Research Submission

Frequency and Type of Red Flags in Patients With Covid-19 and Headache: A Series of 104 Hospitalized Patients

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Objective.—In this study, we aimed to evaluate the frequency of the main red flags in patients with headache who do have Covid-19.

Background.—Headache is one of the most frequent neurologic symptoms of Coronavirus disease 2019 (Covid-19). Diagnosis of secondary headache disorders is still based on the presence of red flags.

Design and Methods.—Cross-sectional study of hospitalized patients with confirmed Covid-19 disease. We interrogated every patient about the presence of headache and if so, a headache expert conducted a structured interview assessing the presence and type of the main red flags. We evaluated the presence of laboratory abnormalities on admission.

Results.—We screened 576 consecutive patients, 130/576 (22.6%) described headache, and 104 were included in the study. Mean age of patients was 56.7 (standard deviation: 11.2) and 66/104 (63.4%) were female. Red flags concerning prior medical history were present in 79/104 (76.0%) cases, and those related to the headache itself were observed in 99/104 (95.2%) patients. All patients 104/104 (100%) described systemic symptoms and 86/104 (82.7%) some neurologic symptoms. Laboratory results were abnormal in 98/104 (94.2%) cases. The most frequent red flags were fever, in 93/104 (89.4%) patients, cough, in 89/104 (85.6% cases), and increased C-reactive protein in 84/100 (84.0%) cases.

Conclusion.—In patients with Covid-19 that described the headache red flags were present in most cases. There was not any universal red flag, being necessary the comprehensive evaluation of all of them.

Key words: Covid-19, neurology, headache, coronavirus, diagnosis

Abbreviations: ACEi angiotensin-converting enzyme inhibitors, ADRS acute distress respiratory syndrome, AT-II angiotensin-II receptor blockers, Covid-19 Coronavirus disease, CI confidence interval, CRP C-reactive protein, INR international normalized ratio, IQR inter-quartile range, LDH lactate dehydrogenase, mRS modified Rankin Scale, PCT procalcitonin, RT-PCR real-time reverse-transcriptase-polymerase-chain-reaction, RV reference value, SD standard deviation

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INTRODUCTION

The pandemic caused by the Coronavirus disease 2019 (Covid-19) has changed our lives and the way in which we treat our patients.[1] Now, that the situation gradually improves,[2] we will have to assure both the quality in the assistance and the protection of healthcare workers.[3-5] One of the presenting symptoms of Covid-19 is headache, described in around 13% of hospitalized patients.[6-9] Thus, it seems pertinent to question how the Covid-19 presence can be suspected in patients that complain of headache.

Covid-19 diagnosis is based on the microbiological confirmation.[10,11] The main problems associated with this are the need of laboratory facilities, the delay in the confirmation of the results, the possible false negative result in the first days of the disease, and the risk of false positives, particularly high in the case of rapid tests.[11,12] In the clinical setting, diagnosis of secondary headache disorders is still based on the presence of red flags.[13-15] The above-mentioned are elements of the prior medical history, anamnesis, or examination that associate with a secondary headache disorder with a higher frequency than the expected by chance. Some of the red flags refer to systemic symptoms, older age, or new onset of the headache,[15] which might be frequent in Covid-19 patients.[7,8]

Now that the situation caused by Covid-19 gradually improves and the discontinuation of the lockdown permits to resume the consultation activity, clinicians might be exposed to headache patients infected by Covid-19. We hypothesized that the red flags or the laboratory abnormalities might be ubiquitous in patients with headache and Covid-19 disease. In this study, we aimed to evaluate the frequency and type of red flags in patients with headache who do have Covid-19. We also analyzed the frequency and type of general and frequency of abnormal laboratory parameters in Covid-19 in patients with headache.

METHODS

This is an observational descriptive study with a cross-sectional design. The study was done according

to the STROBE guidelines.[16] The study population was patients with headache and confirmed Covid-19 disease. The study setting was the Hospital Clinico, tertiary university public hospital from Valladolid, Spain. The study was approved by the Ethics Review Board (ERB) of Valladolid East health area (code: PI 20-1738). Written or oral informed consent was obtained from each participant, after explaining the aim the study, the approval by the ERB, the duration of the study, and the implications of the participation. Only participants that explicitly agreed to participate were included. This was the primary analysis of the data regarding hospitalized Covid-19 patients with headache. All the hospitalized patients were studied but the information about the whole series is not published yet. This is the first analysis of these data.

