

Intraoperative Opioid Waste and Association of Intraoperative Opioid Dose with Postoperative Adverse Outcomes: A Hospital Registry Study

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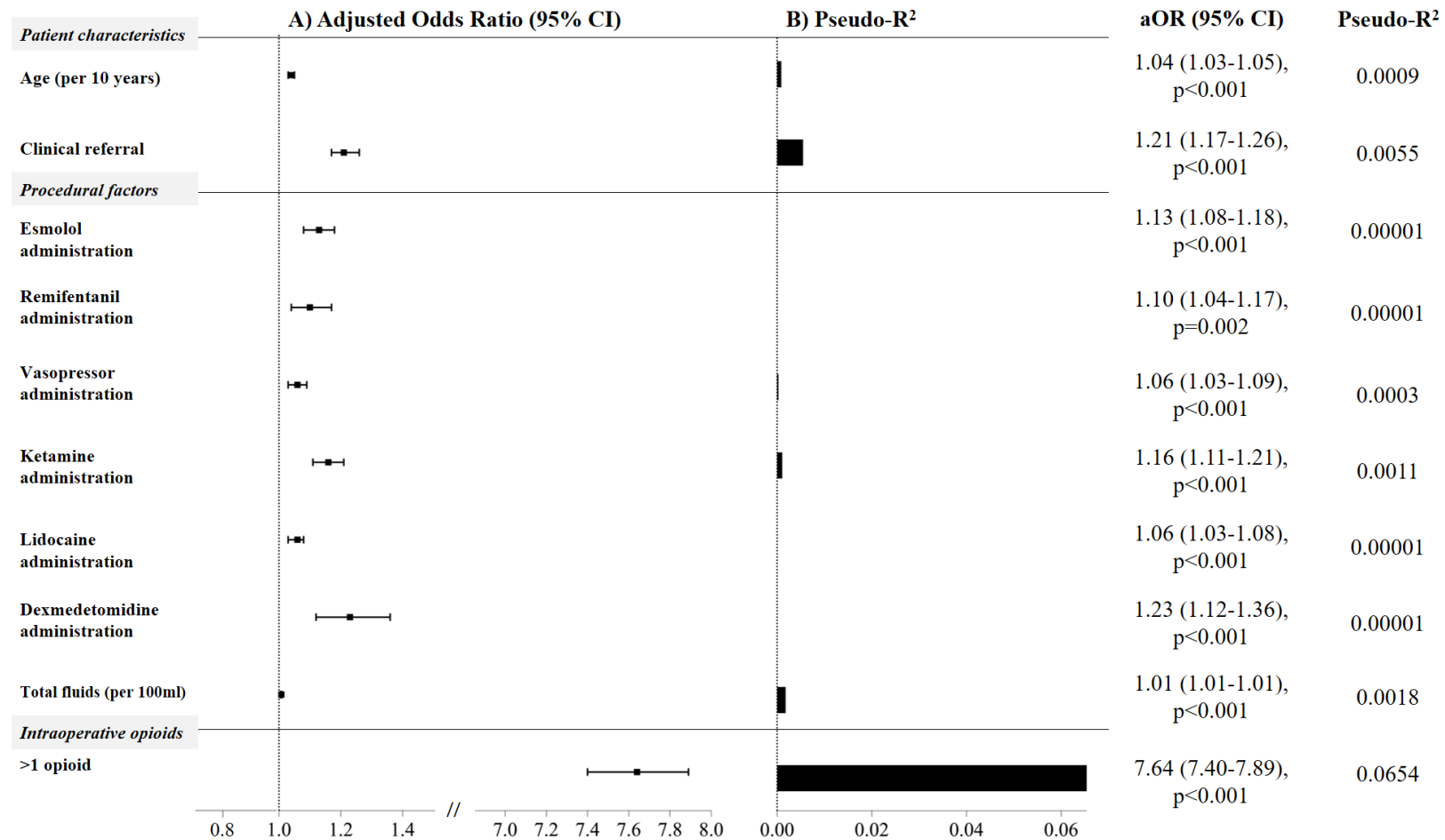
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Section S1. ACTUAL PRODUCT WASTE

During the study period from June 5th, 2020 to June 15th, 2022, intraoperative fentanyl, hydromorphone, or morphine were administered in 39,298 cases. Specifically, fentanyl was administered in 32,938 (83.8%) cases, hydromorphone in 17,459 (44.4%) cases, and morphine in 1,181 (3.0%) cases. Out of a total 51,578 opioid administrations, 17,994 (34.9%) distinct waste events occurred. The number of waste events were 7,767 (43.2%), 9,473 (52.6%), and 754 (4.2%) for fentanyl, hydromorphone and morphine, respectively. The median (IQR) amount of waste was 75 (50-100) mcg for fentanyl, 0.5 (0.4-0.6) mg for hydromorphone and 0.25 (0.25-0.25) mg for morphine.

