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Does admission acetylsalicylic acid uptake in hospitalized COVID-19 patients have a protective role? Data from the Spanish SEMI-COVID-19 Registry

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Abstract
Acetylsalicylic acid (ASA) is widely used in the treatment and prevention of cardiovascular disorders. Our objective is to evaluate its possible protective role, not only in mortality but also in other aspects such as inflammation, symptomatic thrombosis, and intensive care unit (ICU) admission in hospitalized COVID-19 patients. We realized an observational retrospective cohort study of 20,641 patients with COVID-19 pneumonia collected and followed-up from Mar 1st, 2020 to May 1st, 2021, from the nationwide Spanish SEMI-COVID-19 Registry. Propensity score matching (PSM) was performed to determine whether treatment with ASA affected outcomes in COVID-19 patients. On hospital admission, 3291 (15.9%) patients were receiving ASA. After PSM, 3291 patients exposed to ASA and 2885 not-exposed patients were analyzed. In-hospital mortality was higher in the ASA group (30.4 vs. 16.9%, $p<0.001$) in the global sample. After PSM, no differences were found between groups (30.4 vs. 30.3%, $p=0.938$). There were no differences in inflammation, symptomatic thrombosis, or ICU admission. In conclusion, ASA intake is not associated with in-hospital mortality or any other health outcome evaluated after applying PSM analysis in a real-world large sample of hospitalized COVID-19 patients.

Keywords Acetylsalicylic acid · Coronavirus · COVID-19 · Mortality

Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), produces severe respiratory symptoms such as bilateral pneumonia associated with high morbidity and mortality, especially in patients of advanced age [1]. At this time, there is no known active treatment to fight this virus. Corticosteroids and biological immunosuppressants are being used to treat the inflammatory phase of the disease [1].

As severe COVID-19 infection is mainly a multisystem inflammatory process with an increased risk of hypercoagulability, the use of acetylsalicylic acid (ASA) can theoretically provide positive outcomes [2, 3]. It inhibits platelet aggregation triggered by the release of arachidonic acid from platelet cells [4]. Thus, the possible mechanism of the protective effects of ASA may be related to its antithrombotic and anti-inflammatory effects and also to its possible immunomodulatory effects (antiviral activity against DNA and RNA viruses, including different human coronaviruses) [5].

The role of ASA in patients with COVID-19 is not studied in depth. A first meta-analysis, including three studies

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A complete list of the SEMI-COVID-19 Network members is provided in the Appendix.

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evaluating the association between ASA at admission use and mortality in COVID-19 hospitalized patients, suggested no association between the use of ASA and mortality in patients with COVID-19 [6]. Although patients on ASA tend to have more risk factors for severe COVID-19 infection (older age, high cardiovascular risk, pre-existing coronary artery disease, etc.), the low heterogeneity in this analysis despite differences in characteristics of the population of the included studies [7–9] likely suggests no protective effect of ASA among different groups of patients [6].

As ASA was widely used in the treatment and prevention in the real world in cardiovascular disorders, our study aimed to check its possible protective role, not only in mortality but in other aspects such as inflammation, symptomatic thrombosis, and intensive care unit (ICU) admission.

Materials and methods

Study design, patient selection, and data collection

The analysis was performed in the large cohort of consecutive patients included in the Spanish SEMI-COVID-19 Registry, created by the Spanish Society of Internal Medicine (SEMI). This is a multicenter, nationwide registry with over 150 hospitals registered so far. From March 1st, 2020 to May 1st, 2021, 21,962 hospitalized patients were included in the Registry. Methods of the study have been previously described [10]. In brief, all included patients were diagnosed by polymerase chain reaction (PCR) test or rapid antigenic test for SARS-CoV-2 taken from a nasopharyngeal sample, sputum, or bronchoalveolar lavage. The collection of data from each patient in terms of sociodemographic data, comorbidities, laboratory data, treatments, and outcomes was verified by the principal investigator of each center through the review of clinical records. All participating centers in the register received confirmation from the relevant Ethics Committees, including Bellvitge University Hospital (PR 128/20).

The inclusion criteria were all patients in the registry with a community (non-nosocomial) SARS-CoV-2 infection. We included all patients with valid information on whether or not they were taking ASA at the time of hospital admission. The patient sample was divided into 2 groups: patients with ASA admission intake and patients without.

The treatments received were in accordance with the medical guidelines available at the time of the pandemic [10]. In the absence of clinical evidence of any of the treatments at the initial time of the pandemic, their use was allowed off-label.

