Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Anosmia is associated with lower in-hospital mortality in COVID-19

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ABSTRACT

Background: Anosmia is common in Coronavirus disease 2019, but its impact on prognosis is unknown. We analysed whether anosmia predicts in-hospital mortality; and if patients with anosmia have a different clinical presentation, inflammatory response, or disease severity.

Methods: Retrospective cohort study including all consecutive hospitalized patients with confirmed Covid-19 from March 8th to April 11th, 2020. We determined all-cause mortality and need of intensive care unit (ICU) admission. We registered the first and worst laboratory parameters. Statistical analysis was done by multivariate logistic and linear regression.

Results: We included 576 patients, 43.3% female, and aged 67.2 years in mean. Anosmia was present in 146 (25.3%) patients. Patients with anosmia were more frequently females, younger and less disabled and had less frequently hypertension, diabetes, smoking habit, cardiac and neurological comorbidities. Anosmia was independently associated with lower mortality (OR: 0.180, 95% CI: 0.069–0.472) and ICU admission (OR: 0.438, 95% CI: 0.229–0.838, p = 0.013). In the multivariate analysis, patients with anosmia had a higher frequency of cough (OR: 1.96, 95%CI: 1.18–3.28), headache (OR: 2.58, 95% CI: 1.66–4.03), and myalgia (OR: 1.74, 95% CI: 1.12–2.71). They had higher adjusted values of hemoglobin (+0.87, 95% CI: 0.40–1.34), lymphocytes (+849.24, 95% CI: 157.45–1541.04), glomerular filtration rate (+6.42, 95% CI: 2.14–10.71), and lower D-dimer (−4886.52, 95% CI: −8655.29-(−1117.75)), and C-reactive protein (−24.92, 95% CI: −47.35-(−2.48)).

Conclusions: Hospitalized Covid-19 patients with anosmia had a lower adjusted mortality rate and less severe course of the disease. This could be related to a distinct clinical presentation and a different inflammatory response.

1. Introduction

Anosmia is one of the most characteristic symptoms of Coronavirus disease 2019 (Covid-19) [1], however the pathophysiology of the loss of smell remains unclear [2–4]. It seems to be one of the commonest symptoms, however the reported frequency varies from 5.1% to 98.3% depending on the study and the studied population [5].

Abbreviations: Coronavirus disease 2019, (Covid-19); intensive care unit, (ICU); strengthening the reporting in observational studies in epidemiology, (STROBE); real-time reverse-transcriptase-polymerase-chain-reaction, (RT-PCR); emergency department, (ED); standard of care, (SOC); chronic obstructive pulmonary disease, (COPD); chronic neurological disorders, (CND); modified Rankin scale, (mRS); Computerized Tomography, (CT); reference value, (RV); hemoglobin, (Hb); lactate dehydrogenase, (LDH); creatine-kinase, (CK); international normalized ratio, (INR); glomerular filtration rate corrected by body area, (GFR); C-reactive protein, (CRP); procalcitonin, (PCT); interleukine-6, (IL-6); standard deviation, (SD); interquartile range, (IQR); odds ratio, (OR); confidence intervals, (CI).

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2. Theory/ calculation

It is suggested that anosmia might be related to a milder course, implying a less symptomatic course and a lower probability of hospitalization [6,7]. The affected population is usually younger and more frequently female, two variables that are also associated with better prognosis of Covid-19, and which could partially justify it [1,8,9]. However, the role of anosmia on Covid-19 severity and mortality in hospitalized patients has not been elucidated yet.

Therefore, our aim was to evaluate whether the presence of anosmia influences the prognosis of Covid-19 in hospitalized patients. As secondary objectives, we analysed whether patients with anosmia had a distinct clinical presentation and/or laboratory profile, and we aimed to assess the course of the disease in these patients.

3. Material and methods

3.1. Study oversight

This is an observational study with a retrospective cohort design, conducted according to the strengthening the reporting in observational studies in epidemiology (STROBE) [10] statement. The study was approved by the institutional review board of the Valladolid Este health area (PI-20-1751). Due to the emergency situation and risk of contagion, written informed consent was not required. The study setting was Hospital Clínico Universitario de Valladolid, a public tertiary academic hospital with a reference population of 280,000 habitants. Data were collected, analysed and interpreted by all authors, who reviewed and approved the manuscript.