Section S2. SUPPLEMENTARY FIGURES

Figure S1. Independent predictors of intraoperative opioid waste.



A) Adjusted odds ratios of the independent variables predicting the intraoperative opioid waste. B) Dominance analysis depicting the individual contribution to prediction of waste among the independent predictors of opioids waste. The longer the bar, the higher the contribution of the independent predictor to predict the waste. Administration of more than one opioid intraoperatively had the strongest dominance, as determined by its contribution to waste prediction (ranking 1, pseudo-R²=0.0654).

Section S3. SUPPLEMENTARY TABLES

Table S1. Patient characteristics and distribution of variables in patients receiving fentanyl versus hydromorphone vs morphine as the highest dose of opioid.

	Fentanyl	Hydromorphone	Morphine	Std diff (Fentanyl vs Hydromorphone)	Std diff (Fentanyl vs Morphine)	Std diff (Morphine vs Hydromorphone)
	N=143,812	N=24,785	N=2,010			
Age, years	57.0 (43.0 - 67.0)	54.0 (41.0 - 65.0)	53.0 (40.0 - 65.0)	0.130	0.158	0.030
Sex						
Female	64,792 (45.1%)	9,664 (39.0%)	809 (40.2%)	-0.123	-0.097	0.026
Ideal Body Weight, kg/m²	61.6 (54.1 - 70.7)	59.3 (52.4 - 70.7)	59.3 (52.4 - 70.7)	0.076	0.051	-0.026
Ethnicity				-0.014	-0.020	-0.005
<i>Asian</i>	5,196 (4.0%)	888 (4.0%)	63 (3.5%)			
<i>Black</i>	13,760 (10.7%)	2,427 (11.0%)	179 (10.0%)			
<i>Hispanic</i>	6,863 (5.3%)	1,211 (5.5%)	98 (5.5%)			
<i>White</i>	90,873 (70.8%)	15,238 (69.2%)	1,290 (72.2%)			
<i>Pacific Islanders and Hawaii</i>	22 (0.0%)	6 (0.0%)	1 (0.1%)			
<i>Other</i>	11,629 (9.1%)	2,243 (10.2%)	155 (8.7%)			
ASA physical status				0.131	0.244	0.119
<i>1</i>	16,272 (11.3%)	2,926 (11.8%)	301 (15.0%)			
<i>2</i>	65,089 (45.3%)	12,752 (51.5%)	1,074 (53.4%)			

3	54,192 (37.7%)	8,288 (33.4%)	572 (28.5%)			
4	8,259 (5.7%)	819 (3.3%)	63 (3.1%)			
Year of surgery				-0.577	0.482	1.165
2010	13,674 (9.5%)	137 (0.6%)	147 (7.3%)			
2011	14,505 (10.1%)	1,275 (5.1%)	401 (20.0%)			
2012	15,253 (10.6%)	781 (3.2%)	595 (29.6%)			
2013	15,756 (11.0%)	1,064 (4.3%)	256 (12.7%)			
2014	14,548 (10.1%)	2,722 (11.0%)	158 (7.9%)			
2015	13,974 (9.7%)	3,173 (12.8%)	37 (1.8%)			
2016	12,865 (8.9%)	4,275 (17.2%)	25 (1.2%)			
2017	12,283 (8.5%)	4,287 (17.3%)	50 (2.5%)			
2018	13,417 (9.3%)	2,536 (10.2%)	322 (16.0%)			
2019	13,794 (9.6%)	3,613 (14.6%)	16 (0.8%)			
2020	3,743 (2.6%)	922 (3.7%)	3 (0.1%)			
Charlson Comorbidity Index	0.0 (0.0 - 2.0)	0.0 (0.0 - 2.0)	0.0 (0.0 - 2.0)	0.115	0.166	0.052
SPORC≥7	6,945 (5.2%)	632 (2.6%)	62 (3.1%)	0.130	0.102	-0.029
Opioid use within 90 days before surgery	24,872 (17.3%)	4,766 (19.2%)	342 (17.0%)	-0.050	0.007	0.058
Duration of surgery, median (IQR) (min)	123.0 (82.0 - 182.0)	146.0 (100.0 - 210.0)	119.5 (79.0 - 169.0)	-0.232	0.135	0.380

