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Article

Perioperative Analgesia in Crisis Situation SARS-CoV-2. Patient Characteristics in COVID-19 in Pain Out Registry

Maria A. Perez Herrero [1,*], Manuel Carrasco [2,3], Berta Velasco [4], Sara Cocho [1], Carla del Rey [5] and Hermann Ribera [6]

[1] MD Department of Anaesthesia and Intensive Care, Clinical University Hospital in Valladolid, Spain. mapeherrero@gmail.com
[2] MsC. Cardiology Department. Hospital Clinico Universitario, Valladolid, Spain. manuelhcuv@gmail.com
[3] MsC. Center for Biomedical Research in Cardiovascular Diseases Network, CIBERCV, Madrid, Spain. manuelhcuv@gmail.com
[4] Project Manager. Cardiology Department. ICICOR, Spain. bvelasco@icicor.es
[5] MD Department of Anaesthesia and Intensive Care, Clinical Hospital in Zamora, Spain. carlareycabo@gmail.com
[6] MD Department of Anaesthesia and Intensive Care, section head of the pain unit, Son Espases University Hospital, Balearic Islands, Spain. hermannribera@gmail.com
* Correspondence: mapeherrero@gmail.com; Tel.: 34630750263

Abstract: To evaluate analgesic practices in perioperative treatment during SARS-CoV-2 pandemic; recording parameters collected in the PAIN OUT database, and to compare COVID and no-Covid data. Data were analyzed for 277 patients (87 with COVID-19 confirmed diagnosis): 67.55 +/- 15.714 years aged; predominance of male gender (54.02%), 200.67+/118.582 minutes of surgery, Likert Scale punctuation 1.55+/-1.461; 4.63+/-3.233 hours in severe pain; minimum pain intensity of 1.11+/-1.582 and maximum of 5.68+/-2.166; interference with sleep quality 4.45 +/-2.867; 0-10); anxiety of 4.83 +/-3.175; need for help 3.83 +/-3.100; nausea 1.75 +/- 2.469; drowsiness of 3.70+/-2.694; itching of 2.80+/-2.102; dizziness of 3.78+/-2.347; perception of care of 51.75+/-28.315; pain relief of 6.65+/-2.477, participation of 7.27+/-2.892; satisfaction of 79.84 +/-17.459, and information received of 81.75 +/-17.647. Postoperative mortality one month after surgery was recorded at 25.3% in COVID-19. Significant differences were found in postoperative pain intensity ($p=0.019$), time with severe pain ($p<0.01$), lower sleep quality ($p<0.01$); and better outcomes in functional ítems ($p>0.01$), more side effects and satisfaction with pain relief ($p<0.01$) in Covid-patients than no COVID-19 patients. In conclusion, COVID-19 patients presented. greater intensity and duration of severe postoperative pain, greater somnolence, pruritus, and dizziness, lower physical activity limitation, and higher quality index.

Keywords: analgesia; COVID-19; pain; postoperative pain; SARS-CoV2

1. Introduction

The coronavirus SARS-CoV-2 was identified as the etiologic agent of a newly emerging clinical picture named COVID-19 (Coronavirus Disease) [1]. This syndrome is characterized by respiratory manifestations from mild cough, asthenia, and fever to severe acute distress syndrome and sepsis. Other less common symptoms are neurological (headache, anosmia, dysgeusia), cardiovascular (thromboembolism, myocarditis, shock), digestive (diarrhea, vomiting), and skin [2]. Despite the limited scientific evidence, an increase in perioperative morbidity and mortality in surgical patients with SARS-CoV-2 infection has been reported [3].

At present, there are no protocols and guidelines for the administration of drugs and non-pharmacological analgesic measures to treat acute postoperative pain in these patients, so multicenter studies are needed to adopt best practices. This is crucial in the global crisis caused by the SARS-CoV-2 pandemic, where greater efficiency is required in managing limited resources, using the minimum

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occupancy of operating rooms and hospital beds [4,5]. The use of opioids and other analgesic drugs could influence the evolution of the syndrome [6], and the COVID-19 pandemic worsened the opioid crisis [7].