Outcomes definition

The primary outcome of the study was in-hospital mortality. Secondary outcomes were the development of symptomatic deep venous thrombosis (DVT) or pulmonary embolism (PE), the requirement of high-flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIMV), invasive mechanical ventilation (IMV), ICU admission, and the combined variable of in-hospital mortality, the requirement of HFNC, NIMV, IMV, or ICU admission. Also, the development of inflammation in the high-risk category according to the categories previously defined by our group [10]. This was defined when the patient met 1 of the following criteria: lymphocyte count $< 760 \times 106$/L, C-reactive protein (CRP) > 101.5 mg/L, lactate dehydrogenase (LDH) > 394 U/L, ferritin > 1359.9 mcg/L, or D-dimer > 1580 ng/mL.

Statistical analysis

Multiple imputations of missing data were performed. To minimize differences between groups and improve comparability, logistic-regression propensity score nearest neighbor matching (PSM) with replacement and caliper 0.2 was performed. The PSM included sociodemographic variables (age and sex), days from symptom onset to hospital admission, smoking behavior, body mass index (BMI), comorbidities as arterial hypertension, diabetes mellitus, dyslipidemia, chronic liver disease, severe chronic renal failure, chronic obstructive pulmonary disease (COPD), asthma, obstructive sleep apnea syndrome (OSAS), chronic heart failure, ischemic heart disease, cerebrovascular disease, cancer, dementia, degree of dependency, and Charlson index, tachypnea and laboratory variables on admission as PaO2/FiO2, ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), lymphocyte count, D-dimer, albumin, creatinine, platelets count, and hemoglobin), and treatments during admission (corticosteroids, tocilizumab, and remdesivir).

Categorical variables were expressed as absolute numbers and percentages. Continuous variables are expressed as mean plus standard deviation (SD) in the case of parametric distribution or median [IQR] in the case of non-parametric distribution. Differences among groups were assessed using the chi-square test for categorical variables and T-test or Mann–Whitney test as appropriate for continuous variables. p values < 0.05 indicated statistical significance.

Statistical analysis was performed by IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY, USA: IBM Corp.

Results

We included 20,641 patients in the study. There were 11,879 men (57%). On hospital admission, 3291 (15.9%) patients were detected as receiving ASA. In an attempt to differentiate the ASA effect from other effects, 3,291 exposed to ASA and 2885 not-exposed patients were matched.

General baseline data between groups

In the unadjusted analysis, patients on admission ASA were significantly older, predominantly male, and with fewer days between the start of symptoms at admission. Furthermore, patients on ASA were more frequently former smokers and had higher dependence, more comorbidities (arterial hypertension, dyslipidemia, diabetes mellitus, ischemic cardiopathy, cerebrovascular disease, peripheral arterial disease, dementia, chronic heart failure, severe chronic renal failure, cancer, COPD, and OSAS), and higher score in the Charlson Index. In contrast, the percentage of patients with atrial fibrillation and asthma was lower in patients with admission ASA use (Table 1).

The differences regarding days from onset to admission, degree of dependency, arterial hypertension, diabetes mellitus, cerebrovascular disease, dementia, and chronic heart failure disappeared after PSM analysis.

Regarding symptoms, ASA patients had a lower percentage of cough, arthromyalgias, ageusia, anosmia, sore throat, headache, fever, diarrhea, and abdominal pain with a similar percentage of dyspnea and vomiting. Heart rate was lower in ASA patients on admission, although in this group there was a higher percentage of patients with respiratory rate > 20 bpm (Table 2). All symptoms and physical examination differences lost the statistical association after PSM.

Laboratory tests between groups

Concerning to the analytical values, the group with ASA admission use had lower PaO2/FiO2, lymphocyte count, platelet figures, and albumin. In contrast, they presented with higher values of CRP, LDH, D-dimer, and creatinine. In the group without ASA, they presented higher values of ferritin and alanine transferase (ALT) (Table 3). Except for the Ddimer, all variables lost their association after PSM.

Treatments during admission

During admission (Table 4), patients with ASA use were treated less frequently with oral anticoagulants, tocilizumab, and remdesivir. In contrast, they were treated more often with prophylactic doses of low-molecular-weight heparin (LMWH) and corticosteroids. Only treatment with LMWH retained significance when applying PSM.