Emergency surgery	14,336 (10.0%)	1,999 (8.1%)	188 (9.4%)	0.066	0.021	-0.046
Anesthesia technique				-0.020	0.042	0.062
<i>General anesthesia only</i>	129,552 (90.1%)	22,181 (89.5%)	1,836 (91.3%)			
<i>General plus MAC</i>	57 (0.0%)	3 (0.0%)	0 (0.0%)			
<i>General plus MAC plus Regional</i>	39 (0.0%)	6 (0.0%)	0 (0.0%)			
<i>General plus Regional</i>	14,164 (9.8%)	2,595 (10.5%)	174 (8.7%)			
Age-adjusted mean alveolar concentration of inhalation anesthetics, median (IQR)	1.0 (0.8 - 1.1)	1.0 (0.9 - 1.2)	1.0 (0.9 - 1.2)	-0.200	-0.167	0.032
Use of succinylcholine	55,224 (38.4%)	6,946 (28.0%)	736 (36.6%)	0.222	0.037	-0.184
Use of Non-depolarizing NMBA	94,000 (65.4%)	18,131 (73.2%)	1,125 (56.0%)	-0.169	0.193	0.365
Crystalloid and colloid infusion, median (IQR) (ml)	1000.0 (700.0 - 1400.0)	1000.0 (750.0 - 1550.0)	1000.0 (700.0 - 1400.0)	-0.119	0.022	0.151
Units of packed red blood cells	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.013	0.050	0.046
Use of vasopressors	77,015 (53.6%)	13,201 (53.3%)	790 (39.3%)	0.006	0.289	0.283
Minutes of mean arterial pressure below 55 mmHg, median (IQR)	0.0 (0.0 - 2.0)	0.0 (0.0 - 3.0)	0.0 (0.0 - 2.0)	-0.034	0.013	0.047
Number of intraoperative opioids administered				0.602	0.458	-0.132
1	78,485 (54.6%)	20,210 (81.5%)	1,537 (76.5%)			
2	65,057 (45.2%)	4,552 (18.4%)	463 (23.0%)			
3	270 (0.2%)	23 (0.1%)	10 (0.5%)			

Fentanyl, median (IQR) (mcg)	100.0 (100.0 - 200.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	2.070	1.995	-0.096
Hydromorphone, median (IQR) (mg)	0.0 (0.0 - 0.6)	1.0 (0.7 - 1.6)	0.0 (0.0 - 0.0)	-1.438	0.898	2.814
Morphine, median (IQR) (mg)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	8.0 (4.0 - 10.0)	0.297	-3.012	-3.542
Intraoperative Remifentanyl administration	7,078 (4.9%)	864 (3.5%)	51 (2.5%)	0.072	0.126	0.056
Premedication with acetaminophen	13,420 (9.3%)	4,095 (16.5%)	41 (2.0%)	-0.216	0.319	0.515
Premedication with gabapentinoids	6,236 (4.3%)	2,658 (10.7%)	30 (1.5%)	-0.244	0.170	0.393
Intraoperative Ketamine administration	9,598 (6.7%)	5,399 (21.8%)	152 (7.6%)	-0.443	-0.035	0.410
Intraoperative Lidocaine administration	95,399 (66.3%)	18,621 (75.1%)	1,181 (58.8%)	-0.194	0.157	0.353
Intraoperative Esmolol administration	10,717 (7.5%)	3,541 (14.3%)	189 (9.4%)	-0.221	-0.070	0.152
Intraoperative Magnesium administration	710 (0.5%)	141 (0.6%)	9 (0.4%)	-0.010	0.007	0.017
Intraoperative NSAIDS administration	27,034 (18.8%)	6,931 (28.0%)	468 (23.3%)	-0.218	-0.110	0.107
Intraoperative Dexmedetomidine administration	2,060 (1.4%)	1,088 (4.4%)	102 (5.1%)	-0.177	-0.206	-0.032
Anesthesia Provider				-0.255	-0.240	-0.004
<i>Resident</i>	86,323 (60.5%)	10,571 (42.9%)	1,061 (53.1%)			
<i>Nurse anesthetist</i>	29,457 (20.6%)	8,824 (35.8%)	303 (15.2%)			
<i>Attending</i>	27,012 (18.9%)	5,243 (21.3%)	635 (31.8%)			

Data are presented as median (IQR) for continuous variables, and n (%) for categorical variables. The standardized difference was calculated as the difference in mean between exposure groups, divided by a pooled estimate of the standard deviation in the entire population. Some of the patients received more than one opioid. We attributed patients to a specific opioid cohort based on the opioid that was used at the highest dose (in oral morphine equivalent). For example, a patient was attributed to the fentanyl cohort if fentanyl was the opioid administered at the highest dosage compared to hydromorphone and morphine.

Abbreviations: ASA, American Society of Anesthesiology; SPORC, Score for the Prediction of Postoperative Respiratory Complications; MAC, Monitored Anesthesia Care; NMBA, Neuromuscular Blocking Agents; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs.

Table S2. Hypothetical estimates of product waste, loss of provider time and related costs of different vial sizes of fentanyl, hydromorphone and morphine.