3.2. Eligibility criteria

We included all consecutive patients that fulfilled the following criteria: 1) had a confirmed Covid-19 disease, 2) were hospitalized, 3) had a minimum of 18 years old. They were excluded if the clinical records were not available, or in case that they were hospitalized prior to the Covid-19 outbreak for a different serious condition.

3.3. Covid-19 disease diagnosis

Only symptomatic patients with a confirmed diagnosis according to the WHO protocols [11] were included. The diagnostic tests were either real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay (LightMix Modular SARS-CoV-2, E-gene and LightMix Modular SARS-CoV-2 RdRP, Roche Diagnostics S.L.) of oropharyngeal-nasopharyngeal swab, sputum sample or lower respiratory tract sample; or serological tests with anti-SARS-CoV-2 IgM + IgA antibodies (ELISA; Vircell, S.L. Granada, Spain).

3.4. Data sources

The Covid-19 symptom checklist of the emergency department (ED) of our hospital includes anosmia as one of the typical symptoms. We defined anosmia as the partial or complete loss of the sense of smell [12]. We included both hyposmia and anosmia altogether. We collected data from the electronic medical records, including primary care, ED and hospitalization. According to the local protocol, every patient under Covid-19 suspicion was followed up daily or every other day in primary care since the first contact until the complete resolution of symptoms. In those cases, in which the presence of anosmia was not described, we contacted all the patients or relatives by phone afterwards, and enquired about it. Patients were treated according to the national Covid-19 management protocol standard of care (SOC) [13]. Recruitment was probabilistic, and all consecutive patients were included. Data was extracted according to a predefined protocol by thirteen neurologists that were involved in the treatment of Covid-19 patients. The study period encompassed from March 8th to April 11th, 2020. The follow-up of the patients included a minimum of 20 days since the hospitalization in all cases.

3.5. Variables

We analysed demographic variables, comorbidities, clinical presentation, complementary exams, treatment (including the use of angiotensin converting enzyme inhibitors), complications and severity of Covid-19. Demographic variables included age, sex, date of general symptoms onset, and date of anosmia onset. The analysed comorbidities were hypertension, diabetes, current or recent smoking habit, if it was stopped in the preceding 6 months, coronary artery disease, congenital heart diseases, cardiomyopathies, arrythmias, valvular heart disease, aortic aneurysms, peripheral artery disease, chronic obstructive pulmonary disease (COPD), asthma, occupational lung diseases, interstitial lung diseases, pulmonary hypertension, cancer (excluding cutaneous epidermoid and basal cell carcinoma), congenital or acquired immunosuppression and the presence of chronic neurological disorders (CND). Finally, the degree of disability/dependence prior to admission was determined by using the modified Rankin scale (mRS) [14].

Clinical presentation included whether there was a suspected source of contagion or not, the time between the first symptom and the emergency department (ED) visit, and the presence of symptoms as fever, cough, expectoration, dyspnea, asthenia, chest pain, headache, myalgia, cutaneous rash, nausea, odynophagia, rhinorrhea, arthralgia, diarrhea, or vomiting.

Complementary tests variables included the modality of Covid-19 diagnosis, either by RT-PCR or serological tests, and the results of chest imaging (X-ray or Computerized Tomography (CT)). We analysed the results of laboratory work-up, including parameters upon admission and the worst values during the entire hospitalization, including platelets (reference value (RV): 150–400 count $\times$ 10^9 /L), hemoglobin ((Hb), RV: 12–16 g/dL), leukocytes (RV:4–10 cell count x 10^9 /L), lymphocytes (RV: 0.9–5.2 count $\times$ 10^9/L), lactate dehydrogenase ((LDH) RV: 135–250, U/L,), creatine-kinase ((CK) RV: 20–170 U/L), international normalized ratio ((INR) RV: 0.8–1.3), D-dimer (RV: < 500 ng/dL), glomerular filtration rate corrected by body area ((GFR) RV > 90 mL/min/1.73m^2), C-reactive protein ((CRP) RV: 1–5 mg/L), procalcitonin ((PCT) RV: < 5 ng/mL), interleukine-6 ((IL-6) RV < 5.9 pg/mL), ferritin (RV: 15–150 ng/mL). IL-6 and ferritin were not tested on admission.

