from Model 3 with variables that had a significant association shown in the figure.

Consistent across the 3 models, patients who were older, female, non-Hispanic black, obese, had a history of diabetes, chronic lung disease, dialysis, lower LVEF, and increased CPB time were also more likely to have longer stay in the intensive care unit. The use of intraoperative fentanyl, sufentanil, and total crystalloid volume were also associated with increased intensive care unit hours, though the effect was very small.

Association Between the Use of Multimodal Analgesia and Postoperative Outcomes

As shown in Supplemental Digital Content 4, Supplemental Table 4, https://links.lww.com/AA/F355 the use of multimodal analgesia (Yes versus no) was not associated with negative postoperative outcomes, after controlling for predicted morbidity/mortality (Model 1). When individual analgesics were included in Model 3, the results showed that the use of acetaminophen was associated with a reduced likelihood of delirium (odds ratio [OR] = 0.75, 95% CI, 0.57–0.94, $P = .02$), whereas the use of a regional nerve block was associated with increased likelihood of unplanned reintubation (OR = 1.59, 95% CI, 1.12–2.27, $P = .01$).

DISCUSSION

In an observational cohort study examining the association between multimodal analgesia and outcomes in patients having elective CABG, valve, or combined CABG-valve surgery we did not find associations between use of multimodal analgesia, the number of multimodal analgesics used, or specific analgesics and lower maximum postoperative pain score on POD3. Our secondary analysis suggested that use of multimodal analgesia and use of multiple nonopioid analgesics was associated with reduced initial mechanical ventilation time. In addition, our exploratory analysis suggested that acetaminophen use was associated with reduced initial mechanical ventilation time, while dexmedetomidine use was associated with increased mechanical ventilation time. Acetaminophen use was also associated with less postoperative delirium and slightly decreased initial ICU hours.

Table 3. Linear Mixed-Effects Regression Models Estimating the Association Between Multimodal Analgesia and Initial Mechanical Ventilation Hours

Variable	Value	Model 1		Model 2		Model 3	
		Est	95% CI	Est	95% CI	Est	95% CI
Multimodal analgesia	No	.45	.04 to –.86*	-	-	-	-
Number of multimodal analgesics used	1	-	-	–.33	–.76 to –.10	-	-
	2	-	-	–.44	–.89 to 0	-	-
	3	-	-	–.88	–1.36 to –.40***	-	-
	4	-	-	–.74	–1.32 to –.15*	-	-
	5	-	-	–1.98	–3.79 to –.18*	-	-
Ketamine	Yes	-	-	-	-	–.01	–.27 to –.25
Dexmedetomidine	Yes	-	-	-	-	.57	.29 to –.85***
Regional nerve block	Yes	-	-	-	-	–.27	–.66 to –.11
Acetaminophen	Yes	-	-	-	-	–.93	–1.20 to –.65***
Lidocaine	Yes	-	-	-	-	.05	–.39 to –.50
NSAIDs	Yes	-	-	-	-	–1.44	–1.91 to –.97***
Age (y)	45–54	.78	.25–1.30**	.77	.25–1.29**	.73	.21–1.25**
	55–64	.77	.29–1.25**	.75	.27–1.23**	.71	.23–1.19**
	65–74	1.34	.87–1.82***	1.32	.85–1.80***	1.28	.81–1.76***
	≥75	2.18	1.67–2.69***	2.14	1.64–2.65***	2.08	1.58–2.59***
Gender	Female	.89	.69–1.09***	.89	.68–1.09***	.89	.69–1.09***
Race	Non-Hispanic African American	1.11	.71–1.51***	1.11	.71–1.51***	1.11	.71–1.51***
	Non-Hispanic other	1.17	.83–1.51***	1.17	.83–1.50***	1.15	.81–1.48***
	Hispanic	.54	.18 to –.90**	.52	.16 to –.88**	.51	.15 to –.86**
Body mass index	Overweight	–.32	–.56 to –.09**	–.32	–.56 to –.08**	–.33	–.57 to –.09**
	Obesity	.07	–.17 to –.32	.08	–.17 to –.32	.06	–.18 to –.30
Diabetes	Yes	.46	.26 to –.65***	.45	.26 to –.65***	.46	.26 to –.65***
Hypertension	Yes	.28	.01 to –.55*	.27	.01 to –.54*	.27	0 to –.53*
Chronic lung disease	Yes	.77	.56 to –.99***	.78	.56 to –.99***	.76	.55 to –.98***
Dialysis	Yes	2.82	2.27– 3.36***	2.28	2.26– 3.35***	2.78	2.23– 3.32***
Active smoking	Yes	.02	–.16 to –.21	.03	–.16 to –.21	.02	–.16 to –.20
LVEF (%)		–.03	–.04 to –.02***	–.03	–.04 to –.02***	–.03	–.04 to –.02***
CPB time (h)		1.83	1.71– 1.95***	1.83	1.71– 1.96***	1.81	1.68– 1.93***
Intraoperative fentanyl dose (μg)		.29	–.04 to –.61	.24	–.08 to –.56	.26	–.06 to –.59
Intraoperative sufentanil dose (μg)		.71	–1.50 to – 2.92	.61	–1.60 to 2.82	.35	–1.86 to 2.55
Intraoperative midazolam dose (mg)		.05	.01 to –.09*	.05	.01 to –.09*	.05	.01 to –.09*
Total crystalloid volume (L)		.14	.03 to –.25*	.14	.03 to –.25*	.14	.03 to –.25*