PAIN OUT is an international project for quality improvement in postoperative pain management, registered in ClinicalTrials.gov with code NCT02083835, approved and financed by the European Commission; 7th Framework Programme (Grant Agreement no. 223590). This study registered variables of health conditions (cerebrovascular accidents, hypertension, heart disease, diabetes mellitus) and chronic treatments with corticosteroids, NSAIDs, and other medications used in the treatment of pain in surgical patients [8,9] .

This study aimed to evaluate analgesic practices in perioperative treatment during the SARS-CoV-2 pandemic. The specific objectives were recording parameters collected in the PAIN OUT database in patients with positive serology to SARS-CoV-2, analgesic treatments, pain intensity, and infection severity data. Correlation between pain and analgesic treatment variables recorded in the Pain Out database and compared with surgical non-Covid patients.

2. Materials and Methods

A prospective study approved by the local Ethical Committee on April 30, 2020, with code PI 20-1774 in patients with positive SARS-CoV-2 serology (rapid antibody test or ELISA) or positive naso/oropharyngeal Polymerase Chain Reaction (PCR) swab, undergoing surgery in centers that expressed agreement and signed written informed consent to participation in the study, between June 16 and December 20, 2020, who met the inclusion criteria (more than 18 years aged, scheduled or urgent surgery in the hospitals participating in the study, positive serology for SARS-CoV-2 or positive PCR, with signed consent for entry into the study and do not meet exclusion criteria (no inclusion criteria, no signed study entry consent acceptance, inability to understand the questionnaire: hearing impairment, cognitive dysfunction, not fluent in the language of the questionnaire; and drug addicts.

Data were recorded on the comorbidities most frequently associated with expressions of COVID-19 severity and variables collected in the Pain Out database and clinical expression data as it recorded the variables summarized in Table 1.

In all cases, the delivery of the questionnaires to the patients and the entry of the data in the database designed for the study were carried out by researchers outside the healthcare personnel responsible for the patient´s care. Data were collected at three points in time: in the immediate postoperative period (in the first 24 hours after the end of the operation and at least 6 hours later), one week, and one month after the operation.

Finally, statistical analysis of all the data collected in the study. To define the continuous variables, the mean was used as a measure of central tendency and the standard deviation as a measure of dispersion. The Shapiro-Wilk test was applied to demonstrate the tendency of a normal distribution in the quantitative and qualitative variables according to their frequency distribution.

The sample size was calculated taking into account a population of 1,006 people with laboratory COVID-19 diagnostic and surgical indication, a margin of error of 10%, and a confidence interval of 95%, obtaining a result of 88 patients.

The association of qualitative variables was analyzed using Pearson´s Chi-square test. If the number of cells with expected values less than 5 is greater than 20%, Fisher´s exact test or the likelihood ratio test for variables with more than two categories was used. Significant values were considered in the case of p-values ≤ 0.05.

In case of correlation between postoperative pain intensity, certain drugs recorded, and disease evolution data, Fisher´s exact test was used, after designing the necessary 2×2 contingency tables. The statistical data analysis was performed by applying descriptive statistics using the SPSS vs. 22 statistical packages for Windows.

Table 1. Variables in the study.