	Fentanyl Vial Sizes		Hydromorphone Vial Sizes		Morphine Vial Sizes	
	50 mcg	100 mcg	1 mg	2 mg	2 mg	4 mg
Cases with product waste, n (% of total cases)	13,868 (9.3)	68,668 (46.1)	52,052 (63.6)	71,742 (87.7)	3,038 (28.4)	7,782 (72.8)
Product waste amount, median (IQR)*	25 (25-25)	50 (50-50)	0.5 (0.4-0.6)	1.2 (1-1.5)	1 (1-1)	2 (2-2)
Product waste amount in OME (mg), median (IQR)	7.5 (7.5-7.5)	15 (15-15)	10 (8-12)	24 (20-30)	3 (3-3)	6 (6-6)
Number of used vials per case, median (IQR)	2 (2-4)	1 (1-2)	1 (1-2)	1 (1-1)	3 (2-4)	2 (1-2)
Total number of used vials during the study period	446,476	254,718	105,538	81,916	33,210	19,814
Cost of vial drawing up per case, median (IQR)	3.13 (3.13-6.27)	1.57 (1.57-3.13)	1.57 (1.57-3.13)	1.57 (1.57-1.57)	4.70 (3.13-6.27)	3.13 (1.57-3.13)
Loss of provider time per year**, median (IQR), min	2,491 (1,651-4,460)	15,664 (10,313-21,316)	11,864 (8,015-15,428)	17,260 (11,146-20,299)	215 (81-1,342)	720 (211-3,462)
Total product cost, \$	1,183,161.40	613,870.38	455,924.16	353,877.12	114,242.40	68,160.16
Product waste associated cost per case (in only cases with waste), \$	6.21	5.97	7.88	7.88	7.00	7.00
Product waste associated cost per case (cases with and without waste), \$	0.58	2.75	5.01	6.91	0.26	0.67
Total product waste associated cost per year**, median (IQR), \$	6,811 (4,515-12,194)	41,179 (27,111-56,037)	41,168 (27,815-53,537)	59,895 (38,677-70,456)	661 (250-4,136)	2,218 (651-10,671)

Product waste associated cost is defined as the sum of the cost of vial wasted and of the provider time spent to draw up the vial and to accomplish the product waste report. Loss of provider time to draw up the vial is assumed 60 seconds and to accomplish waste report is equivalent to 76.2 seconds for each waste event (1). Cost of vials are based on average wholesale prices in the USA (2). Cost of provider time is calculated using the median hourly wage for nurse anesthetists (3).

* unit of measurement is mcg for fentanyl, and mg for hydromorphone and morphine.

** based on a yearly caseload of 14,477 (13,854-15,154) for fentanyl, 8,809 (5,768-10,188) for hydromorphone and 831 (122-1,946) for morphine.

Abbreviations: OME, Oral Morphine Equivalent

Table S3. Patient characteristics and distribution of variables by intraoperative opioid waste.

	No Waste	Waste	Std diff
	N=49,219	N=90,155	
Age, years	56.0 (43.0 - 66.0)	57.0 (44.0 - 67.0)	-0.07
Female (%)	27,505 (55.9%)	51,444 (57.1%)	-0.02
Ideal Body Weight, kg/m2	61.6 (54.6 - 70.7)	61.5 (52.4 - 70.7)	0.03
Ethnicity			0.01
<i>Asian</i>	1,930 (3.9%)	3,708 (4.1%)	
<i>Black</i>	5,565 (11.3%)	9,562 (10.6%)	
<i>Hispanic</i>	2,648 (5.4%)	4,825 (5.4%)	
<i>White</i>	34,157 (69.4%)	64,078 (71.1%)	
<i>Pacific Islanders and Hawaii</i>	12 (0.0%)	17 (0.0%)	
<i>Other</i>	4,907 (10.0%)	7,965 (8.8%)	
ASA physical status			-0.01
1	5,344 (10.9%)	9,946 (11.0%)	
2	23,693 (48.1%)	42,357 (47.0%)	
3	17,965 (36.5%)	33,683 (37.4%)	
4	2,217 (4.5%)	4,169 (4.6%)	
Year of surgery			0.51
2010	2,844 (5.8%)	8,986 (10.0%)	
2011	3,532 (7.2%)	10,258 (11.4%)	
2012	3,164 (6.4%)	10,858 (12.0%)	
2013	3,776 (7.7%)	10,598 (11.8%)	
2014	4,433 (9.0%)	10,147 (11.3%)	
2015	4,579 (9.3%)	10,001 (11.1%)	
2016	4,519 (9.2%)	9,583 (10.6%)	
2017	5,779 (11.7%)	7,846 (8.7%)	
2018	8,083 (16.4%)	5,100 (5.7%)	
2019	6,782 (13.8%)	5,499 (6.1%)	
2020	1,728 (3.5%)	1,279 (1.4%)	
Charlson Comorbidity Index	0.0 (0.0 - 2.0)	0.0 (0.0 - 2.0)	0.00
SPORC$\geq$7	2,194 (4.5%)	4,577 (5.1%)	-0.03
Source of Admission			-0.07
<i>Physician Referral</i>	40,949 (83.2%)	69,346 (76.9%)	
<i>Clinical Referral</i>	5,363 (10.9%)	16,051 (17.8%)	
<i>Other Hospital</i>	2,460 (5.0%)	3,697 (4.1%)	
<i>Skilled Nurse Facility</i>	164 (0.3%)	271 (0.3%)	
<i>Other Healthcare Facility</i>	75 (0.2%)	127 (0.1%)	
<i>Emergency Room</i>	200 (0.4%)	655 (0.7%)	
Opioids use within 90 days before surgery	9,466 (19.2%)	16,489 (18.3%)	0.02
Duration of surgery, median (IQR) (min)	119.0 (79.0 - 178.0)	129.0 (88.0 - 188.0)	-0.08
Emergency surgery	4,006 (8.1%)	8,822 (9.8%)	-0.06
Anesthesia technique			0.08