Abbreviations: CI, confidence interval; CPB, cardiopulmonary bypass time; LVEF, left ventricular ejection fraction; NSAIDs, nonsteroidal anti-inflammatory drugs.
*P <.05, **P <.01, and ***P <.001.

ERACS programs have become increasingly popular and have been promoted as an opportunity to improve care for cardiac surgical patients, decrease postoperative complications, reduce length of hospital and ICU stay and potentially reduce cost.[2,3] In 2 recently published ERACS guidelines multimodal analgesia was recommended by the authors.[2,3] Engelman et alendorsed multimodal analgesia with a Class I recommendation and suggested that providers consider use of acetaminophen, tramadol, dexmedetomidine, and gabapentinoids for postoperative pain.[2] The authors acknowledged that there is no single pathway for multimodal analgesia and the primary potential benefit is reduction in postoperative opioid consumption.[2] Mertes et al recommended multimodal analgesia with strong agreement, but recommended against the use of gabapentin.[3] The authors acknowledged that there are few studies demonstrating a benefit to multimodal analgesia or specific nonopioid drugs.[3] The potential benefit described again was reduction in postoperative opioid use and possibly shorter postoperative mechanical ventilation time and ICU length of stay.[3]

We did not find that multimodal analgesia was associated with reduced maximum postoperative pain score 3 days after cardiac surgery. In fact, in our exploratory findings, patients who received NSAIDs had slightly higher maximum pain scores on postoperative day 3, even when controlling for baseline pain and other potential confounders. Our findings differ from prior studies where NSAID use was associated with an approximately 1-point reduction in postoperative pain score.[15] Our study was limited by the select availability of maximum pain score on POD3, and it is possible that an association with pain scores existed on other postoperative days but was not captured in our study analysis. Caution should be exercised in interpreting our findings, as only 10% of patients