Treatment variables included the need of oxygen therapy, and the administration of any drugs according to the local standard of care (SOC), including hydroxychloroquine 400 mg bid for 5 days, lopinavir/ritonavir 400/100 mg bid, remdesivir 200 mg first day followed by 9 days with 100 mg, a single dose of 400 mg of tocilizumab, methylprednisolone 250 mg three consecutive days or interferon beta-1b [13]. We assessed the presence of complications, including the confirmed use of mechanical ventilation, invasive ventilation, Intensive Care Unit (ICU) admission, and mortality. We analysed the all-cause in-hospital mortality rate.

3.6. Study outcomes

The primary endpoint was to compare in-hospital mortality of Covid-19 patients with anosmia, calculated by multivariate regression, adjusted by all the variables that might influence the prognosis, including age, sex, baseline performance, presence of vascular risk factors, and comorbidities, with those withoug anosmia.

As secondary endpoints, we studied the relationship between presence of anosmia and the need for ICU admission, and analysed whether anosmia was associated with distinct clinical and laboratory profiles in hospitalized COVID-19 patients.

3.7. Statistical analysis

Continuous variables are described using the mean and standard deviation (SD), or median and interquartile range (IQR). Discrete variables are expressed as number of cases and percentage. Comparison between variables was performed using the two-sided chi-square tests for discrete variables, or Fisher's exact tests for the contrast of hypothesis with categorical variables, adjusting p-value by Bonferroni method for multiple comparisons. We used Student *t*-test for hypothesis testing of quantitative variables with a normal distribution. Statistical significance was defined as a P value < 0.05. For the primary endpoint and the secondary endpoints of severity of the disease, we conducted firstly a univariate regression analysis. To adjust for the possible confounders and effect modifiers, those variables that showed a p-value ≤ 0.2 were included in a multivariate regression analysis. To compare if the frequency of clinical symptoms and laboratory results were associated with anosmia, we did a multivariate analysis and adjusted all the variables that had a p-value ≤ 0.2 when comparing the frequency between patients with and without anosmia. Discrete variables were analysed by a subsequent multivariable regression analysis and continuous variables by using multivariate linear regression. We present the odds ratio (OR) and 95% confidence intervals (CI). We assessed multicollinearity by using Variance Inflation Factor, considering critical multicollinearity if the value was > 5. We did not estimate sample size in advance. Missing data was managed by complete case analysis. Statistical analyses were carried out using SPSS v.26 (IBM Corp. Armonk, NY).

4. Results

During the study period, 580 consecutive patients were admitted to our hospital with a positive test for SARS-CoV-2, being excluded four of them (three patients were diagnosed while asymptomatic and were previously hospitalized by another mayor cause and one did not have an accessible admission record). The sample included, thus, 576 patients, 250 (43.3%) female, with a mean age of 67.2 (SD ± 14.7) years, ranging from 23 to 98 years. Anosmia was present in 146 (25.3%) cases. Patients with anosmia were more frequently female, younger, less disabled at baseline, and had hypertension, diabetes, smoking habit, cardiac disease, and CND less frequently. Table 1 shows demographic variables, vascular risk factors frequency, and comorbidities in the whole sample and in both groups, depending on the presence of anosmia.

All patients were able to answer the question about their olfactory capacity, because there was no patient that had to be intubated directly on admission with no later record on that question.

Table 1
Demographic variables, vascular risk factors frequency and comorbidities.

	All patients (n = 576)	Anosmia (n = 146)	No-anosmia (n = 430)	Adjusted p-value
Mean age	67.18 (14.75)	61.31 (13.13)	69.18 (14.75)	< 0.001†
Female sex	250 (43.4%)	75 (51.4%)	175 (40.7%)	0.031‡
Mean mRS	0.61 (1.12)	0.2 (0.535)	0.74 (1.225)	< 0.001†
Hypertension	300 (52.1%)	54 (37%)	246 (57.2%)	< 0.001‡
Diabetes	113 (19.6%)	25 (17.1%)	88 (20.5%)	0.448‡
Smoking habit	118 (20.5%)	20 (13.7%)	98 (22.8%)	0.026‡
Cardiac disease	154 (26.7%)	23 (15.8%)	131 (30.5%)	0.001‡
Respiratory disease	145 (25.2%)	29 (19.9%)	116 (27%)	0.109‡
Cancer	94 (16.3%)	23 (15.8%)	71 (16.5%)	0.933‡
Immunosuppression	15 (2.6%)	1 (0.7%)	14 (3.3%)	0.166
Chronic neurological disorders	105 (18.2%)	11 (7.5%)	94 (21.9%)	< 0.001‡