<i>General anesthesia only</i>	43,189 (87.7%)	81,384 (90.3%)	
<i>General plus MAC</i>	24 (0.0%)	17 (0.0%)	
<i>General plus MAC plus Regional</i>	8 (0.0%)	28 (0.0%)	
<i>General plus Regional</i>	5,998 (12.2%)	8,726 (9.7%)	
Age-adjusted mean alveolar concentration of inhalation anesthetics, median (IQR)	1.0 (0.8 - 1.1)	1.0 (0.9 - 1.1)	-0.04
Use of succinylcholine	16,973 (34.5%)	33,975 (37.7%)	-0.07
Use of Non-depolarizing NMBA	31,413 (63.8%)	61,205 (67.9%)	-0.09
Crystalloid and colloid infusion, median (IQR) (ml)	1000.0 (700.0 - 1300.0)	1000.0 (700.0 - 1500.0)	-0.14
Units of packed red blood cells	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	-0.01
Use of vasopressors	24,877 (50.5%)	48,399 (53.7%)	-0.06
Minutes of mean arterial pressure below 55 mmHg, median (IQR)	0.0 (0.0 - 2.0)	0.0 (0.0 - 3.0)	-0.07
Number of intraoperative opioids administered			-0.65
1	37,512 (76.2%)	41,521 (46.1%)	
2	11,688 (23.7%)	48,384 (53.7%)	
3	19 (0.0%)	250 (0.3%)	
Fentanyl, median (IQR) (mcg)	100.0 (100.0 - 100.0)	125.0 (50.0 - 225.0)	-0.25
Hydromorphone, median (IQR) (mg)	0.0 (0.0 - 1.0)	0.4 (0.0 - 0.8)	-0.04
Morphine, median (IQR) (mg)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	-0.25
Intraoperative Remifentanyl administration	2,064 (4.2%)	3,924 (4.4%)	-0.01
Premedication with acetaminophen	7,948 (16.1%)	6,294 (7.0%)	0.29
Premedication with gabapentinoids	4,106 (8.3%)	3,245 (3.6%)	0.20
Intraoperative Ketamine administration	5,366 (10.9%)	7,428 (8.2%)	0.09
Intraoperative Lidocaine administration	33,745 (68.6%)	61,920 (68.7%)	0.00
Intraoperative Esmolol administration	4,222 (8.6%)	7,604 (8.4%)	0.01
Intraoperative Magnesium administration	202 (0.4%)	465 (0.5%)	-0.02
Intraoperative NSAIDS administration	11,618 (23.6%)	16,851 (18.7%)	0.12
Intraoperative Dexmedetomidine administration	916 (1.9%)	1,620 (1.8%)	0.00
Anesthesia Provider			0.22
<i>Resident</i>	24,702 (50.2%)	56,652 (62.8%)	
<i>Nurse anesthetist</i>	13,710 (27.9%)	18,127 (20.1%)	
<i>Attending</i>	10,807 (22.0%)	15,376 (17.1%)	

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

Abbreviations: ASA, American Society of Anesthesiology; SPORC, Score for the Prediction of Postoperative Respiratory Complications; MAC, Monitored Anesthesia Care; NMBA, Neuromuscular Blocking Agents; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs.

Table S4. Patient characteristics and distribution of variables by intraoperative opioid in the cohorts included to investigate the association of intraoperative opioid dose and adverse postoperative outcomes.