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Pain out questionary
1. Demographic characteristics**: gender, weight, height, country of birth, comorbidities (cancer, renal failure, psychiatric disease, diabetes, arterial hypertension, ischemic heart disease, hematologic disease, digestive disorders such as liver cirrhosis, peptic ulcer, irritable bowel, respiratory disease such as chronic bronchitis, asthma, sleep apnea; fibromyalgia; musculoskeletal systems such as rheumatoid arthritis, fibromyalgia or osteoarthritis; recent surgeries; polytrauma, etc.), pregnancy or lactation; chronic treatments (opioids, corticosteroids, NSAIDs, Cox-inhibitors, acetaminophen, antidepressants, antiepileptics, others)**
2. Anesthetic-surgical data of the intervention**: premedication (sedatives, analgesics, opioids or others), data of the intervention (surgical procedure, duration of the intervention, anesthetic technique used (general: inhalation or intravenous; regional: epidural, intradural, truncal, or interfascial), analgesics used during the intervention (clonidine, dexamethasone, dexketoprofen, diclofenac, ibuprofen, ketamine, ketoprofen, metamizole, naproxen, nefopam, paracetamol or others), as well as the route of administration and dosage; infiltration of the surgical wound; use of opioid drugs and local anesthetics, route of administration and dosage.**
3. Data collected in the post-anesthesia recovery unit**: drugs used (non-opioids, opioids), route of administration, and dosage.**
4. Medication administered in the hospitalization unit**, at least 5 hours after the operation and the degree of pain intensity.**
5. Pain intensity: **the maximum and minimum postoperative pain (according to the NVS scale, or VNPS (where 0 is no pain and 10 is the maximum intensity) endured at the time of data collection, percentage of pain duration of high intensity.**
6. Interference of pain **with in-bed and out-of-bed activity: deep inspiration, mobility (ambulation, sitting in a chair), time and intensity of sleep, percentage of time up.**
7. Psycho-physical repercussions of pain or its treatments: anxiety, need for help, adverse effects (nausea, drowsiness, dizziness, pruritus, others).
8. Perceived quality of analgesic treatment: **the possibility of requesting further analgesic treatment, degree of satisfaction with analgesic treatment, quality of the information received about analgesic options, degree of pain relief received, and the possibility of participation in decisions about their treatment.**
Clinical expression: Likert severity scale (0-4)
0: asymptomatic patients, **1: uncomplicated disease (local symptoms: sore throat fever, myalgias/arthralgias, ageusia, anosmia, atypical symptoms);** **2: mild symptoms: pneumonia confirmed by chest X-ray without signs of severity (SaO2 greater than 90% with FiO2 0.21), CURB65 Scale >1; or existence of any of the following parameters: age >65 years, confusion, urea nitrogen >19 mg/dl or 7 mmol/l, respiratory rate greater than 30/minute);** **3: severe pneumonia: more than one organ failure or SaO2 less than 90% on room air or respiratory rate greater than 30 or systolic blood pressure less than 90 mmHg or diastolic blood pressure less than 60 mmHg);** **4: respiratory distress, sepsis, or septic shock, defined as respiratory distress by clinical and radiographic findings (bilateral infiltrates) and mild PaO2/FiO2 of 200-300 mmHg, moderate PaO2/FiO2 of 100-200 mmHg or severe PaO2/FiO2 of less than 100 mmHg; sepsis: defined as organ dysfunction and can be identified as an acute change in the SOFA scale >2 points (http://www. samiuc.es/sofa-score/) or a quick SOFA (qSOFA) with 2 of the 3 following clinical variables: Glasgow < 13, systolic pressure < 100 mmHg and respiratory rate > 22/minute. Organ failure may be manifested by the following alterations: acute confusional state, respiratory failure, oliguria, tachycardia, coagulopathy, metabolic acidosis, lactate elevation, and septic shock: arterial hypotension if response to volumetric refill and vasopressors to maintain mean arterial pressure of 65 mmHg and lactate > 2 mmol/L (18 mg/dl) in the absence of hypovolemia.**
Microbiological data**: results of serological tests, quantification, and/or PCR.**

NSAID: Non-Steroidal Anti-Inflammatory Drugs, PCR Polymerase Chain Reaction, NVS Numerical Visual Scale, VNPS Verbal Numerical Pain Scale

**Symptomatology: fever, respiratory symptoms (dry or productive cough, sore throat, dyspnea, cold, nasal congestion), fatigue, headache, myalgia, digestive (diarrhea), anosmia, ageusia, or others).*

3. Results

During the study period, 10,702 COVID-19 patients were assisted in hospital centers, and 2,980 (27.84%) of them were scheduled for surgery. Their age was 64.77 +/- 21.10 (0-105) years and the gender distribution was predominantly female (1,934 patients) (54.9%). COVID-19 or a compatible clinic attended the majority (88.63%) of patients (9,485), but only 1,006 cases had a laboratory-confirmed diagnosis (10.61%). A mortality rate of 24.1% (2,575 cases) was recorded.