Outcomes between groups (Fig. 1)

In-hospital mortality was higher in the ASA group (30.4 vs. 16.9%, $p < 0.001$). ASA patients presented also more frequently with high-risk-inflammatory categories (80.1 vs. 75.3%, $p < 0.001$), the requirement of NIMV (6.7 vs. 5.7%, $p = 0.028$), and the combined variable (38.1 vs. 27.4%, $p < 0.001$). In contrast, ASA patients required less frequent IMV (6.5 vs. 7.7%, $p = 0.014$) and ICU admission (8.6 vs. 9.9%, $p = 0.018$). There were no differences in the number of DVT (0.5 vs. 0.6%, $p = 0.851$), PE (1.7 vs. 1.7%, $p = 0.851$), DVT + PE (0.1 vs. 0.2%, $p = 0.851$), or HFNC use (9.7 vs. 9.5%, $p = 0.720$). As shown in Table 5, none of the outcomes assessed remained associated with admission ASA use after PSM. In-depth, in-hospital mortality was practically identical in the two groups after matching (30.4 vs. 30.3%, $p = 0.938$), same as DVT (0.5 vs 0.8%, $p = 0.508$), PE (1.7 vs. 1.4%, $p = 0.508$), DVT + PE (0.1 vs 0.2%, $p = 0.508$), high-risk inflammation category (80.1 vs. 79.1%, $p = 0.316$), HFNC (9.7 vs. 9.1%, $p = 0.411$), NIMV (6.7 vs. 6.3%, $p = 0.518$), IMV (6.5 vs. 6.3%, $p = 0.750$), ICU (8.6 vs. 8.2%, $p = 0.622$), and the combined variable (38.1 vs. 38%, $p = 0.946$).

Risk factors for in-hospital mortality (Table 6)

Despite PSM some variables were not correctly matched so we performed a logistic regression to really investigate the possible effectiveness of ASA. The factors that were related to higher in-hospital mortality were older age, male sex, higher degree of dependency, chronic heart failure, higher Charlson index, tachypnea on admission, higher CRP, LDH, and ferritin levels. Lower PaO2/FiO2 and lymphocyte count levels were also associated with higher in-hospital mortality. The use of ASA was not related to in-hospital mortality.

Discussion

The main result of our study in a very large sample of patients (more than 20,000 patients) is the fact that there is no relationship between the intake of ASA at admission and the main outcome (in-hospital mortality), nor the secondary outcomes (inflammation, symptomatic thrombosis, and ICU admission) in Spanish hospitalized patients with COVID-19 infection after the correcting impact of PSM analysis.

ASA-related antiplatelet and anti-inflammatory effects could lead to better health outcomes in patients hospitalized for COVID-19 but our study failed to demonstrate that.