	Fentanyl	Hydromorphone	Morphine
	N=119,113	N=71,483	N=8,906
Age, years	56.0 (43.0 - 67.0)	55.0 (43.0 - 66.0)	54.0 (41.0 - 65.0)
Sex			
Female	67,163 (56.4%)	42,080 (58.9%)	5,223 (58.6%)
BMI, kg/m2	27.4 (23.8 - 31.9)	27.5 (24.1 - 32.3)	27.4 (24.0 - 32.1)
ASA physical status			
1	14,191 (11.9%)	7,389 (10.3%)	1,186 (13.3%)
2	57,889 (48.6%)	36,248 (50.7%)	4,519 (50.7%)
3	43,209 (36.3%)	26,105 (36.5%)	2,991 (33.6%)
4	3,824 (3.2%)	1,741 (2.4%)	210 (2.4%)
Year of surgery			
2010	10,478 (8.8%)	2,339 (3.3%)	1,913 (21.5%)
2011	11,366 (9.5%)	4,169 (5.8%)	1,730 (19.4%)
2012	12,214 (10.3%)	4,509 (6.3%)	2,298 (25.8%)
2013	13,008 (10.9%)	6,654 (9.3%)	1,142 (12.8%)
2014	12,346 (10.4%)	8,905 (12.5%)	375 (4.2%)
2015	12,371 (10.4%)	9,268 (13.0%)	96 (1.1%)
2016	11,430 (9.6%)	9,823 (13.7%)	58 (0.7%)
2017	10,810 (9.1%)	9,275 (13.0%)	124 (1.4%)
2018	11,601 (9.7%)	6,231 (8.7%)	1,134 (12.7%)
2019	10,656 (8.9%)	8,161 (11.4%)	30 (0.3%)
2020	2,833 (2.4%)	2,149 (3.0%)	6 (0.1%)
Charlson Comorbidity Index	0.0 (0.0 - 2.0)	0.0 (0.0 - 2.0)	0.0 (0.0 - 2.0)
Chronic heart failure	5,484 (4.6%)	2,786 (3.9%)	280 (3.1%)
Smoking	12,906 (10.8%)	8,562 (12.0%)	609 (6.8%)
OSAS	7,777 (6.5%)	4,592 (6.4%)	473 (5.3%)
Obstructive pulmonary disease	29,296 (24.6%)	17,126 (24.0%)	2,071 (23.3%)
Restrictive pulmonary disease	5,057 (4.2%)	2,405 (3.4%)	386 (4.3%)
SPORC$\geq$7	4,595 (3.9%)	2,258 (3.2%)	319 (3.6%)
Type of surgery			
<i>Colorectal</i>	3,229 (2.7%)	3,340 (4.7%)	292 (3.3%)
<i>Dentistry</i>	385 (0.3%)	276 (0.4%)	29 (0.3%)
<i>Otorhinolaryngology</i>	5,266 (4.4%)	1,897 (2.7%)	319 (3.6%)
<i>Ophthalmology</i>	225 (0.2%)	19 (0.0%)	n.a.
<i>General</i>	16,515 (13.9%)	9,094 (12.7%)	1,841 (20.7%)
<i>Gastrointestinal</i>	60 (0.1%)	8,692 (12.2%)	n.a.
<i>Gynecology</i>	14,031 (11.8%)	4,923 (6.9%)	1,022 (11.5%)
<i>Neurosurgery</i>	6,968 (5.8%)	18,961 (26.5%)	351 (3.9%)
<i>Orthopedics</i>	29,598 (24.8%)	6,697 (9.4%)	2,116 (23.8%)
<i>Plastic</i>	8,091 (6.8%)	178 (0.2%)	729 (8.2%)
<i>Podiatry</i>	580 (0.5%)	3,183 (4.5%)	42 (0.5%)