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Data from 2,425 surgical patients were analyzed, who had undergone major surgeries included in the Pain Out database. under thoracic, general, digestive, otorhinolaryngology, urology, vascular, plastic, pediatric, neurosurgery, and cardiac surgeries. (Table 2).

Table 2. Distribution of surgical interventions.

	Frequency	Percentage
Vascular surgeries	131	.6
Anesthesiology	83	.4
Cardiology	547	2.5
Cardiac surgery	25	.1
General and digestive surgery	960	4.3
Maxillofacial surgery	12	.1
Pediatric Surgery	23	.1
Plastic surgery	73	.3
Thoracic surgery	59	.3
Dermatology	5	.0
Digestive	603	2.7
Endocrinology	16	.1
Gynecology	176	.8
Geriatrics	143	.6
Hematology	226	1.0
Internal Medicine	12850	58.1
Intensive Medicine	289	1.3
Nuclear Medicine	5	.0
Nephrology	223	1.0
Neumology	1562	7.1
Neurosurgery	162	.7
Neurology	448	2.0
Obstetrics	414	1.8

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	Oftamology	33	.1
	Medical Oncology	461	2.1
	Radiation Oncology	11	.0
	Otolaryngology	214	1.0
	Pediatrics	341	1.5
	Psychiatry	273	1.2
	Radiology	1	.0
	Rheumatology	5	.0
	Orthopedics	989	4.5
	Perinatal Care Unit	77	.3
	Pain Unit	34	.2
	Emergencies	118	.5
	Urology	527	2.4
	Renal transplant unit	6	.0
	Transplant unit	10	.0
	Total	22,135	100.0

After crossing the databases of hospitalized patients and the patients undergoing surgeries studied in the PainOut study, only 604 met the study criteria. Among these 604 patients, 41 patients had a laboratory-confirmed diagnosis of COVID-19 disease at the time of the procedure (6.8%), 143 (23.7%) presented compatible symptoms and there was no information in 387 patients (64.1 %). Only 33 patients (5.5%) had laboratory confirmation of being free of SARS-Cov2. (Table 3).

Table 3. Preoperative PCR results in surgical Covid-19 patients.

		Frequency	Percentage	Valid Percentage	Accumulated percentage
Válido	Negative	33	5.5	5.5	5.5
	Positive	41	6.8	6.8	12.3
	Possibility	143	23.7	23.7	35.9
	No information	387	64.1	64.1	100.0
	Total	604	100.0	100.0	

Data from 277 patients registered in the Pain Out database were analyzed, during the study period; 87 of them with a clinical/radiological or microbiological diagnosis of COVID-19. The sample population was 67.55 +/- 15.714 (27-97) years aged; with predominance of the male gender (47 men

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and 40 women). The data that could be obtained from the PainOut study questionnaire were studied. (Table 4)

Table 4. Characteristics of patients undergoing surgery with clinical suspicion of COVID-19 disease until June 30, 2020, at the Hospital Clínico Universitario de Valladolid. .

	Mínimum	Maximum	Media	Standard deviation
Duration (minutes)	33	600	200.7	118.6
Age (years)	27	97	67.6	15.7
Likert Scale (0-4)	0	4	1.6	1.5
Time in severe pain (hours)	0	15	4.6	3.2
Minimum pain intensity (EVA scale)	0	6	1.1	1.6
Maximum pain intensity (EVA Scale)	0	9	5.7	2.2
Interference of pain with movement in bed (0-10)	0	7	2.3	2.4
Time to get out of bed (hours)	0	8	3.7	2.4
Exacerbation of pain with cough (0-10)	0	7	3.6	1.7
Interference with sleep quality (0-10)	0	8	4.4	2.9
Out-of-bed activities (0-10)	0	5	1.9	1.8
Anxiety (0-10)	0	10	4.8	3.2
Need for help (0-10)	0	10	3.8	3.1
Nausea (0-10)	0	9	1.7	2.5
Drowsiness (0-10)	0	9	3.7	2.7
Itching (0-10)	0	9	2.8	2.1
Dizziness (0-10)	0	8	3.8	2.3
Perception of care (10-100)	10	100	51.7	28.3
Pain relief (0-10)	2	10	6.6	2.5
Participation (0-10)	2	10	7.3	2.9
Satisfaction (0-100)	50	100	79.8	17.5
Information received (0-100)	50	100	81.7	17.6