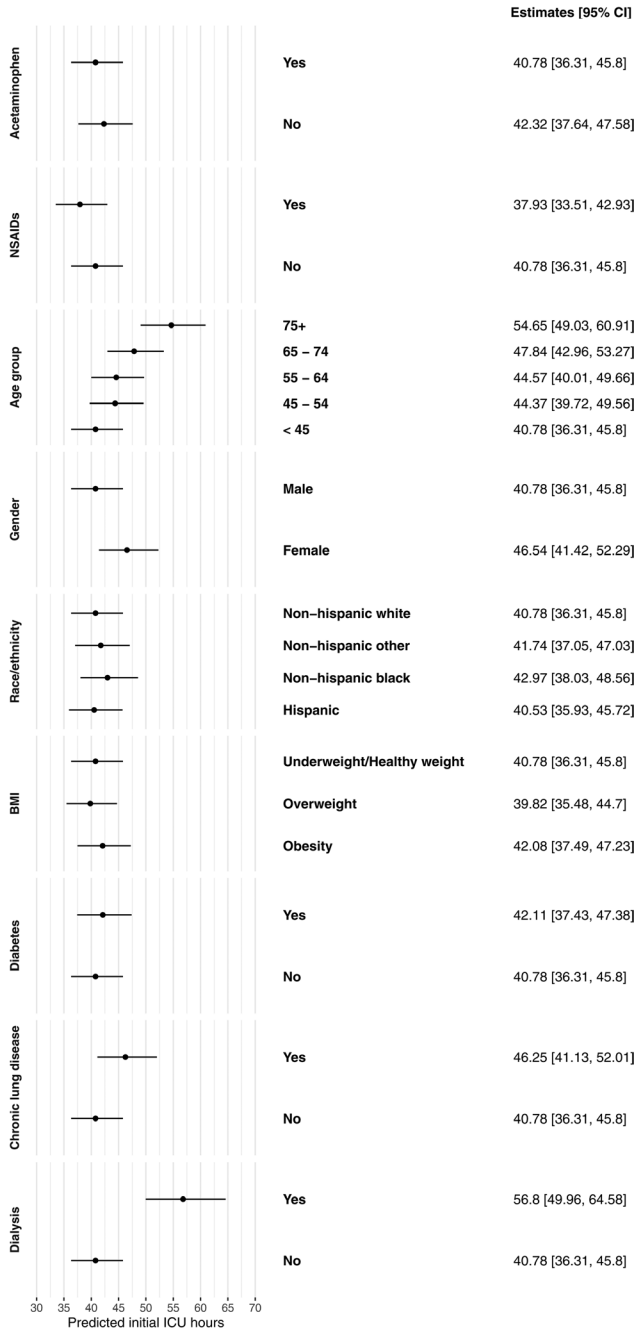

Figure 3. Forest plot showing marginal effect estimates for predicted postoperative ICU hours with variables that had a significant association shown in the figure. Marginal effect estimates represent the average effect of a variable across the studied population. ICU indicates intensive care unit.

in our cohort received NSAIDs and there may be unobserved confounders that we did not control for. Nevertheless, there are relatively few prior studies that have explored the impact of multimodal analgesia on postoperative pain scores, which highlights a significant knowledge gap in ERACS. One meta-analysis suggested that regional nerve blocks reduced postoperative maximum pain by approximately 0.8 points on average after cardiac surgery, but 85% of included studies had a high risk of bias.[16] At least 1 randomized controlled trial suggested that ketamine did not reduce postoperative pain after cardiac surgery, which is consistent with findings from noncardiac surgical patients where ketamine did not reduce postoperative pain or delirium and increased adverse reactions.[17,18] Acetaminophen has some evidence to support reduction in postoperative pain after cardiac surgery,[19] however several studies have also found that acetaminophen does not reduce postoperative pain after cardiac surgery.[20–22] Rafiq et al found that a combination of multiple nonopioid analgesics significantly reduced pain, nausea, and vomiting after cardiac surgery in an open label nonblinded trial.[23] Putting our study results into the context of prior published studies, it seems plausible that the impact of multimodal analgesia on postoperative pain scores is relatively minimal and that multiple complimentary drugs are more likely to have a beneficial impact on pain scores than a single drug.

Importantly, pain score as an outcome measure has significant limitations, as pain score provides only a limited "snapshot" view of patients' pain. Other characteristics including pain tolerance, emotional state/catastrophizing, and history of pain are not incorporated into pain scores. Pain scores are also subjective and it can be difficult to interpret what a number means to an individual patient.

In our study, patients who received multimodal analgesia, had approximately 30 minutes less of initial mechanical ventilation time on average and patients who received multiple nonopioid analgesics had progressively shorter mechanical ventilation time. Specifically, patients who received 3 or 4 nonopioid analgesics had close to a 45 minutes reduction in initial mechanical ventilation time and those who received 5 drugs had an approximately 2 hour reduction in mechanical ventilation time. Several prior studies have explored the relationship between multimodal analgesia and mechanical ventilation time after cardiac surgery. In a small randomized controlled trial, Jin et al randomized patients to receive either 5 multimodal analgesics along with sufentanil or "standard care" with sufentanil analgesia.[24] The authors found no difference in mechanical ventilation time in this study.[24] In a second randomized controlled trial, Stepan et al randomized patients to multimodal analgesia (including lidocaine, ketamine, and dexmedetomidine) with "low dose" opioids and compared outcomes against "standard care."[25] In this study, patients who received multimodal analgesia had shorter postoperative mechanical ventilation time and lower interleukin-6 levels suggesting a less proinflammatory state with multimodal analgesia.[25] Cozowicz found that the use of multimodal