Eligibility Criteria.—We included patients that: 1) had a confirmed Covid-19 disease; 2) were hospitalized; and 3) described headache during the course of the disease. We excluded patients if they were deceased at the time of the evaluation, they had a poor medical condition that did not allow to enquiry about the headache, had psychiatric or cognitive impairment that difficulted the evaluation, or if they did not agree to participate. We screened all consecutive cases since March 8th to April 11th, 2020.

We did not restrict the headache to those that fulfilled the International Classification of Headache Disorders, third version, criteria for specific secondary headaches,[13] and every patient that described headache during the course of the disease was included. Diagnosis of Covid-19 was done with real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay (LightMIx Modular SARS-CoV (COVID19) E-gene and LightMIx Modular SARS-CoV (COVID19) RdRP, Roche Diagnostics S.L.) from oropharyngeal-nasopharyngeal swab, sputum, or lower respiratory tract sample; or by the presence of anti-SARS-CoV-2 IgM + IgA antibodies (COVID-19 ELISA IgM + IgA; Vircell, S.L. Granada, Spain) in serological test in patients with clinical symptoms.[11,12]

Exposure.—We screened the electronic records of the patients that had a positive result of Covid-19 and were hospitalized. In those in which the presence of headache was not described, we contacted by phone and

enquired about it. We invited all the patients with headache to participate in the study. In those who agreed, a neurologist with expertise on headache medicine and involved in the management of Covid-19 patients conducted a predefined structured interview, either by phone or by physical consult. All the interviews took place within 45 days since the admission. We collected additional data from primary care medical records, emergency department charts, and hospitalization reports.

Variables.—We assessed demographic variables, including age, sex, prior history of hypertension, diabetes, smoking habit (current or in the preceding 6 months), cardiovascular diseases, chronic pulmonary diseases, cancer (except for cutaneous epidermoid and basal cell carcinoma), and immunocompromised conditions. We analyzed the prior history of headache and family history of headache. Baseline performance was described using the modified Rankin Scale (mRS).[17] We assessed the use of Angiotensin-converting-enzyme inhibitors (ACEi), angiotensin-II receptor blockers (AT-II), and systemic steroids.

We counted the percentage of patients that were diagnosed by RT-PCR and by serology.[10,11] We describe the percentage of patients that had an abnormal result in chest imaging, either X-ray or computerized tomography scan. We graded the severity of the disease according to the American Thoracic Society guidelines for community-acquired pneumonia in mild disease, pneumonia, severe pneumonia, and acute distress respiratory syndrome (ADRS)[18] (Supporting Information). Patients were treated according to the national guidelines for Covid-19 management.[12]

Red flags concerning prior medical history included onset of the headache after 50 years, current or prior history of cancer, or presence of immune compromised states. Red flags regarding the headache included thunderclap onset (defined as abrupt onset of severe headache that reaches the maximum intensity within 1 minute and lasts for at least 5 minutes), recent onset of the headache (defined by coincidental with Covid-19 symptoms onset or within the preceding 2 weeks of the diagnosis), change in the pattern in patients with preexistent headache (defined by the patient as a similarity equal or lower to 30% in a 0-100% scale, compared with the preceding headache),

treatment resistance (defined as the complete lack of response to acute medications), precipitation of the headache by sneezing, coughing or exercise; progressive worsening of the headache, ocular pain (defined as pain localized in the eye-ball), presence of cranial autonomic features (including lacrimation, nasal congestion, conjunctival injection, rhinorrhea, eyelid edema, ear fullness or ptosis), positional pattern (defined as worsening or improvement after sitting upright, after standing or after lying horizontally), interruption of the sleep (if the patient declares to be woken up by the headache and not solely with the headache), worst headache ever experienced, and strict unilaterality. We describe how many days after the first Covid-19 symptom did the headache start, and if it was already present at the moment of the ED visit.