Table 1 Patient characteristics before and after propensity score matching

	All cohort				Propensity Score Matched Cohort			
	ASA	No ASA	% or mean difference	*p* value	ASA	No ASA	% or mean difference	*p* value
N	3291	17,350			3291	2885		
Age, median [IQR]	77.6 [70–85.2]	66.9 [54.4–78.4]	+ 10.7	< 0.001	77.6 [70–85.2]	79 [70.6–86.1]	− 1.4	0.003
Gender (males), *n* (%)	2053 (62.4)	9826 (56.6)	+ 5.8%	< 0.001	2053 (62.4)	1704 (59.1)	+ 3.3%	0.008
Race, *n* (%)	3174 (96.4)	15,292 (88.1)	+ 8.3%	< 0.001	3174 (96.4)	2782 (96.4)	0	0.859
Caucasian	10 (0.3)	105 (0.6)	− 0.3%		10 (0.3)	9 (0.3)	0	
Black	71 (2.2)	1629 (9.4)	− 7.2%		71 (2.2)	68 (2.4)	+ 0.2%	
Hispanic	7 (0.2)	95 (0.5)	− 0.3%		7 (0.2)	7 (0.2)	0	
Asian	29 (0.9)	229 (1.3)	− 0.4%		29 (0.9)	29 (0.9)	0	
Others								
Days from onset to admission, median [IQR]	5 [3–8]	7 [4–9]	− 2	< 0.001	5 [3–8]	5 [3–8]	0	0.647
BMI, median [IQR]	28.6 [25.4–32]	28.5 [25.3–32.1]	+ 0.1	0.793	28.6 [25.4–32]	28.5 [25.3–32]	+ 0.1	0.653
Smoking behavior, *n* (%)	1912 (58.1)	12,460 (71.8)	− 13.7%	< 0.001	1912 (58.1)	1805 (62.6)	− 4.5%	< 0.001
Never smoker	1220 (37.1)	4055 (23.4)	+ 13.7%		1220 (37.1)	925 (32.1)	+ 5%	
Former smoker	159 (4.8)	834 (4.8)	0		159 (4.8)	155 (5.4)	− 0.6%	
Current smoker								
Degree of dependency, *n* (%)	2340 (71.1)	14,847 (85.6)	− 14.5%	< 0.001	2340 (71.1)	2021 (70.1)	+ 1%	0.498
None or mild	532 (16.2)	1419 (8.2)	+ 8%		532 (16.2)	468 (16.2)	0	
Moderate	419 (12.7)	1084 (6.2)	+ 6.5%		419 (12.7)	396 (13.7)	− 1%	
Severe								
Arterial hypertension, *n* (%)	2599 (79)	8109 (46.7)	+ 32.3%	< 0.001	2599 (79)	2260 (78.3)	+ 0.7%	0.542
Dyslipidemia, *n* (%)	2140 (65)	6046 (34.8)	+ 30.2%	< 0.001	2140 (65)	1790 (62)	+ 3%	0.015
Diabetes mellitus, *n* (%)	1235 (37.5)	3000 (17.3)	+ 20.2%	< 0.001	1235 (37.5)	1021 (35.4)	+ 2.1%	0.082
Atrial fibrillation, *n* (%)	283 (8.6)	1941 (11.2)	− 2.6%	< 0.001	283 (8.6)	322 (11.2)	− 2.6%	0.001
Ischemic cardiopathy, *n* (%)	953 (29)	665 (3.8)	+ 25.2%	< 0.001	953 (29)	538 (18.6)	+ 10.4%	< 0.001
Cerebrovascular disease, *n* (%)	662 (20.1)	847 (4.9)	+ 15.2%	< 0.001	662 (20.1)	524 (18.2)	+ 1.9%	0.052
Peripheral arterial disease, *n* (%)	402 (12.2)	471 (2.7)	+ 9.5%	< 0.001	402 (12.2)	275 (9.5)	+ 2.7%	0.001
Dementia, *n* (%)	567 (17.2)	1,459 (8.4)	+ 8.8%	< 0.001	567 (17.2)	521 (18.1)	− 0.9%	0.393
Chronic heart failure, *n* (%)	434 (13.2)	946 (5.5)	+ 7.7%	< 0.001	434 (13.2)	338 (11.7)	+ 1.5%	0.081
Chronic liver disease, *n* (%)	124 (3.8)	578 (3.3)	+ 0.5%	0.205	124 (3.8)	133 (4.6)	− 0.8%	0.098
Severe chronic renal failure, *n* (%)	390 (11.9)	816 (4.7)	+ 7.2%	< 0.001	390 (11.9)	312 (10.8)	+ 1.1%	0.201
Cancer, *n* (%)	372 (11.3)	1566 (9)	+ 2.3%	< 0.001	372 (11.3)	353 (12.2)	− 0.9%	0.256
COPD, *n* (%)	371 (11.3)	1029 (5.9)	+ 5.4%	< 0.001	371 (11.3)	317 (11)	+ 0.3%	0.722
Asthma, *n* (%)	195 (5.9)	1257 (7.2)	− 1.3%	0.007	195 (5.9)	188 (6.5)	− 0.6%	0.336
OSAS, *n* (%)	271 (8.2)	966 (5.6)	+ 2.6%	< 0.001	271 (8.2)	222 (7.7)	+ 0.5%	0.435
Charlson index median [IQR]	2 [1–3]	0 [0–2]	+ 2	< 0.001	2 [1–3]	1 [1–3]	+ 1	< 0.001

ASA Acetylsalicylic acid, *BMI* body mass index, *IQR* interquartile range, *COPD* chronic obstructive pulmonary disease, *OSAS* obstructive sleep apnea syndrome, Severe chronic renal failure: Creatinine > 300 mg/dl or dialysis

Table 2 Symptoms and physical examination upon admission between groups before and after propensity score matching

	All cohort				Propensity score matched cohort			
	ASA	No ASA	% or mean difference	*p* value	ASA	No ASA	% or mean difference	*p* value
Cough, *n* (%)	2148 (65.3)	12,534 (72.2)	− 6.9%	< 0.001	2148 (65.3)	1864 (64.6)	+ 0.7%	0.588
Arthromyalgias, *n* (%)	736 (22.4)	5375 (31)	− 8.6%	< 0.001	736 (22.4)	637 (22.1)	+ 0.3%	0.789
Ageusia, *n* (%)	184 (5.6)	1730 (10)	− 4.4%	< 0.001	184 (5.6)	164 (5.7)	− 0.1%	0.874
Anosmia, *n* (%)	151 (4.6)	1535 (8.8)	− 4.2%	< 0.001	151 (4.6)	146 (5.1)	− 0.5%	0.387
Sore throat, *n* (%)	230 (7)	1683 (9.7)	− 2.7%	< 0.001	230 (7)	209 (7.2)	− 0.2%	0.697
Headache, *n* (%)	230 (7)	2264 (13)	− 6%	< 0.001	230 (7)	196 (6.8)	+ 0.2%	0.763
Fever, *n* (%)	2487 (75.6)	14,261 (82.2)	− 6.6%	< 0.001	2487 (75.6)	2168 (75.1)	+ 0.5%	0.701
Dyspnea, n (%)	1928 (58.6)	10,200 (58.8)	− 0.2%	0.826	1928 (58.6)	1685 (58.4)	+ 0.2%	0.887
Diarrhea, *n* (%)	692 (21)	4257 (24.5)	− 3.5%	< 0.001	692 (21)	588 (20.4)	+ 0.6%	0.532
Vomiting, *n* (%)	246 (7.5)	1367 (7.9)	− 0.4%	0.429	246 (7.5)	210 (7.3)	+ 0.2%	0.769
Abdominal pain, *n* (%)	179 (5.4)	1128 (6.5)	− 1.1%	0.022	179 (5.4)	188 (6.5)	− 1.1%	0.074
Heart rate, bpm median [IQR]	83 [73–95]	88 [77–100]	− 5	< 0.001	83 [73–95]	84 [74–95]	− 1	0.077
Respiratory rate > 20 bpm, *n* (%)	1142 (34.7)	5429 (31.3)	+ 3.4%	< 0.001	1142 (34.7)	1037 (35.9)	− 1.2%	0.307