Postoperative mortality was recorded in 22 patients (25.3%) one month after surgery. The surgeries were as follows: tracheotomy in 11 patients, right colectomy (2), femoral osteosynthesis (2), thoracoscopy (1), surgical wound dehiscence (1), radical hysterectomy (1), femoral-popliteal bypass (1), pectoral hematoma (1), sigmoidectomy (1) and intestinal resection and anastomosis (1). All of them presented confirmed COVID-19.

General anesthesia was more frequently used (67 cases, 77%) versus regional (18 cases, 20.7%) or sedation (2 cases, 2.3%).

Symptoms compatible with Covid appeared in only 21 cases (24.1%). In 54 cases (62.1%), after a negative preoperative PCR test, the laboratory result was positive during postoperative admission.

Of the 87 patients studied, 61 (70.1%) had risk factors included in the Pain out study. There were 4 cases of depression (4.6%), 3 strokes (3.4%), 11 dyslipidemia (12.6%), 13 arterial hypertension (14.9%), 8 alcoholism (9.2%), 2 psychiatric diseases (2.3%), 8 type 2 diabetes (9.2%), 1 asthma (1.1%), 3 irritable bowel syndrome (3.4%), 10 cancer (11.5%), 2 coronary heart disease (2, 3%), 2 patients cirrhosis (2.3%), 2 osteoporosis (2.3%), 7 renal failure (8%), 4 anemia (4.6%), 10 atrial fibrillation

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(11.5%), 4 pulmonary thromboembolism (PTE) (4.6%), 3 deep vein thrombosis (DVT) (3.4%), 3 obesity (3.4%), 10 smokers (11.5%) and 9 former smokers (10.3%).

Regarding chronic treatments, 2 patients were taking corticosteroids (2.3%), and 38 (43.7%) were taking opioids/IECAs or NSAIDs.

Data from 190 no-COVID-19 surgical patients registered in the Pain Out database were compared with the 87 COVID-19 patients operated on during the study period.

General anesthesia was the most frequently used technique in COVID-19 (77% of cases) versus locoregional anesthesia in no-COVID (56%). The differences were significant with p≤0.01.

There were no significant differences in gender between groups, with a greater predominance of the male sex in COVID (54%) compared to no-COVID (50.2%).

The presence of comorbidities was higher in COVID (69%) than in no-COVID (32.1%), with a statistical significance of p<0.001. Risk factors related to the occurrence of chronic pain appeared significant differences (p<0.05) in alcoholism (higher in COVID), inflammatory bowel disease (higher in COVID); renal failure (higher in COVID), and obesity (higher in no-COVID).

The chronic drug treatments associated with increased incidence or severity of SARS-Cov2 infection, including opioids, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory drugs (NSAID) were found in 26 (29.9%) of the patients studied.

The enrollment of patients on chronic opioid therapy was significantly higher (p=0.001) in no-COVID base (20%) versus COVID (4.6%). The most commonly used were transdermal fentanylor oral morphine.

NSAIDs were used in higher proportion (p≤0.001) in no-COVID (57.3%) than in COVID (17.2%).

Angiotensin inhibitors were used in 10.3% of COVID-19 patient cases. (Table 5)

Table 5. Correlation in risk factors between COVID and no-COVID patients. Significant differences in bold type letter.