We also analyzed the general and neurologic symptoms. Red flags concerning general symptoms included arthralgias, asthenia, chest pain, cough, cutaneous rash, diarrhea, dyspnea, emesis, expectoration, fever, generalized weakness, light-headedness, odynophagia, and rhinorrhea. With regards to neurologic symptoms, we assessed the presence of anosmia, myalgia, loss of consciousness, visual disturbances, speech disorders, focal or generalized weakness, hypoesthesia, vertigo, ataxia, altered mental status, and seizures.

We analyzed the frequency of typical Covid-19 laboratory abnormalities[19] on the first laboratory determination, including abnormal leukocyte count (reference value [RV]: 4-10 cell count $\times$ 10^9/L), lymphopenia (RV > 900 cells $\times$ 10^9/L), increased lactate dehydrogenase (LDH) (RV > 250 U/L), increased international normalized ratio (INR) (RV < 1.3), increased D-dimer (RV < 500 ng/dL), increased C-reactive protein (CRP) (RV < 5 mg/L), and increased procalcitonin (PCT) (RV < 5 ng/mL).

Statistical Analysis.—We present data nominal variables regarding sex, frequency of comorbidities, prior headache history, prior treatment, red flags, frequency of abnormal laboratory parameters, and frequency of general symptoms as frequency and percentage. We describe ordinal variables as Rankin as median and standard deviation (SD) and severity of Covid-19 disease as frequency and percentage per group. Continuous variables as age were presented mean and SD or median and inter-quartile range (IQR) if the distribution

was not normal, determined by Q-Q plots. We did not calculate the sample size in advance and the analysis proceeded on the available data. We describe the proportion of patients with headache and Covid-19 that presented each red flag or laboratory abnormality. We compared demographic variables in patients in which headache was the first symptom and the rest of the sample using Fisher's exact test and independent Student's *t*-test. In all comparisons, tests were 2-tailed and statistical significance was accepted if the *P* value was <.05. We analyzed the number of days after the first Covid-19 symptom in which headache started by the Kaplan-Meier 1-minus survival curve. The analysis of the data of this study was preplanned. We used SPSS v.26 (IBM Corp. Armonk, NY) for the statistical analysis. We managed the missing data by complete case analysis.

RESULTS

During the study period, 576 patients had a positive Covid-19 test. Headache was described by 130 (22.6%) of them. We excluded 8 patients because we were not able to reach them, 8 patients because of decease, 5 because of poor medical condition, 3 because of cognitive impairment, and 2 patients rejected to participate. The final sample included 104 patients, 66/104 (63.5%) female, with a mean age of 56.7 (SD: 11.2; minimum 25, maximum 83).

The number of patients with each comorbidities was 36/104 (34.6%) for hypertension, 12/104 (11.5%) for diabetes, 12/104 (11.5%) for smoking habit, 9/104 (8.7%) for cardiovascular disorders, 24/104 (23.1%) for pulmonary disorders, 13/104 (12.5%) for cancer, and 5/104 (4.8%) for immune compromised states. Prior history of headache disorders was described by 60/104 (57.7%) patients, being migraine in 17/104 (16.3%) of cases and tension-type headache in 30/104 (28.8%). In the rest of the cases, diagnosis was not specified. Family history of headache was described by 39/104 (37.5%) patients. Patients were under chronic treatment with ACEi or AT-II in 30/104 (28.8%) cases, and steroids in 5/104 (4.8%) patients. The mean score mRS was 0.1 (SD: 0.4).

Mean time between the onset of symptoms and the ED presentation was 8.8 (SD: 6.4) days. Headache was the first Covid-19 symptom in 27/104 (26.0%) patients. We did not find differences in demographic

variables in patients in whom headache was the first Covid-19 symptom (Table 1). In 91/104 (87.5%) patients, the headache was present at the moment of emergency department visit. Figure 1 shows the Kaplan-Meier 1-minus survival curve showing the onset of the headache over the course of Covid-19. Chest imaging was abnormal in 99/104 (95.2%) cases. Diagnosis was based on oropharyngeal RT-PCR in 100/104 (96.1%) cases, sputum RT-PCR in 1/104 (0.96%) case, and serology in 34/104 (32.7%). The severity of the disease corresponded to a mild disease in 5/104 (4.8%) cases, pneumonia in 46/104 (44.2%) cases, severe pneumonia in 45/104 (43.3%), and ADRS in 8/104 (7.7%). Oxygen therapy was needed in 52/104 (50.0%) patients, noninvasive ventilation in 3/104 (2.9%) patients, and invasive ventilation in 3/104 (2.9%) additional cases.