ASA Acetylsalicylic acid, *IQR* interquartile range

Table 3 Laboratory tests upon admission between groups before and after propensity score matching

	All cohort				Propensity score matched cohort			
	ASA	No ASA	Mean difference	*p* value	ASA	No ASA	Mean difference	*p* value
PaO2/FiO2, median [IQR]	290.7 [235–347.6]	300 [242.9–358.5]	− 9.3	< 0.001	290.7 [235–347.6]	289.5 [233–347.2]	+ 1.2	0.595
Lymphocytes × 10^6/l, median [IQR]	900 [600–1232]	950 [690–1300]	− 50	< 0.001	900 [600–1232]	900 [610–1280]	0	0.195
CRP mg/l, median [IQR]	72 [27.7–139]	64 [21.5–130]	+ 8	< 0.001	72 [27.7–139]	69.2 [23.8–138]	+ 2.8	0.151
LDH U/l, median [IQR]	335 [251–463]	325 [248–440.9]	+ 10	0.005	335 [251–463]	331 [248.5–454]	+ 4	0.602
Ferritin mcg/l, median [IQR]	630 [222–1328.1]	751.1 [273.5–1450.2]	− 121.1	< 0.001	630 [222–1328.1]	653.8 [221.5–1331.8]	− 23.8	0.883
Ddimer ng/ml, median [IQR]	920 [454–2200]	631 [315–1400]	+ 289	< 0.001	920 [454–2200]	846 [411–2072]	+ 74	0.034
Hemoglobin g/dl, median [IQR]	13.2 [11.9–14.6]	13.9 [12.7–15]	− 0.7	< 0.001	13.2 [11.9–14.6]	13.3 [12–14.6]	− 0.1	0.077
Platelets × 10^9/l, median [IQR]	184 [142–246]	192 [149–250]	− 8	< 0.001	184 [142–246]	187 [145–244]	− 3	0.332
Creatinine mg/dl, median [IQR]	1.06 [0.82–1.45]	0.9 [0.72–1.13]	+ 0.7	< 0.001	1.06 [0.82–1.45]	1.03 [0.81–1.45]	+ 0.3	0.179
Albumin g/dl, median [IQR]	3.6 [3.17–4]	3.7 [3.3–4.1]	− 0.1	< 0.001	3.6 [3.2–4]	3.6 [3.2–3.9]	0	0.676
ALT U/l, median [IQR]	26 [17–42]	30 [19–49]	− 4	< 0.001	26 [17–42]	26 [17–42]	0	0.568

ASA Acetylsalicylic acid, *ALT* alanine transferase. *CRP* C-reactive protein, *LDH* lactate dehydrogenase, *IQR* interquartile range

Table 4 Treatments during admission between groups before and after propensity score matching

	All cohort				Propensity score matched cohort			
	ASA	No ASA	% difference	*p* value	ASA	No ASA	%difference	*p* value
Oral anticoagulants, *n* (%)	33 (1)	293 (1.7)	− 0.7%	< 0.001	33 (1)	46 (1.6)	− 0.6%	0.051
Anti vitamin k	46 (1.4)	402 (2.3)	− 0.9%		46 (1.4)	52 (1.8)	− 0.4%	
DOAC								
LMWH, *n* (%)	371 (12.3)	2737 (16.3)	− 4%	< 0.001	404 (12.3)	406 (14.1)	− 1.8%	< 0.001
None	2208 (67.1)	10,991 (63.3)	+ 3.8%		2208 (67.1)	1812 (62.8)	+ 4.3%	
Prophylactic doses	315 (9.6)	1493 (8.6)	+ 1%		364 (11.1)	403 (14)	− 2.9%	
Intermediate doses	364 (11.1)	2032 (11.7)	− 0.6%		315 (9.6)	264 (9.2)	+ 0.4%	
Full doses								
Steroids, *n* (%)	1663 (50.9)	7817 (45.3)	+ 5.6%	< 0.001	1663 (50.5)	1439 (49.9)	+ 0.6%	0.609
Tocilizumab, *n* (%)	272 (8.3)	1748 (10.1)	− 1.8%	0.001	272 (8.3)	236 (8.2)	+ 0.1%	0.904
Remdesivir, *n* (%)	126 (3.8)	823 (4.7)	− 0.9%	0.022	126 (3.8)	106 (3.7)	+ 0.1%	0.750