	COVID-19	Non COVID-19	p
Arterial hypertension	14.9 %	11.5 %	0.4
Alcoholism	9.2%	0.9%	**0.01**
Psychiatric diseases	2.8%	4.6%	0.4
Diabetes	9.2%	7.8%	0.7
Type 1 diabetes	0	6.9%	0.07
Type 2 diabetes	9.2%	0.9%	**0.01**
Asthma	1	0	0.3
Inflammatory bowel disease	3.4%	0	**0.02**
Oncologic pathology	11.5%	12%	0.99
Chronic bronchitis	0	1.4%	0.56
Coronary artery disease	2.3%	4.6%	0.52
Chronic corticosteroid therapy	2.3%	1.4%	0.63
Fibromyalgia	0	0.5 %	0.999
Peptic ulcus	0	0.5%	0.999
Cirrhosis	2.3%	0	0.081
Rheumatoid arthritis	0.5 %	0.5%	
Osteoporosis	3.4%	3.4%	
Renal insufficiency	8%	2.8%	**0.057**
Renal insufficiency (dialysis)	1.4%	1.4%	
Anemia	4.6%	2.9%	0.7
Smokers	11.5%	2.9%	**0.045**

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Non smokers	10.3%	10.3%	
Atrial fibrillation	11.5%	11.5%	
Pulmonary thromboembolism	4.6%	4.6%	
Deep vein thrombosis	3.4%	3.4%	
Obesity	3.4%	15.1%	**0.005**
Chronic drug treatments*	29.9%		
Opioids	4.6%	20%	**0.001**
NSAIDs	17.2%	57.3%	**<0.001**

4. Discussion

Surgical activity had to be interrupted due to the extraordinary demand for medical care caused by the pandemic. In Leon and Castille, in Spain, 22,135 patients were attended, and 10,702 (48.35%) of them required hospital admission. This resulted in an overload of the hospital system. Only 2,980 were operated on. This would be equivalent to less than one-tenth of the usual surgical activity [10] .

In our work, 9,425 (81%) of the hospitalized patients were attended by COVID-19 or a compatible clinic, but only 1,006 of them (13.5%) presented conclusive laboratory tests (PCR tests or serology). This fact is by Arevalo-Rodriguez et al´s article, where they included 34 studies enrolling 12,057 COVID-19 confirmed cases. The findings reinforce the need for repeated testing in patients with suspicion of SARS-Cov-2 infection given that up to 54% of COVID-19 patients may have an initial false-negative RT-PCR [11] .

Despite a negative preoperative PCR test, the laboratory result was positive in 62.1% of the cases after surgery. This may be due to the low negative predictive value of the test used or to the low clinical expressivity of the new SARS-Cov-2 variants. In contrast, retrospective studies such as that of Mavrothalassitis et al concluded that outcomes of patients undergoing surgery and 30-day mortality after surgery were not compromised even in states with the highest severity of COVID-19 in patients undergoing surgery during the first wave of the COVID-19 pandemic in 2020. [12]

A mortality rate of 24.1% was very high and the most frequent cause of hospital admission was COVID-19. These data are in line with published mortality data for 2020, where 493,776 deaths were recorded and Covid was the leading cause with 60,358 in Spain [13]; the Kivrak S et al´s study, which found postoperative mortality of 25.3% one month after surgery in COVID-19 patients [14], and the multicenter study in 2,132 from 25 Spanish hospitals found similar rates of 30-day mortality among surgical patients with and without SARS-CoV-2 infection (12.6% vs. 4.6%) [15]. However, other studies described that SARS-CoV-2 infection was associated with higher rates of 90-day mortality and 30-day postoperative complications [16] .

General anesthesia was the most frequently used technique in COVID-19 patients (77% of cases) versus locoregional anesthesia (56%), despite recommendations of various scientific societies to avoid aerosol-generating procedures, such as intubation or airway management maneuvers and preservation of respiratory function with regional anesthesia techniques [17,18,19,20].

In addition, several publications have demonstrated the presence of thrombopenia in COVID-19 patients, and therefore, the possible contraindication to regional blockades [21,22,23].

Of the patients studied, 70.1% had risk factors listed in the Pain Out database, the most frequent being hypertension (14.9%), dyslipidemia (12.6%), atrial fibrillation (11.5%), and smokers (11.5%), and former smokers (10.3%). All of them associated were with high mortality [24]. This finding could explain the high mortality recorded, in line with Silvapulle´s article that recommended hospitalized or persistent symptoms patients, undergo targeted organ-specific assessment using a combination of echocardiography, lung function tests, and biomarkers to provide quantitative estimation of perioperative risk [25]. Such information is crucial for the complex surgical decision-making and counseling of patients presenting with positive SARS-CoV-2 infection status. Further studies are required to understand the impact of new variants, large-scale vaccination, and new therapeutics on the postoperative outcomes of COVID-19 patients [26] .