mRS: Modified Rankin Scale.
† Student *t*-Test.
‡ Two-sided Fisher's Exact test.

4.1. Latency between symptom onset and ED presentation

The mean time between symptom onset and ED visit was 7.34 (SD ± 6.16) days), being more prolonged in patients with anosmia, 8.64 (SD ± 5.46) days vs. 6.9 (SD ± 6.33) days ($p = 0.003$). Anosmia was present since the first day of symptoms in 89 (60.9%) cases, since the second day in 105 (71.9%) and within the first five days in 123 (84.2%) cases.

4.2. Clinical diagnosis and management of patients

Diagnosis was confirmed by RT-PCR in 546 (94.8%) of cases and/or serology in 175 (30.4%). Chest imaging was abnormal in 549 (95.3%) patients. The use of hydroxychloroquine (patients with anosmia 94.5% vs. patients without anosmia 89.8%), lopinavir/ ritonavir (93.2% vs. 89.8%), remdesevir (0.7% vs. 2.3%), methylprednisolone (48.6% vs. 53.5%), tocilizumab (4.8% vs. 6.5%) or interferon beta (37.7% vs. 39.1%) was similar between both groups. Need of oxygen therapy (63% vs. 71.6%) and ventilatory support (13% vs. 19%) were similar as well ($p > 0.05$ all). However, frequency of ICU admission (8.9% vs 16.5%, $p = 0.034$), and need of invasive ventilation (8.9% vs. 16%, $p = 0.046$) were less frequent in the group with anosmia. The detailed list of administered therapies within groups is available in Supplementary table 1.

4.3. Course of the disease

The severity of the Covid-19 disease corresponded to mild disease in 32 (5.6%) patients, pneumonia in 142 (24.7%), severe pneumonia in 269 (46.7%), and ADRS in 124 (21.5%). Nine patients (0.8%) had a septic shock, two patients (0.3%) had pulmonary embolism without pneumonia, one patient (0.1%) had a lithium intoxication, and one case (0.1%) had fatal gastrointestinal bleed. The total number of deceased patients was 127 (22.0%). Mortality rate of patients with anosmia was 5/146 (3.4%), compared with 122/430 (28.4%) in the rest of the sample ($p < 0.001$). Supplementary table 1 depicts the course of the disease in both groups and the whole sample.

4.4. Primary endpoint: predictors of mortality

In the univariate regression analysis, time from clinical onset to ED, baseline disability, age, sex, hypertension, diabetes, smoking habit, cardiological disorders, pulmonary disorders, cancer, and chronic neurological disorders were associated with higher odds of mortality, whereas anosmia was associated with a lower odds of death. In the multivariate regression analysis, baseline disability, age, and anosmia (OR: 0.180, 95% CI: 0.069–0.472) remained statistically significant. Table 2 presents the results of the univariate and multivariate regression analysis.

4.5. Predictors of severe Covid-19 disease

Patients with anosmia had less odds (OR: 0.438, 95% CI: 0.229–0.838, $p = 0.013$) for being admitted to the ICU. The multivariate regression analysis was adjusted to time from clinical onset to ED, baseline disability, age, sex, diabetes, and smoking habit. The complete univariate and multivariate regression analysis for ICU admission is available on supplementary table 2.

4.6. Clinical presentation

The Fig. 1 presents the differences in the frequency of symptoms between patients with anosmia and without it. The most frequent symptoms on presentation were fever, in 462 (80.2% patients) and

Table 2
Predictors of mortality: univariate and multivariate regression analysis.