ASA Acetylsalicylic acid, *DOACs* direct oral anticoagulants, *LMWH* low-mollecular-weight heparin

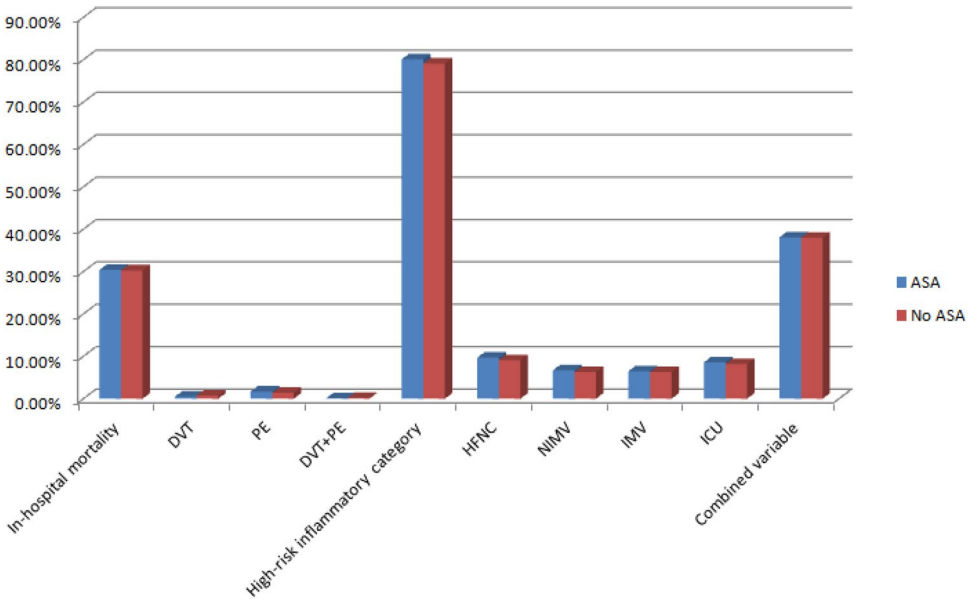

Fig. 1 Outcomes between groups after propensity score matching. *ASA* Acetylsalicylic acid, *HFNC* high Flow nasal cannula, *NIMV* non-invasive mechanical ventilation, *IMV* invasive mechanical ventilation, *ICU* intensive care unit, *DVT* deep venous thrombosis, *PE* pulmonary embolism

When evaluating the data globally, the percentage of in-hospital mortality was much higher in the ASA group (30.4 vs. 16.9%, $p < 0.001$). The most obvious hypothesis is that occurs because the ASA patients were older and with more comorbidities. When applied PSM, we found identical rates of 30% of in-hospital mortality irrespective of whether or not they had previously taken ASA.

ASA is inexpensive, widely available, and with clear indications of prescription and a well-known risk profile. Of all the patients admitted for COVID-19 in Spain, 15.9% were under ASA before hospital admission. The percentage of patients admitted for COVID-19 who were under ASA is slightly lower than the 19.2% reported in a recent meta-analysis [6] and the 24% reported in a Veterans Health Administration study in patients with COVID-19 infection [11]. Our results confirm, as previously reported in COVID-19 patients, that ASA users tend to have more risk factors for severe COVID-19 infection (older age, diabetes mellitus, ischemic cardiopathy, etc.,)[6].

In-hospital mortality among ASA users in the meta-analysis by Salah et al.[6] was 22.6 vs. 18.3% among non-ASA users (RR = 1.12, 95% CI 0.84–1.50). It is important to take into account the few patients included in the 3 studies, and none of them assessing a European population. So, in the study by Alamdari et al. [7] they evaluated 459 patients (53 under ASA) from Iran, Chow et al. [9] included 419 USA patients (98 under ASA), and Yuan et al. [8] 183 Chinese patients, all with coronary artery disease (52 under ASA). We evaluated higher figures of patients (20,641 patients) of whom 3291 were treated with ASA before hospital admission. Sahai et al. [12] concluded in 248 USA-matched patients with COVID-19 that ASA