Frequency and Type of Red Flags.—Red flags concerning prior medical history were present in 79/104 (76.0%) patients. In 99/104 (95.2%) cases, red flags regarding the headache were present, however, no single red flag was present in more than half of the patients, being the most frequent the change in the pattern of a preexistent headache, in 51/104 (49.0%) cases. Table 2 shows the frequency and type of each red flag.

The presence of systemic symptoms was described in 104/104 (100%) patients and neurologic symptoms were described by 86/104 (82.7%), patients. Table 3 presents the frequency and type of general and neurologic symptoms. There were not any case of visual disturbance, speech disorder, focal weakness, hypoesthesia, ataxia, or seizures.

Laboratory Parameters.—In the first laboratory determination, there was at least 1 abnormal laboratory value in 98/104 (94.2%) cases, being the most frequently abnormal CRP, in 84/100 (84.0%) of cases. Table 4 shows the frequency of each laboratory parameter abnormality. Figure 2 represents the most frequent red flags within the sample.

DISCUSSION

In the present study, we analyzed the frequency and the type of headache red-flags in patients with Covid-19. We assessed if the presence of Covid-19 in headache patients could be suspected by the presence of other typical Covid-19 symptoms, red flags related with

Table 1.—Comparison of Demographic Variables and Prior History Between Patients in Whom Headache was the First Symptom and the Rest of the Sample

Variable	Headache as the First Symptom (n = 27)	Rest of the Sample (n = 77)	*P* Value
Female sex (n, %) (n = 104)	20/27 (74.1%)	46/77 (59.7%)	.247†
Age (years) (mean, SD) (n = 104)	67.6 (12.2)	56.4 (10.9)	.634‡
Hypertension (n, %) (n = 104)	9/27 (33.3%)	27/77 (35.1%)	>.999†
Diabetes (n, %) (n = 104)	2/27 (7.4%)	10/77 (13.0%)	.727†
Smoking (n, %) (n = 104)	1/27 (3.7%)	11/77 (14.3%)	.178†
Cardiac disorders (n, %) (n = 104)	3/27 (11.1%)	6/77 (7.8%)	.693†
Pulmonary disorders (n, %) (n = 104)	4/27 (14.8%)	20/77 (26.0%)	.296†
Cancer (n, %) (n = 104)	1/27 (3.7%)	12/77 (15.6%)	.176†
Immunocompromised states (n, %) (n = 104)	1/27 (3.7%)	4/77 (5.2%)	>.999†
Prior history of headache (n, %) (n = 104)	16/27 (59.2%)	44/77 (57.1%)	>.999†
ACE-I/AT-2 use (n, %) (n = 104)	10/27 (37.0%)	20/77 (26.0%)	.326†
Steroids use (n, %) (n = 104)	2/27 (7.4%)	3/77 (3.9%)	.609†

