Dear Editor,

We found the report on “Ocular manifestation of coronavirus disease 2019” by Bostanci Ceran B. and Ozates S. very interesting [1]. In fact, ocular symptoms may occur in COVID-19 since entry of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) into human cells occurs after viral protein binds to an angiotensin converting enzyme 2 (ACE2) receptor [2], also present on the ocular surface cells [3, 4]. There is, however, little information about the conditions that predispose or protect patients from ocular involvement during COVID-19 infections. We therefore share results of our study, conducted in order to confirm ocular symptoms occurring during acute COVID-19 and to investigate on correlations with both systemic symptoms and elements of ocular history.

A multicenter, retrospective, cross-sectional, descriptive study was conducted in May and June 2020 in five French university hospitals (Strasbourg, Dijon, Colmar, Nice and Brest) in accordance with the tenets of the Declaration of Helsinki. The study was approved by the national ethics committee. Symptomatic patients diagnosed positive for COVID-19 by polymerase chain reaction were eligible. We used a consecutive sampling method among those diagnosed at least 3 weeks earlier (each center had updated lists of patients having consulted for emergency care). We excluded patients who couldn’t give consent or be joined by phone. Sample size was calculated based on a previously suggested one-third frequency of ocular symptoms in COVID-19 infections [4].

Variables of interest were collected using medical records and phone interviews. Data was gathered using a standardized questionnaire and collated using a structured electronic collection form. Patients were asked to report the presence or absence of symptoms during the acute phase of COVID-19. All univariate statistical analyses (Pearson’s $\chi^2$ test) were performed using R version 3.6.3.

Four hundred eighty-one patients were assessed for eligibility. Twelve (2.5%) refused to participate, and 33 (6.9%) were unreachable. Thus, 436 patients were included. Patients’ demographic and clinical characteristics are summarized in Table 1. Relations between general symptoms, ocular history, and the occurrence of ocular surface involvement during the infection are presented in Table 2.

Our results are consistent with those of Bostanci Ceran and Ozates. Ocular symptoms reported by COVID-19 patients resembled non-specific mild conjunctivitis. With an incidence of 36.7%, they were the fourth most frequent, on par with digestive symptoms. The fact that conjunctivitis is less common than pulmonary involvement is consistent with studies showing lower ACE2 protein levels on conjunctival epithelial cell membranes than in the lungs [5]. Another reason might be the protective effect of tears although dry eye disease was not associated with a higher ocular involvement rate.

Unlike Bostanci Ceran and Ozates, some authors like Xia J. et al. [6] found correlation between ocular symptoms and the severity of COVID-19. Our study is consistent with the results of Bostanci Ceran and Ozates: we did not find any such correlation.

As to the relationship between COVID-19 ocular symptoms and ocular history, the protective effect of contact lenses and spectacle wear [7] was not established. Results about the correlation of ocular symptoms with a history of infectious conjunctivitis and ocular allergy must be tempered as data might have been misreported (memorization bias) and allergy
might also be a confounding factor as the study was conducted in spring. However, previously aggressed conjunctiva might be more susceptible, via the upregulation of ocular surface receptors as ACE2; this offers a subject for further investigation that might allow for deeper understanding of a complex illness.

Acknowledgment
Zsolt Böcskei had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Conflict of interest for authors: none

Authors’ contribution All authors contributed to the study conception and design. The first draft of the manuscript was written by Zsolt Böcskei, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Table 1 Demographic and clinical characteristics of the COVID-19 symptomatic and PCR positive patients