analgesia was consistently associated with reduced mechanical ventilation time after surgery in a 13-year cohort study of almost 350,000 CABG patients.[26] Limitations of this study include a lack of granular data on patient comorbidities and predicted risk of morbidity with surgery. Further studies that compare different multimodal analgesia regiments and extubation time can be helpful in elucidating, which medications have the most impact.

In our exploratory findings, acetaminophen was associated with both reduced mechanical ventilation time and reduced risk for postoperative delirium in our study. This finding is notable, as a recent randomized controlled trial found that acetaminophen decreased delirium incidence after cardiac surgery by 18% (10% vs 28% in controls) when administered routinely during the first 48 hours after surgery.[22] In this study, acetaminophen also decreased length of ICU stay and the need for breakthrough analgesics. The finding that peripheral nerve block/fascial plane block was associated with a 2-fold increased risk of reintubation was not anticipated. The reintubation rate in our cohort was 2.0%, so this finding should be interpreted prudently.

Our study has multiple limitations that should be considered including the retrospective nature of the study. First, the only postoperative pain score data that is available in the STS database is maximum numeric pain score on POD3. It is possible that multimodal analgesia has a more proximate effect, impacting early postoperative pain on the first and second days after surgery, and this was not able to be detected in our study. Second, the overwhelming majority of patients in the study received some form of multimodal analgesia (approximately 90%) and hence the patients who did not receive multimodal analgesia may have represented a very specific subgroup of patients that differed from the main cohort. Third, we could not control for individual ICU provider or respiratory therapist patterns, which may have impacted postoperative patient management. Fourth, we did not have access to doses or durations of multimodal analgesic medications and many medications may have dose-specific effects. Without data on the duration of administration, it is also difficult to determine the true association with pain on POD3. Fifth, we did not have data on postoperative opioid use and 1 of the primary benefits of multimodal analgesia is likely reduced opioid consumption after surgery.[11,26,27] Likewise, the data within the database was pooled without any information regarding how or when the pain scores were collected (ie with activity or at rest). Pooled data prevents standardization of collection methods which may bias results. Finally, not all centers contribute to the anesthesiology module of the adult cardiac surgery STS database, and hence our findings may not be generalizable to all centers.

In summary, our study represents one of the largest clinical cardiac surgery analyses to explore the impact of multimodal analgesia, during surgery or in the first 24 hours after surgery, on patient-centered postoperative outcomes including pain, postoperative mechanical ventilation time, ICU hours and delirium. Our exploratory results suggest that intraoperative, or early postoperative, multimodal analgesia is associated with early extubation and use of select analgesics such as acetaminophen may be associated with less postoperative delirium. Future prospective clinical trials comparing different multimodal regiments will be helpful in optimizing ERACS moving forward.

ACKNOWLEDGMENTS

We would like to thank the Society of Cardiovascular Anesthesiologists for funding this project. The data for this research were provided by The Society of Thoracic Surgeons' National Database Participant User File Research Program. Data analysis was performed at the investigators' institution(s). This was determined to be exempt research with a waiver of informed consent from Advarra Institutional Review Board (Mod01760092, Version 1.1, Approval date July 17, 2023). The views and opinions presented in this article are solely those of the author(s) and do not necessarily represent those of the Society of Thoracic Surgeons.

DISCLOSURES

Conflicts of Interest: Dr. Mazzeffi received consulting fees from Hemosonics, Octapharma, and NovoNordisk. He also received research funding from Takeda. No other authors declared Conflicts of Interest. **Funding:** The project was funded by a Society of Cardiovascular Anesthesiologists STS Participant User File (PUF) Grant (PUF-ACSD-2023-004). **This manuscript was handled by:** Lisa Rong, MD.

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