<i>Surgical Oncology</i>	4,900 (4.1%)	2,963 (4.1%)	371 (4.2%)
<i>Thoracic</i>	6,381 (5.4%)	1,671 (2.3%)	346 (3.9%)
<i>Transplant</i>	2,584 (2.2%)	2,842 (4.0%)	139 (1.6%)
<i>Trauma</i>	4,008 (3.4%)	4,340 (6.1%)	347 (3.9%)
<i>Urology</i>	10,750 (9.0%)	2,407 (3.4%)	595 (6.7%)
<i>Vascular</i>	5,542 (4.7%)	21,058 (29.5%)	367 (4.1%)
Emergency surgery	8,788 (7.4%)	5,360 (7.5%)	929 (10.4%)
Duration of surgery, min	126.0 (84.0 - 186.0)	157.0 (113.0 - 224.0)	143.0 (105.0 - 201.0)
Work RVU	12.1 (7.0 - 17.9)	15.8 (10.5 - 21.8)	14.4 (9.4 - 18.5)
Fentanyl, mcg	100.0 (100.0 - 200.0)	100.0 (25.0 - 200.0)	150.0 (100.0 - 250.0)
Morphine, mg	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	5.0 (4.0 - 8.0)
Hydromorphone, mg	0.0 (0.0 - 0.8)	1.0 (0.6 - 1.2)	0.0 (0.0 - 0.0)
Ketamine administration	9,120 (7.7%)	9,383 (13.1%)	395 (4.4%)
Dexmedetomidine administration	1,732 (1.5%)	1,782 (2.5%)	161 (1.8%)
Regional anesthesia (adjuvant)	12,989 (10.9%)	6,145 (8.6%)	670 (7.5%)
Age-adjusted MAC, %	1.0 (0.9 - 1.1)	1.0 (0.9 - 1.2)	1.0 (0.9 - 1.2)
Non-depolarizing NMBA, ED95	1.7 (0.0 - 2.8)	2.3 (1.3 - 3.3)	2.0 (0.8 - 3.0)
Succinylcholine administration	44,461 (37.3%)	25,376 (35.5%)	4,216 (47.3%)
Neostigmine dose, mg/kg	0.0 (0.0 - 3.0)	2.0 (0.0 - 3.0)	2.0 (0.0 - 3.5)
Sugammadex use	12,404 (10.4%)	10,568 (14.8%)	473 (5.3%)
Crystalloid and colloid infusion, mL	1000.0 (700.0 - 1500.0)	1150.0 (800.0 - 1700.0)	1200.0 (900.0 - 1700.0)
Vasopressor dose, mg norepinephrine equivalents	0.0 (0.0 - 0.1)	0.0 (0.0 - 0.1)	0.0 (0.0 - 0.0)
Apfel Score			
Risk of PONV Low (10-20%)	34,448 (28.9%)	19,136 (26.8%)	2,366 (26.6%)
Risk of PONV Moderate (40%)	48,382 (40.6%)	29,410 (41.1%)	3,685 (41.4%)
Risk of PONV Severe (60%)	25,609 (21.5%)	16,137 (22.6%)	2,003 (22.5%)
Risk of PONV Very Severe (80%)	10,674 (9.0%)	6,800 (9.5%)	852 (9.6%)
Number of administered antiemetics			
<i>0</i>	10,073 (8.5%)	3,817 (5.3%)	614 (6.9%)
<i>1</i>	50,995 (42.8%)	28,254 (39.5%)	3,665 (41.2%)

2	48,185 (40.5%)	31,478 (44.0%)	3,692 (41.5%)
3	8,913 (7.5%)	7,212 (10.1%)	834 (9.4%)
4	906 (0.8%)	698 (1.0%)	94 (1.1%)
5	41 (0.0%)	23 (0.0%)	7 (0.1%)
6	n.a.	1 (0.0%)	n.a.
Minutes of mean arterial pressure below 55 mmHg	0.0 (0.0 - 2.0)	1.0 (0.0 - 3.0)	1.0 (0.0 - 3.0)
FiO₂, %	56.0 (50.5 - 64.0)	56.0 (51.0 - 61.3)	54.5 (48.5 - 60.0)
PEEP, cmH₂O	4.1 (2.0 - 5.1)	5.0 (2.0 - 5.1)	4.0 (2.0 - 5.0)
PIP, cmH₂O	19.3 (15.2 - 24.0)	20.8 (17.2 - 25.3)	21.0 (17.0 - 25.3)
Tidal Volume, mL	522.0 (431.5 - 592.0)	535.5 (471.0 - 597.0)	560.0 (485.5 - 620.0)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

Abbreviations: BMI, Body Mass Index; ASA, American Society of Anesthesiology; OSAS, Obstructive Sleep Apnea Syndrome; SPORC, Score for the Prediction of Postoperative Respiratory Complications; RVU, Relative Value Units; MAC, minimal alveolar concentration; NMBA, Neuromuscular Blocking Agent; ED95, amount of NMBA required to reduce twitch height by 95%; PONV, postoperative nausea and vomit; FiO₂, Fraction of Inspired Oxygen; PEEP, Positive End Expiratory Pressure; PIP, Peak Inspiratory Pressure; n.a., not applicable.