Variables	Type of analysis	OR	95% CI	p-value
Anosmia	Univariate	0.090	0.036–0.224	< 0.001
	Multivariate	0.180	0.069–0.472	< 0.001
Time from clinical onset to ED	Univariate	0.908	0.870–0.947	< 0.001
	Multivariate	0.968	0.931–1.006	0.093
Age	Univariate	1.090	1.069–1.112	< 0.001
	Multivariate	1.056	1.032–1.081	< 0.001
Prior mRS ≥ 3	Univariate	11.371	6.376–20.278	< 0.001
	Multivariate	3.595	1.794–7.204	< 0.001
Female sex	Univariate	0.682	0.454–1.024	0.065
	Multivariate	0.670	0.391–1.148	0.145
Hypertension	Univariate	3.534	2.272–5.495	< 0.001
	Multivariate	1.312	0.757–2.275	0.333
Diabetes	Univariate	2.129	1.353–3.351	0.001
	Multivariate	1.333	0.759–2.343	0.317
Smoking	Univariate	1.589	1.004–2.514	0.048
	Multivariate	1.706	0.933–3.121	0.083
Cardiological disorders	Univariate	2.955	1.950–4.478	< 0.001
	Multivariate	1.201	0.716–2.016	0.487
Pulmonary disorders	Univariate	1.434	0.928–2.217	0.105
	Multivariate	0.830	0.477–1.446	0.511
Cancer	Univariate	1.641	1.001–2.690	0.049
	Multivariate	1.397	0.764–2.557	0.278
Immunosuppression	Univariate	1.295	0.405–4.138	0.663
Chronic neurological disorders	Univariate	3.961	2.516–6.234	< 0.001
	Multivariate	1.535	0.868–2.715	0.140

mRS: Modified Rankin Scale. OR: Odds Ratio. CI: Confidence Interval. ED: Emergency Department.

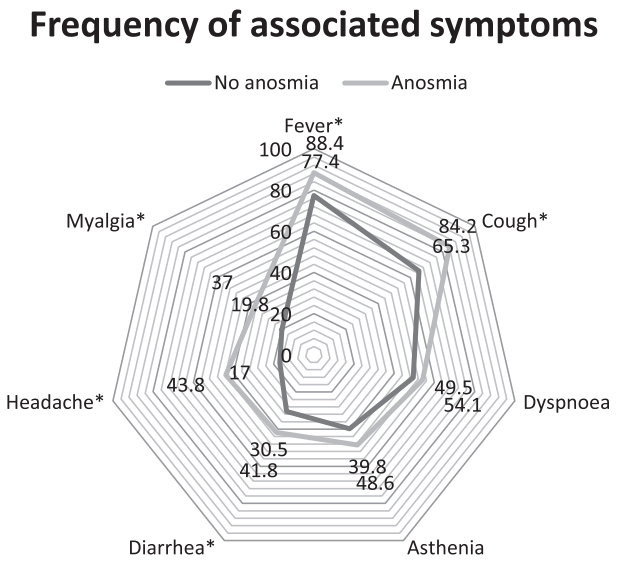

Fig. 1. Frequency of the different type of symptoms presented in patients with anosmia (grey line) and without it (black line). *Means adjusted p-value < 0.05.

cough, in 403 (69.9%), overall. Patients with anosmia presented with a higher frequency of arthralgia (patients with anosmia 10.3% vs. patients without anosmia 4.7%, p = 0.024), fever (88.4% vs. 77.4%, p = 0.006), cough (84.2% vs. 65.3%, p < 0.001), diarrhea (41.8% vs. 30.5%, p = 0.016), myalgia (37% vs. 19.8%, p < 0.001), and headache (43.8% vs. 17%, p < 0.001), than those without anosmia. Supplementary table 3 shows frequency and type of general presenting symptoms, in the whole sample, and the two groups. After adjusting for all the variables that were different between the two groups at the baseline; including time from the clinical onset to the arrival to the ED, baseline mRS, age, sex, chronic neurological disorders, hypertension, and smoking habit; patients with anosmia had 1.967 times (95% CI: 1.177–3.288) more odds for having cough, 2.587 times (95% CI: 1.660–4.033) more odds for headache, and 1.748 times (95% CI: 1.126–2.713) more odds for having myalgia than those without anosmia. The full multivariate regression analysis is available on Table 3.