†Fisher 2-tailed exact test.
‡Independent Student *t*-test.
SD = standard deviation.
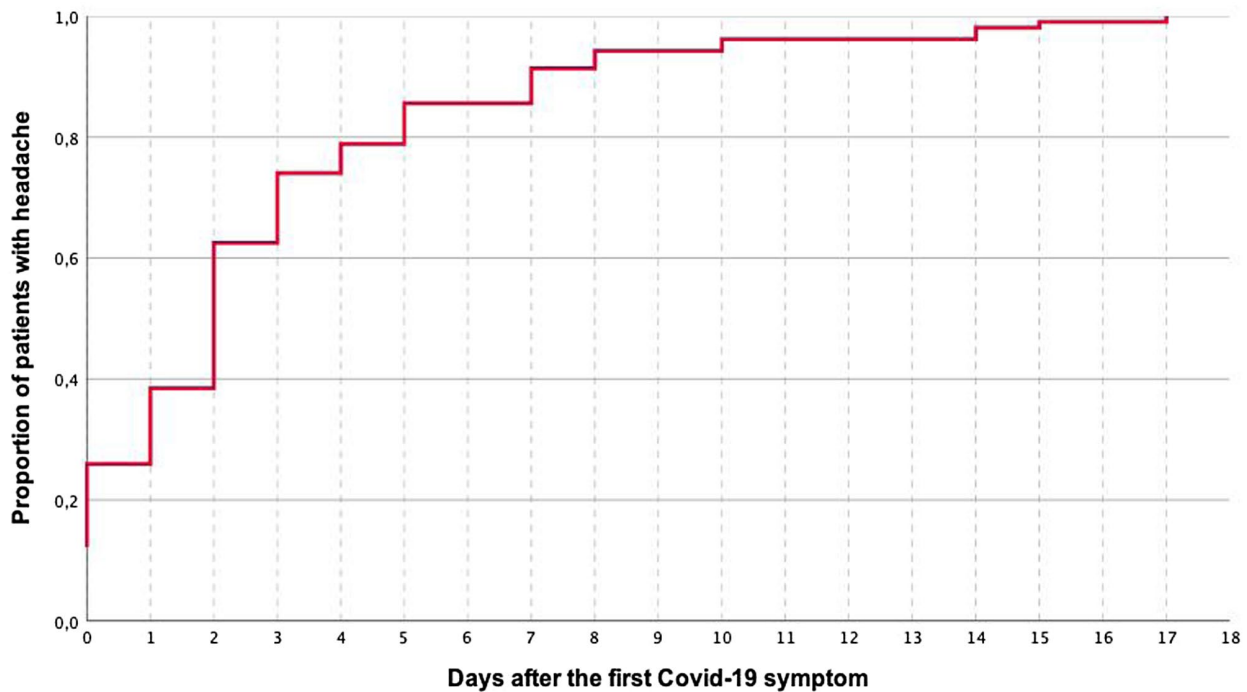
Fig. 1.—Headache onset in the course of Covid-19 disease. Number of days after the first Covid-19 symptom in which headache started. Kaplan-Meier 1-minus survival curve (n = 104). [Color figure can be viewed at wileyonlinelibrary.com]

the headache or laboratory abnormalities. For this, we systematically tested the main red flags in a series of patients with confirmed Covid-19 infection. In our sample, red flags were common, but there was not a single, perfect, red flag. This reinforces how important the anamnesis is, and in particular in headache medicine.[13]

There are many different lists of red flags.[14,15,20,21] The secondary headache Special Interest Group of the

**Table 2.—Frequency and Type of Red Flags Related
With Prior Medical History and Related to the Headache
Phenotype**

Variable	Frequency (%)
Red flags related to prior medical history	
Prior medical history (n = 104)	79/104 (76.0%)
Age > 50 (n = 104)	75/104 (72.1%)
Neoplasm in history (n = 104)	13/104 (12.5%)
Pathology of the immune system (n = 104)	5/104 (4.8%)
Red flags related to the headache	
Pattern change (n = 104)	51/104 (49.0%)
Recent onset (n = 104)	44/104 (42.3%)
Worst headache (n = 104)	39/104 (37.5%)
Precipitated by sneezing, coughing or exercise (n = 104)	39/104 (37.5%)
Painful eye (n = 104)	32/104 (30.8%)
Progressive headache (n = 104)	18/104 (17.3%)
Wake up (n = 104)	17/104 (16.3%)
Strict unilaterality (n = 104)	16/104 (15.4%)
Treatment resistant (n = 104)	15/104 (14.4%)
Autonomic features (n = 104)	6/104 (5.8%)
Positional headache (n = 104)	7/104 (6.7%)
Sudden onset (n = 104)	5/104 (4.8%)

**Table 3.—Frequency and Type of Red Flags Related to
the Presence of Systemic Symptoms and the Presence of
Neurologic Symptoms**