| Demographic characteristics              | Female sex, No. (%) | Age, mean (SD) | Systemic symptomatology, No. (%) | Influenza-like illness | Fever | Muscle aches | Chills | Rhinopharyngitis | Pulmonary | Cough | Dyspnea | Thoracic pain | Neurological | Need for mechanical ventilation | Comorbidities | Anti-inflammatory drugs |
|------------------------------------------|---------------------|----------------|---------------------------------|-----------------------|-------|-------------|--------|------------------|-----------|-------|---------|---------------|-------------|------------------------|---------------|------------------------|
| Female sex, No. (%)                     | 302 (69.27)         | 44.03 (16.15)  | 436 (100.00)                    | 375 (86.01)           | 292   | 224         | 160    | 25               | 330       | 258   | 188     | 96            | 361         | 286                    | 268           | 160                    |
| Age, mean (SD)                          |                     |                |                                 |                       |       |             |        |                  |           |       |         |               |             |                        |               |                       |
| Systemic symptomatology, No. (%)        |                     |                |                                 |                       |       |             |        |                  |           |       |         |               |             |                        |               |                       |
| Influenza-like illness                   |                     |                |                                 |                       |       |             |        |                  |           |       |         |               |             |                        |               |                       |
| Fever                                   |                     |                |                                 |                       |       |             |        |                  |           |       |         |               |             |                        |               |                       |
| Muscle aches                            |                     |                |                                 |                       |       |             |        |                  |           |       |         |               |             |                        |               |                       |
| Chills                                  |                     |                |                                 |                       |       |             |        |                  |           |       |         |               |             |                        |               |                       |
| Rhinopharyngitis                         |                     |                |                                 |                       |       |             |        |                  |           |       |         |               |             |                        |               |                       |
| Pulmonary                                |                     |                |                                 |                       |       |             |        |                  |           |       |         |               |             |                        |               |                       |
| Cough                                   |                     |                |                                 |                       |       |             |        |                  |           |       |         |               |             |                        |               |                       |
| Thoracic pain                           |                     |                |                                 |                       |       |             |        |                  |           |       |         |               |             |                        |               |                       |
| Neurological                             |                     |                |                                 |                       |       |             |        |                  |           |       |         |               |             |                        |               |                       |
| Anosmia / ageusia                       |                     |                |                                 |                       |       |             |        |                  |           |       |         |               |             |                        |               |                       |
| Headaches                                |                     |                |                                 |                       |       |             |        |                  |           |       |         |               |             |                        |               |                       |

Table 2 Relations between systemic symptomatology, ocular history and ocular involvement during COVID-19 acute phase

| Systemic symptomatology and history | OR (IC 95) | p    |
|------------------------------------|------------|------|
| Influenza-like illness             | 1.10 (1.02 – 1.19) | 0.0163 * |
| Pulmonary                          | 1.15 (1.04 – 1.28) | 0.0173 * |
| Neurological                       | 1.18 (1.02 – 1.65) | 0.0355 * |
| Digestive                          | 1.31 (1.04 – 1.65) | 0.0340 * |
| Need for mechanical ventilation    | 0.68 (0.35 – 1.32) | 0.2489 |
| Comorbidities                      | 0.90 (0.72 – 1.13) | 0.3822 |
| Anti-inflammatory drugs            | 0.75 (0.45 – 1.25) | 0.2917 |

| Ocular history                     | OR (IC 95) | p    |
|------------------------------------|------------|------|
| Infectious conjunctivitis          | 1.35 (1.04 – 1.76) | 0.0355 * |
| Allergic conjunctivitis            | 1.65 (1.13 – 2.39) | 0.0151 * |
| Dry eye disease                    | 1.27 (0.94 – 1.71) | 0.1342 |
| Other ocular disease               | 1.11 (0.64 – 1.90) | 0.7173 |
| History of eye surgery             | 0.86 (0.43 – 1.73) | 0.6767 |
| Contact lenses wear                | 0.89 (0.48 – 1.69) | 0.7392 |
| Spectacles wear                    | 0.97 (0.86 – 1.08) | 0.5469 |

*p < 0.05. All of the systemic manifestations of COVID-19 were statistically associated with occurrence of ocular symptoms. Previous infectious conjunctivitis and ocular allergy were correlated with the presence of ocular symptoms

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*Comorbidities included history of chronic diseases (obesity, hypertension, diabetes mellitus, oncological history, auto-immune diseases, immunosuppressive treatments)

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