Table 3
Multivariate regression analysis of symptoms that were independently associated with the presence of anosmia.

Symptom	OR	95% CI	p-value
Fever	1.778	0.997–3.169	0.051
Cough	2.183	1.316–3.620	0.002
Dyspnea	1.269	0.857–1.878	0.234
Asthenia	1.27	0.857–1.882	0.234
Diarrhea	1.378	0.92–2.063	0.120
Headache	2.731	1.762–4.234	< 0.001
Myalgia	1.813	1.182–2.782	0.006
Chest pain	1.068	0.649–1.756	0.796
Weakness	1.123	0.659–1912	0.669
Expectoration	0.798	0.459–1.388	0.424
Odynophagia	0.798	0.425–1.5	0.484
Dizziness	0.802	0.417–1.542	0.509
Vomiting	0.960	0.473–1.949	0.910
Arthralgia	1.699	0.829–3.484	0.148
Rhinorrhea	1.621	0.492–5.343	0.427
Rash	1.941	0.551–6.838	0.302

OR: Odds Ratio. CI: Confidence Interval. Adjusted for all the variables with a p-value ≤ 0.2 in the comparison between patients with anosmia and without anosmia: time from the clinical onset to the arrival to the ED, mRS, age, sex, hypertension, smoking habit and chronic neurological disorders.

4.7. Laboratory findings

Laboratory parameters on admission were less abnormal in patients with anosmia in the case of leukocytes (6305 in patients with anosmia vs. 6805 in patients without anosmia count x 10^9/L, p = 0.006), hemoglobin (13.9 vs. 13.3 count × 10^9/L, p = 0.001), LDH (272 vs. 292 U/L, p = 0.014), GFR (85 vs. 76 mL/min/1.73 m3, p < 0.001), INR (1.1 vs. 1.2, p = 0.011), D-dimer (628 vs. 864 ng/dL, p < 0.001), CRP (53 vs. 73 mg/L, p = 0.018), PCT (0.08 vs. 0.12 ng/mL, p < 0.001). Laboratory parameters during hospitalization were less abnormal in patients with anosmia in the case of leukocytes (6650 in patients with anosmia vs. 9820 in patients without anosmia count x 10^9/L, p = 0.004), lymphocytes (795 vs. 650 count × 10^9/L, p = 0.001), hemoglobin (12.6 vs. 11.7 count × 10^9/L, p < 0.001), LDH (305 vs. 357 U/L, p < 0.001), GFR (82 vs. 65 mL/min/1.73m^3, p < 0.001), INR (1.2 vs. 1.3, p = 0.001), D-dimer (881 vs. 1489 ng/dL, p < 0.001), CK (79 vs. 98 U/L, p < 0.001), CRP (78 vs. 109 mg/L, p < 0.001), PCT (0.09 vs. 0.15 ng/mL, p < 0.001), and IL-6 (19.8 vs. 32.3 pg/mL, p = 0.002). The full list of median worst laboratory values on admission and during hospitalization in the whole sample and the comparison between groups is available in supplementary table 4 and 5, respectively. The frequency in which those variables were out of normal range was higher in patients without anosmia for all those variables but leukocytes, CRP, IL-6, and ferritin. The frequency of out of range parameters in the whole sample and groups is described in supplementary table 6.

After adjusting for all the variables that were different between the two groups at the baseline; including time from clinical onset to ED, baseline performance, age, sex, hypertension, smoking habit, and CND; patients with anosmia had a higher adjusted value of lymphocytes, hemoglobin, and lower D-dimer upon admission. During hospitalization, patients with anosmia had a higher adjusted value of lymphocytes, hemoglobin, glomerular filtration rate and lower D-dimer, and C-reactive protein. Table 4 shows the full results of the lineal regression analysis for the laboratory parameters.

Table 4
Multivariate linear regression analysis of laboratory parameters that were independently associated with the presence of anosmia.