Variable	Frequency (%)
Red flags related to systemic symptoms	
Systemic symptoms (n = 104)	104/104 (100%)
Asthenia (n = 104)	54/104 (51.9%)
Arthralgia (n = 104)	13/104 (12.5%)
Chest pain (n = 104)	28/104 (26.9%)
Cough (n = 104)	89/104 (85.6%)
Cutaneous Rash (n = 104)	4/104 (3.8%)
Diarrhoea (n = 104)	49/104 (47.1%)
Dyspnoea (n = 104)	52/104 (50.0%)
Emesis (n = 104)	11/104 (10.6%)
Expectoration (n = 104)	16/104 (15.4%)
Fever (n = 104)	93/104 (89.4%)
Generalized weakness (n = 104)	23/104 (22.1%)
Light-headedness (n = 104)	15/104 (14.4%)
Odynophagia (n = 104)	18/104 (17.3%)
Rhinorrhoea (n = 104)	2/104 (1.9%)
Red flags related to neurologic symptoms	
Neurologic symptoms (n = 104)	86/104 (82.7%)
Anosmia (n = 104)	67/104 (64.4%)
Myalgia (n = 104)	44/104 (42.3%)
Altered mental status (n = 104)	10/104 (9.6%)
Weakness (n = 104)	2/104 (1.9%)
Vertigo (n = 104)	3/104 (2.9%)
Loss of consciousness (n = 104)	6/104 (5.8%)

**Table 4.—Frequency of Laboratory Parameter
Abnormalities**

Variable	Frequency (%)
Abnormal leukocyte count (n = 104)	20/104 (19.2%)
Lymphopenia (n = 104)	22/104 (21.1%)
Increased LDH (n = 102)	49/102 (48.0%)
Increased INR (n = 103)	9/102 (8.7%)
Increased D-dimer (n = 100)	54/100 (54.0%)
Increased CRP (n = 100)	84/100 (84.0%)
Increased PCT (n = 79)	3/79 (3.8%)

CRP = C-reactive protein; INR = international normalized ratio; LDH = lactate dehydrogenase; PCT = procalcitonin.

International Headache Society recently did a comprehensive review that included the main red and orange flags.[15] In the case of headache in Covid-19 patients, items like the presence of systemic symptoms, including fever, the precipitation by sneezing or coughing and the recent onset or change in the pattern were particularly frequent.

We focused on the frequency of red flags, while the sensitivity in the detection of a potentially life-threatening condition, and should be the priority.[22,23] Future studies should analyze the specificity of the red flags with regards to primary headache or compared with other secondary headache disorders. Mean age of our patients notably exceeded the typical age of primary headache patients.[24,25] Median age of the confirmed cases in Spain is 60 (IQR: 46-78).[26] The role of cancer or immunosuppression as red flags in Covid-19 is disputable, but the Covid-19 diagnosis in those patients cannot be missed.

Concerning the headache, our study was not focused on the phenotypic characterization of the acute headache attributed to Covid-19 infection,[9,13] but to the presence of atypical presentations of the headache. A remarkable result of our study was the fact that the red flag "recent onset of headache" was not as frequent as expected, being present in 42% of the patients. This could be related with the high frequency of prior history of headache, in 57% of the patients, a prevalence that exceeds the estimated prevalence of primary headache disorders.[24,25] This fact probably increased the frequency of the red flag "change in the pattern," in 49% of the cases. We deem this hypothesis reinforced
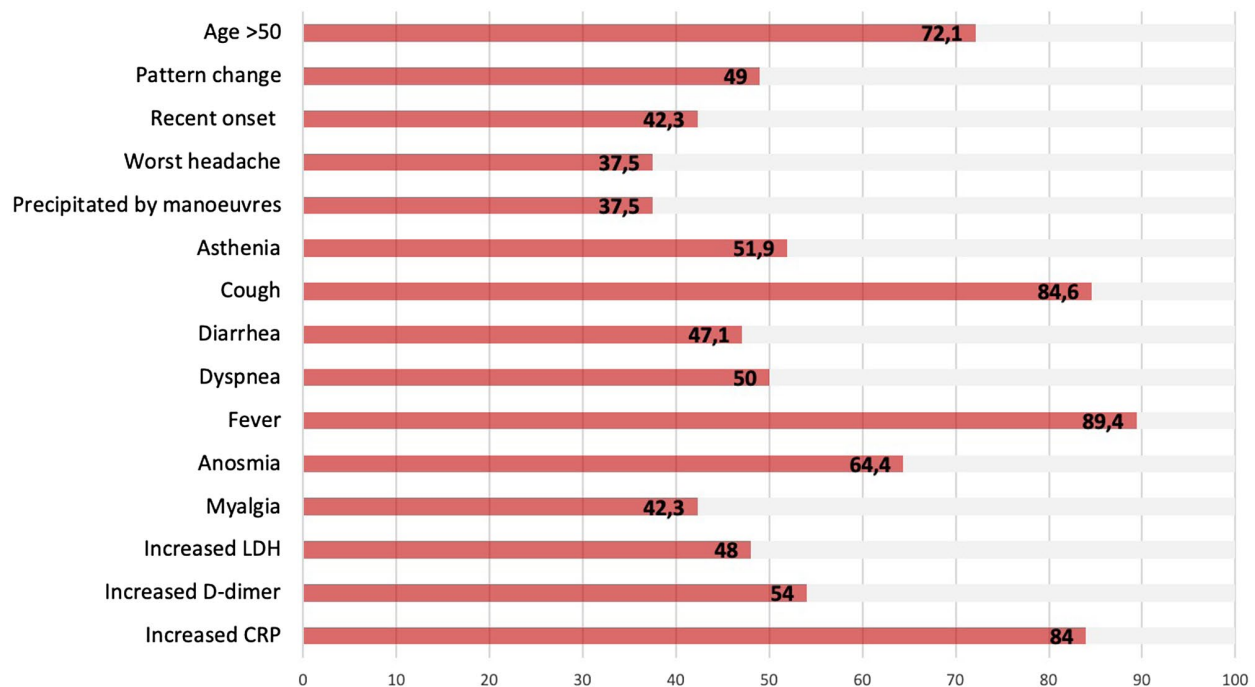
Fig. 2.—Most common red flags in hospitalized patients with Covid-19 disease and headache. [Color figure can be viewed at wileyonlinelibrary.com]