Table 5 Outcomes between groups before and after propensity score matching

	All cohort				Propensity score matched cohort			
	ASA	No ASA	%difference	*p* value	ASA	No ASA	% difference	*p* value
Primary outcome *n* (%)	1000 (30.4)	2929 (16.9)	+13.5%	<0.001	1000 (30.4)	874 (30.3)	+0.1%	0.938
In-hospital mortality								
Secondary outcomes *n* (%)	18 (0.5)	105 (0.6)	− 0.1%	0.851	18 (0.5)	22 (0.8)	− 0.3%	0.508
	57 (1.7)	303 (1.7)	0	0.851	57 (1.7)	41 (1.4)	+0.3%	0.508
	4 (0.1)	32 (0.2)	− 0.1%	0.851	4 (0.1)	5 (0.2)	− 0.1%	0.508
DVT	2637 (80.1)	13,058 (75.3)	+4.8%	<0.001	2637 (80.1)	2282 (79.1)	+1%	0.316
PE	319 (9.7)	1647 (9.5)	+0.2%	0.720	319 (9.7)	262 (9.1)	+0.6%	0.411
DVT + PE	221 (6.7)	994 (5.7)	+1%	0.028	221 (6.7)	182 (6.3)	+0.4%	0.518
High-risk inflammatory category	213 (6.5)	1337 (7.7)	− 1.2%	0.014	213 (6.5)	181 (6.3)	+0.2%	0.750
	283 (8.6)	1723 (9.9)	− 1.3%	0.018	283 (8.6)	238 (8.2)	+0.4%	0.622
	1253 (38.1)	4752 (27.4)	+10.7%	<0.001	1253 (38.1)	1096 (38)	+0.1%	0.946
HFNC								
NIMV								
IMV								
ICU admission								
Combined variable								

ASA Acetylsalicylic acid, *HFNC* High Flow nasal cannula, *NIMV* non-invasive mechanical ventilation, *IMV* invasive mechanical ventilation, *ICU* intensive care unit, *DVT* Deep venous thrombosis, *PE* Pulmonary embolism

had no overall mortality benefit in a retrospective observational study.

A recent study from Iran assessing 991 patients (336 with prior ASA intake or having started ASA on the first day of hospital admission) demonstrated a significant independent association between ASA and lower in-hospital mortality (RR = 0.75, 95% CI 0.56–0.99) [13]. Although the study was not carried out with PSM correction, it is worth highlighting the results taking into account that patients with ASA were older and had more comorbidities. Finally, Chow et al. [9] reported that ASA use was independently associated with decreased risk of MV and ICU admission. Neither Yuan et al. [8] nor our results after PSM could confirm this association.

In a different scenario from our study, ASA has shown good health outcomes. Liu et al. [14] enrolled 24 pairs of patients (after PSM) and reported that among adults (with arterial hypertension and cardiovascular diseases) infected with SARS-CoV-2, low-dose ASA (100 mg/day) was associated with a lower risk of mortality compared with non-ASA users. Among more than 30,000 COVID-19 positive USA Veterans, prior ASA intake was associated with a statistically and clinically significant decrease in overall mortality at 14-days (OR = 0.38, 95% CI 0.32–0.46) and 30-days (OR = 0.38, 95% CI 0.33–0.45) [13]. One possible interpretation of these results is that ASA is beneficial due to its possible antithrombotic, anti-inflammatory, and immunomodulation effects in community cases of COVID-19, but no longer when patients have a severe condition requiring hospital admission. A USA study [15] evaluating 1,956 patients according to the antiplatelet therapy prior to and during admission found lower in-hospital mortality in the group with ASA during admission after applying PSM (HR = 0.52, 95% CI 0.34–0.81). A recent meta-analysis [16] reported that ASA intake (prior or initiated during hospitalization) was independently associated with lower mortality in patients with COVID-19. When analyzing the results of the study, it is important to take into account the possible favorable effects of other important cardiovascular drug classes, especially renin–angiotensin–aldosterone system inhibitors and statins [17, 18].

The main strength of the study is a large number of patients evaluated, which makes it the largest study on the subject to our knowledge. Secondly, its multicentre hospital nature spans a diverse geographic range, from an integrated longitudinal database.