	Adjusted difference in patients with anosmia with respect to non-anosmic patients	95% CI		Adjusted p-value
Leukocyte count on admission (RV 4–10 × 10^9/L)	1145.749	−784.133	3075.632	0.244
Leukocyte count during hospitalization (RV 4–10 × 10^9/L)	1162.990	−2668.012	4993.993	0.551
Lymphocytes on admission (RV > 900 lymphocytes × 10^9/L)	17,748.039	−219.396	35,276.682	0.047
Lymphocytes during hospitalization (RV > 900 lymphocytes × 10^9/L)	849.248	157.455	1541.041	0.016
Hemoglobin on admission (RV > 12^9 g / dL)	0.412	0.051	0.774	0.025
Hemoglobin during hospitalization (RV > 12^9 g / dL)	0.871	0.401	1.340	< 0.001
Platelet count on admission (RV 150–400 count / 10^9 / L)	−5102.749	−22,362.356	12,156.859	0.562
Platelet count during hospitalization (RV 150–400 count / 10^9 / L)	−6945.451	−345,346.715	21,455.813	0.631
LDH on admission (RV > 250 Units / L)	−24.082	−50.760	2.595	0.077
LDH during hospitalization (RV > 250 Units / L)	−301.658	−717.804	114.489	0.155
GFR on admission (RV < 90 mL/min/1.73m^3)	2.547	−1.085	6.179	0.169
GFR during hospitalization (RV < 90 mL/min/1.73m^3)	6.428	2.141	10.714	0.003
INR on admission (RV > 1.3)	−0.067	−0.380	0.246	0.676
INR during hospitalization (RV > 1.3)	−0.151	−0.487	0.185	0.377
D-dimer on admission (RV > 500 ng/dL)	−1493.725	−2821.546	−165.903	0.028
D-dimer during hospitalization (RV > 500 ng/dL)	−4886.528	−8655.296	−1117.759	0.011
CPK on admission (RV > 170 U/L)	−82.758	−231.196	65.681	0.273
CPK during hospitalization (RV > 170 U/L)	−1260.817	−5267.061	2745.427	0.537
CRP on admission (RV > 5 mg/L)	−8.730	−26.978	9.518	0.348
CRP during hospitalization (RV > 5 mg/L)	−24.920	−47.353	−2.486	0.030
Procalcitonin on admission (RV > 0.5 ng/mL)	−0.178	−0.894	0.537	0.625
Procalcitonin during hospitalization (RV > 0.5 ng/mL)	−0.689	−2.381	1.003	0.424
Interleukine-6 (RV > 5.9 pg/mL)	−64.156	−174.035	45.724	0.252
Ferritin (RV > 150 ng/mL)	−107.725	−657.332	441.882	0.700

Beta coefficient of linear regression. CI: Confidence Interval. LDH: Lactate dehydrogenase. GFR: Glomerular Filtration Rate. INR: international normalized ratio. Adjusted for all the variables with a p-value ≤ 0.2 in the comparison between patients with anosmia and without anosmia: time from the clinical onset to the arrival to the ED, mRS, age, sex, hypertension, smoking habit and chronic neurological disorders.

5. Discussion

Anosmia has been described as one of the characteristic symptoms of Covid-19 disease. It is even considered as a key marker for Covid-19 diagnosis for the United States Center for Disease Control and Prevention [15]. Despite of having an estimated frequency of up to 52.7% [5], and being a clinical marker of Covid-19, little has been studied about its relationship with Covid-19 prognosis [8]. Some studies have related anosmia to a milder course of Covid-19, describing a relationship between anosmia and an inverse probability of being admitted to hospital [6]. Contrary, other studies have shown no relationship between the presence of olfactory alteration and severity of COVID-19. In fact, some of them even suggest that the persistence of severe chemosensitive dysfunction could be related to the need of hospitalization after 20 days. However, these studies did not take into account other well-known risk factors from their study population that might cofound the outcomes and one only showed a significant result after 20 days of clinical onset. These 20 days are considered by many to be the limit from when the disease starts to have a lower risk of complications [16–18]. Therefore, we present a study that evaluates whether hospitalized patients with anosmia have a better prognosis, in terms of mortality, and severity of the disease.

The prevalence of anosmia in our inpatient study is 25.3%, lower than the 52.7% prevalence reported in a recent meta-analysis [5]. If anosmia is associated with a less severe course of the disease, then the prevalence of anosmia in hospitalized patients might be lower. Other studies done in-hospital population report a 34% frequency, similar to the rate observed in our study [19].