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It has been proven significantly higher rates of mortality and postoperative complications, especially thromboembolic events, among patients with perioperative SARS-CoV-2 infection compared with patients without SARS-CoV-2 infection. Moreover, matched SARS-CoV-2–infected patients had a higher risk of mortality even if they were asymptomatic at presentation [27] .

Symptoms compatible with COVID-19 appeared in only 24.1% of patients, but in 62.1% of them, after a negative preoperative PCR test, the laboratory result was positive during postoperative admission. This could be explained by the low negative predictive value of PCR, together with contact with asymptomatic patients not diagnosed with COVID-19. These results are in line with Rose´s article which concluded that nucleic acid amplification confirmation is crucial, however, can make nucleic acid amplification in active COVID-19 infections unnecessary and testing cost-efficient [28] .

The mortality that was registered was high but similar to other registries in critical patients [29] and the excess mortality rate due to the COVID-19 pandemic. [30] The difference between excess mortality and reported COVID-19 deaths might be a function of underdiagnosis due to insufficient testing, reporting challenges, or higher-than-expected mortality from other diseases due to pandemic-related changes in behaviors or reduced access to health care or other essential services.

The presence of certain risk factors such as age (younger than 54 years), preoperative pain in the surgical area, female gender, duration of surgery longer than 90 minutes, preoperative opioid administration, anxiety, and the need for help with pain have been associated with a higher frequency and longer time of severe postoperative pain and the need for more analgesic treatment [31] . Stamenkovic´s study demonstrated that a small set of evidence-based interventions is associated with improved outcomes in perioperative pain. The interventions were a full daily dose of 1 to 2 nonopioid analgesics (eg, paracetamol and/or nonsteroidal anti-inflammatory drugs), at least 1 type of local/regional anesthesia, pain assessment by staff, and offering patients information about pain management [8] .

Clinicians are now equipped with an armamentarium of therapies based on high-quality evidence to manage COVID-19 patients: anti-inflammatory agents, antivirals, antithrombotics, therapies for acute hypoxaemic respiratory failure, anti-SARS-CoV-2 (neutralizing) antibody therapies, modulators of the renin-angiotensin-aldosterone system and vitamins [32]. In this study only 43.7% of patients were on opioids, angiotensin inhibitors, and non-steroidal anti-inflammatory drugs treatment; and 2.3% were treated with corticosteroids.

The study´s main limitation is that the recent description of Covid disease, together with the urgency of the pandemic situation, makes clinical suspicion and diagnosis of the disease difficult at the moment the study was done. Proof of this is the large number of errata published in the original studies on this topic. Currently, the most sensitive test is PCR of gold or nasopharyngeal exudate, although the false negative rate is high and depends on numerous factors. On the other hand, the study has the limitations inherent to the Pain Out study: numerous factors are involved in the appearance of postoperative pain (included in the study variables) and it is difficult to establish homogeneous groups for comparison; each center collects and analyzes its data using different statistical analysis methods. The high mortality recorded prevents extrapolation of the results to other COVID-19 patients with fewer preoperative risk factors.

In conclusion, despite the high percentage of patients with risk factors for developing severe postoperative pain, no special analgesic measures were applied. A large margin for improvement is demonstrated in the application of multimodal perioperative analgesic strategies and patient information. It was found greater intensity and duration of severe postoperative pain, greater somnolence, pruritus, and dizziness in COVID-19 patients. The limitation of physical activity was lower and the index of perceived quality higher than in non-COVID patients.

The individualized study of the patients and the severity of the disease establishes the probability of postoperative complications in COVID-19 patients. Pain control must also take into account the variability among surgical patients.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Easth Health Area Ethical Committee on April 30, 2020, with code PI 20-1774.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

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