This study has several limitations. First, it was a retrospective study. Second, the intake of ASA before admission was collected and confirmed but neither the dose nor the reason for its prescription was recorded. Third, as this study was focused on in-patients, it was difficult to reflect the effect of ASA in an outpatient setting. Fourth, our sample is mostly Caucasian with a low representation of other ethnic groups. Fifth, we did not record the presence of other medications that are associated with hypercoagulabilities, such as oral contraceptives and hormone replacement. Sixth, we not explore if there was

Table 6 Risk factors for in-hospital mortality in the matched-cohort

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	1.06 (1.05–1.07)	< 0.001	1.19 (1.02–1.38)	0.030
Gender (female)	0.85 (0.76–0.95)	0.005	0.73 (0.63–0.83)	< 0.001
BMI	1.02 (1.01–1.03)	0.003	NS	
Smoking behavior Never (ref.) Former smoker Current smoker	1 1.19 (1.07–1.34) 0.83 (0.64–1.08)	0.002 0.161	NS	
Degree of dependency Mild (ref.) Moderate Severe	1 2.47 (2.14–2.85) 3.03 (2.60–3.53)	< 0.001 < 0.001	1 1.54 (1.29–1.84) 2 (1.65–2.42)	< 0.001 < 0.001
Arterial hypertension	1.45 (1.26–1.67)	< 0.001	NS	
Dyslipidemia	1.04 (0.93–1.16)	0.545		
Diabetes mellitus	1.17 (1.04–1.30)	0.008	NS	
Ischaemic cardiopathy	1.36 (1.20–1.54)	< 0.001	NS	
Chronic heart failure	2.14 (1.83–2.49)	< 0.001	1.21 (1.01–1.47)	0.049
Atrial fibrillation	1.96 (1.66–2.33)	< 0.001	NS	
Cerebrovascular disease	1.41 (1.23–1.61)	< 0.001	NS	
Peripheral arterial disease	1.53 (1.30–1.81)	< 0.001	NS	
Dementia	2.26 (1.97–2.58)	< 0.001	NS	
COPD	1.46 (1.24–1.72)	< 0.001	NS	
Chronic liver disease	1.04 (0.79–1.36)	0.780		
Severe chronic renal failure	1.85 (1.58–2.17)	< 0.001	NS	
Charlson index	1.19 (1.16–1.22)	< 0.001	1.12 (1.08–1.16)	< 0.001
Respiratory rate > 20 rpm	3.65 (3.26–4.10)	< 0.001	2.49 (2.19–2.84)	< 0.001
PaO2/FiO2	0.99 (0.99–0.99)	< 0.001	0.99 (0.99–0.99)	< 0.001
Lymphocyte count × 10^6/L	0.99 (0.99–0.99)	< 0.001	0.99 (0.99–0.99)	< 0.001
CRP (mg/L)	1.01 (1.01–1,01)	< 0.001	1.01 (1.01–1.01)	< 0.001
LDH (U/L)	1.01 (1.01–1,01)	< 0.001	1.01 (1.01–1.01)	< 0.001
Ferritin (mcg/L)	1.01 (1.01–1,01)	< 0.001	1.01 (1.01–1.01)	0.001
D-dimer (ng/mL)	1.01 (1.01–1.01)	< 0.001	NS	
LMWH None (ref.) Prophylactic doses Intermediate doses Full doses	1 0.48 (0.41–0.56) 0.57 (0.46–0.72) 0.79 (0.65–0.97)	< 0.001 < 0.001 0.025	1 0.44 (0.37–0.54) 0.41 (0.31–0.53) 0.52 (0.41–0.67)	< 0.001 < 0.001 < 0.001
Steroids	1.46 (1.31–1.63)	< 0.001	1.22 (1.07–1.4)	0.003
Tocilizumab	1.29 (1.06–1.56)	0.009	1.71 (1.36–2.16)	< 0.001
ASA	1.01 (0.90–1.12)	0.938	1.05 (0.92–1.19)	0.476

BMI body mass index, *NS* not significant, *COPD* chronic obstructive pulmonary disease, *CRP* C-reactive protein, *LDH* lactate dehydrogenase, *LMWH* low-molecular-weight heparin, *ASA* acetylsalicylic acid

any difference in bleeding events Seventh, among the two groups, in-hospital mortality compared to patients who have undergone the same treatments for COVID was not evaluated. Finally, it is always concerning which variables to include in a PSM model. Including variables that are related to the exposure but not the outcome will decrease the precision of the estimated exposure effect without decreasing bias [20]. In our study, we have included a wide variety of comorbidities, some of them strongly related to ASA use but not so clearly related to the outcomes we describe. This could result in a loss of precision and, therefore, a limitation of the study.

Conclusions

To date, no consensus guidelines are available regarding ASA use in COVID-19, reflecting a paucity of data in this regard. Awaiting results from powered and randomized studies [19],

our results, from a real-world large sample of hospitalized COVID-19 patients, provides information along with the idea that ASA intake at admission is not associated with lower in-hospital mortality or any other health outcome evaluated after applying PSM analysis.

Appendix

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Our study was performed in accordance with the ethical standards of our institutional and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was waived by a central ethics committee, considering this an anonymized observational study in a pandemic situation.

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