The symptom of anosmia itself usually appears at the beginning of the infection [1,9,20,21] with a mean of 4.4 days after the clinical onset and a mean duration of approximately nine days described in a French study [8]. Anosmia was present since the first day in 60.9% of the patients from our study. In some cases, it has been presented as the only symptom of the disease [20,21]. This fact is relevant for public health reasons, as patients with anosmia might be unaware of the disease and contribute to the dissemination of the infection [22,23].

As in other series, in our study, patients with anosmia were younger, with a higher percentage of women, less disability at baseline, and with fewer comorbidities [1–5,7,24]. These characteristics have been associated with a better prognosis independently in Covid-19 [7,25–32]. Therefore, we adjusted the analysis to the known covariates related to Covid-19 mortality, and we still observed a lower probability of in-hospital death in patients with anosmia. However, although the main causes of this association remain unknown, this finding could be related to a different clinical presentation and/or a milder immune or inflammatory response.

In our study, the presence of anosmia was independently associated with a higher odds of having cough, myalgia and headache. The clinical presence of headache has also shown to be associated to a better prognosis in some studies. These clinical features appear at early stages of the disease and are typical symptoms in other viral infections. Despite the physiopathology of these symptoms remains unknown, the higher frequency of systemic symptoms might be linked with an increased systemic response or viral replication and consequently, a sign of an efficient innate immunity response and better prognosis [2,31]. It is important to highlight that rhinorrhea, which is one of the typical causes that could alter the smell, was not significantly associated with anosmia in our study as, in other studies [1]. It has been described its association with rhinorrhea and dysgeusia in 85% of the times [8,31], myalgia [17] and headache [31], though some experts argue that dysgeusia may be caused by a lack of smell rather than affecting taste [24].

We also assessed if the inflammatory response of patients with anosmia was different to the rest of the sample. In the crude comparison, many variables showed statistical signification. However, both populations were not comparable in terms of age, sex distribution, disability at baseline, or time since the onset of symptoms to the ED presentation. For that reason, we conducted a multivariate regression analysis including all those possible confounders and effect modifiers. In our sample, patients with anosmia had higher adjusted levels of lymphocytes, hemoglobin and lower levels of D-dimer on admission; and in the worst observed laboratory results during the whole hospitalization,

they had higher levels of lymphocytes, hemoglobin and GFR, and lower of D-dimer and CRP. The alteration from most of these parameters has been associated with a worse prognosis and as an indirect measure of systemic inflammatory response [8,25–30, 33,34]. In fact, some authors recommend monitoring these parameters in the management of Covid-19 patients [34]. Consequently, patients with anosmia seem more likely to have a better analytical profile, suggesting that the inflammatory or immune response might be different and probably more benign.

Similarly, patients with anosmia were less likely to be admitted to ICU, even though there was no significant difference in the received treatment between the two groups in our study [35]. This finding is in line with other authors results, that described a milder disease course in patients with anosmia [8,34,36]. We encourage other authors to analyze if the clinical presentation of Covid-19 out-patients with anosmia also differs from those without it.

This study has several limitations. Firstly, it is a study conducted in an inpatient population. Likewise, the sample was drawn from a single center in which, the protocols and management may differ from the rest. Consequently, it would be interesting to include other hospitals from different areas for further studies. Secondly, this is a retrospective study in which all the data have been carefully collected and analysed, although some might be incomplete. Thirdly, despite the acute and spontaneous onset of anosmia within the context of the diagnosis of Covid-19, neuroimaging studies were not performed in all the patients with anosmia. Thus, other causes, although infrequent, produced by anosmia could not be excluded, nor could their possible relationship be explained [37]. Fourthly, we did not evaluate the severity of anosmia, nor its duration or characteristics that could play a role in the end-points. Fifth, it might exist some degree of reporting bias and the most severe patients may not be able to describe symptoms by themselves; however we collected information regarding the period since the onset of the symptoms to the ED visit from the primary care electronic records.

6. Conclusion

In our study, the presence of anosmia was an independent predictor of good outcome as reflected by a lower in-hospital mortality rate and less frequent ICU admission. This could be related to a different clinical presentation that may be associated with a more benign immune and inflammatory response to SARS-COV-2.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2020.117163.

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