Table S5. Association of intraoperative opioids dose and the secondary outcomes Category E

		Category E		
	n (%)	aOR (95% CI)	p-value	ARD (%)
Fentanyl	119,113 (100)			
>0-7.5 OME (mg)	12,328 (10.4)	<i>Ref</i>	<i>Ref</i>	<i>Ref</i>
>7.5-15 OME (mg)	52,194 (43.8)	1.17 (1.10-1.25)	<0.001	2
>15 OME (mg)	54,591 (45.8)	1.24 (1.16-1.33)	<0.001	3
Hydromorphone	71,483 (100)			
>0-10 OME (mg)	16,774 (23.5)	<i>Ref</i>	<i>Ref</i>	<i>Ref</i>
>10-20 OME (mg)	33,945 (47.5)	1.05 (1.00-1.10)	0.07	-
>20 OME (mg)	20,764 (29.0)	1.13 (1.06-1.20)	<0.001	2
Morphine	8,906 (100)			
>0-6 OME (mg)	1,105 (12.4)	<i>Ref</i>	<i>Ref</i>	<i>Ref</i>
>6-12 OME (mg)	2,430 (27.3)	1.26 (1.02-1.56)	0.04	3
>12 OME (mg)	5,371 (60.3)	1.45 (1.18-1.77)	<0.001	5

Abbreviations: aOR, adjusted odd ratio; ARD, adjusted risk difference; OME, Oral Morphine Equivalents

Table S6. Association of intraoperative opioids dose and the secondary outcomes *Category F*, *Category G*, and *Category H*.

			Category F			Category G			Category H		
		n (%)	aOR (95% CI)	p- value	ARD (%)	aOR (95% CI)	p- value	ARD (%)	aOR (95% CI)	p- value	ARD (%)
Fentanyl	OME (mg)	119,113 (100)									
>0-50 mcg	>0-7.5	12,328 (10.4)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
>50-100 mcg	>7.5- 15	52,194 (43.8)	1.19 (1.13 - 1.26)	<0.001	3	1.16 (0.31- 4.33)	0.83	-	1.12 (0.96- 1.31)	0.15	-
>100 mcg	>15	54,591 (45.8)	1.39 (1.30 - 1.48)	<0.001	6	0.42 (0.10- 1.88)	0.26	-	1.28 (1.09- 1.50)	<0.01	0.8
Hydromorphone	OME (mg)	71,483 (100)									
>0-0.5 mg	>0-10	16,774 (23.5)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
>0.5-1 mg	>10-20	33,945 (47.5)	1.18 (1.09 - 1.27)	<0.001	2	0.59 (0.17- 1.98)	0.39	-	0.91 (0.83- 1.00)	0.06	-
>1 mg	>20	20,764 (29.0)	1.54 (1.37 - 1.73)	<0.001	5	1.17 (0.25- 5.45)	0.84	-	0.86 (0.77- 0.96)	<0.01	-0.6
Morphine	OME (mg)	8,906 (100)									
>0-2 mg	>0-6	1,105 (12.4)	Ref	Ref	Ref	-	-	-	Ref	Ref	Ref
>2-4 mg	>6-12	2,430 (27.3)	1.08 (0.81 - 1.44)	0.60	-	-	-	-	0.77 (0.49- 1.22)	0.27	-
>4 mg	>12	5,371 (60.3)	1.50 (1.13 - 1.97)	<0.01	5	-	-	-	1.04 (0.69- 1.58)	0.84	-

Logistic regression model for association between morphine dose and *Category G* was not applicable due to absence of the outcome in this population. *Category F* was investigated only in outpatients. Study population for this outcome was 60,368 for fentanyl cohort (9,362 [15.5%], >0-50 mcg; 30,566 [50.6%], >50-100 mcg; 20,440 [33.9%], >100 mcg); 27,553 for hydromorphone cohort (8,434 [30.6%], >0-0.5 mg; 14,111 [51.2%], >0.5-1 mg; 5,008 [18.2%], >1 mg) and 3,424 for morphine cohort (513 [15.0%], >0-2 mg; 1,068 [31.2%], >2-4 mg; 1,843 [53.8%], >4 mg). *Category F* was defined as delayed discharge from post-anesthesia care unit (length of stay $\geq$ 120 minutes), or unplanned admission (booked outpatients who required unplanned admission), or delayed discharge from hospital (length of stay >75th percentile) or readmission within 30 days after hospital discharge). *Category G* was defined by cardiac arrest or stroke within 7 days postoperatively. *Category H* was defined by unplanned intubation or intensive care unit admission (all cause).

Abbreviations: aOR, adjusted odd ratio; ARD, adjusted risk difference; OME, Oral Morphine Equivalents.

Table S7. Association between intraoperative opioid waste and the primary outcome (Category E)

	aOR (95%CI)	p-value
Fentanyl waste (per 10 mcg increase)	1.06 (0.82-1.37)	0.64
Hydromorphone waste (per 1 mg increase)	0.98 (0.79-1.21)	0.84
Morphine waste (per 1 mg increase)	1.08 (0.97-1.21)	0.17

Product waste was defined as the discrepancy between the actual dose administered and an aliquot (or the combination of multiple available aliquots) of 50 mcg for fentanyl, 1 mg for hydromorphone and 4 mg for morphine.

Abbreviations: aOR, adjusted odds ratio; CI, Confidence interval

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