by the frequency of "worst headache ever" frequency, in 37% of patients. Therefore, clinicians must be aware of new onset headache or changes of headache pattern in patients with previous primary headache disorders.

Another finding that deserves further interpretation is the frequency of "treatment resistance." The potential risk of nonsteroidal anti-inflammatory drugs and ACE inhibitors became popular since the first stages of the pandemic, despite the evidence at that time was scarce.[27] Some patients might be reluctant to acute medication. Given the disability that severe headache poses,[24] they should be adequately counselled.[28]

The prevalence of headache in our sample was 22%, almost 2-fold than the previously reported in the literature.[7-9] This could be explained because we enquired every patient about the presence of headache, but the real prevalence of headache in Covid-19 might be underestimated.[6] Studies that systematically analyzed the prevalence of olfactory disorders reported a higher prevalence[29-31] than the first general series[7,8] as well.

The present study has important limitations. The first is the possible selection bias: we studied hospitalized patients and, therefore, the severity of the disease in these patients might be worse. In our sample, 95%

of the patients had pneumonia and 7.7% developed ADRS, in contrast with the 53.9% and 6.7% reported frequency in the nation-wide surveillance reports.[26] Due to the shortage of reactive and protective equipment, at the onset of the pandemic only the severest cases were tested, so further studies should analyze the sensitivity of red flags including patients managed in primary care. Another limitation is that on the other extreme, we could not test 13 patients due to decease or poor medical condition. This could underestimate the frequency of some other red flags, as laboratory parameters, expected to be worse in the most severely affected patients.[19]

The external validity of the study should be contextualized to the setting, a public hospital. Given the disparity in the reports across the nations, multicentric, and multinational studies should be performed to clarify if the headache presentation is uniform or not. Another relevant point is that the Covid-19 headache phenotype might be defined not only by the presence of red flags, but also with a distinct headache phenotype. Future studies should characterize it and evaluate if there is any specific presentation. The frequency and type of red flags in patients who present with headache as the initial symptom of Covid-19 should also be

analyzed in future studies. Both sensitivity and specificity of red flags in Covid-19 patients should be properly studied. We hope that the estimations observed in our study might help in the design of future specific studies.

CONCLUSION

In patients with Covid-19 that described headache, red flags were frequent. There was not any universal red, being necessary the integration of them. Systemic symptoms were present in all cases, red flags concerning the headache were described in almost all cases and red flags related with prior medical history or the presence of neurological symptoms were also common. Laboratory parameters were abnormal in most cases, being the most frequently abnormal parameter the CRP.

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