



Different rates of conjunctivitis in COVID-19 eastern and western hospitalized patients: a meta-analysis

Lorenzo Loffredo¹ · Alessia Fallarino¹ · Aurora Parainfi¹ · Fernanda Pacella² · Elena Pacella² · Alessandra Oliva³ · Francesco Violi¹

Received: 3 August 2021 / Accepted: 26 October 2021 / Published online: 9 November 2021
© Società Italiana di Medicina Interna (SIMI) 2021

Abbreviations

COVID-19 Coronavirus disease 2019
ARDS Acute respiratory distress syndrome
ICU Intensive care units

Dear Editor,

The coronavirus disease 2019 (COVID-19) is a lung infection that in its most severe manifestations leads to ischemic, thrombotic and respiratory complications that can increase mortality and intensive care admission [1].

In the early phase of pandemic infection, we assessed the relationship between conjunctivitis and COVID-19 [2]. Interestingly, we found an association between COVID-19 severe disease and an increased incidence of conjunctivitis [2]. However, the meta-analysis was limited by the low rate of events and by the population composed exclusively by Chinese COVID-19 patients. Thus, after almost 2 years of pandemic, the goal of this meta-analysis is to assess whether the association with COVID-19 severity persists in a larger number of patients with conjunctivitis and different ethnicities.

As eligibility criteria we assessed the following types of studies: clinical studies in hospitalized patients with COVID-19 infection that assessed the severe (as severe pneumonia, mortality, ARDS, and use of mechanical ventilation or ICU

recovery) and non-severe forms of the disease and reported the incidence of conjunctivitis.

No publication date, or publication status restrictions were imposed. Only publications written in English language were included in the meta-analysis.

The studies were identified by searching electronic databases. This search was applied to Pubmed, ISI Web of Science, SCOPUS and Cochrane database. The last search was run on July 28th, 2021. Reference lists of all studies included in the present meta-analysis were screened for potential additional eligible studies. Two investigators (A.F. and L.L.) independently searched in the electronic databases combining the following text terms and MeSH terms: "COVID-19"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] AND ("conjunctivitis"[MeSH Terms] OR "eye"[All Fields] OR ADULTS[All Fields]).

Two authors (L.L., A.F.) independently reviewed titles and abstracts generated by search. Studies were excluded if the title and/or abstract showed that the papers did not meet the selection criteria of our meta-analysis. For potentially eligible studies or if the relevance of an article could not be excluded with certitude, we procured the full text. Disagreements were resolved by discussion between L.L. and A.F.; if no agreement was reached, a third author (A.P.) decided. Studies not including a control group and animal studies were excluded. Case reports, editorials, commentaries, letters, review articles, and guidelines were also excluded from the analysis (Fig. 1).

We evaluated the frequency of conjunctivitis in hospitalized patients affected by severe and non-severe COVID-19 infection. This review was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).

We allocated the results of each trial as dichotomous frequency data. We considered a p value < 0.05 as significant.

✉ Lorenzo Loffredo
lorenzo.loffredo@uniroma1.it

¹ Department of Clinical, Internal Medicine, Anesthesiology and Cardiovascular Sciences, Sapienza University of Rome, Viale del Policlinico 155, 00161 Rome, Italy

² Department of Sense Organs, Faculty of Medicine and Dentistry, Sapienza University of Rome, Rome, Italy

³ Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy

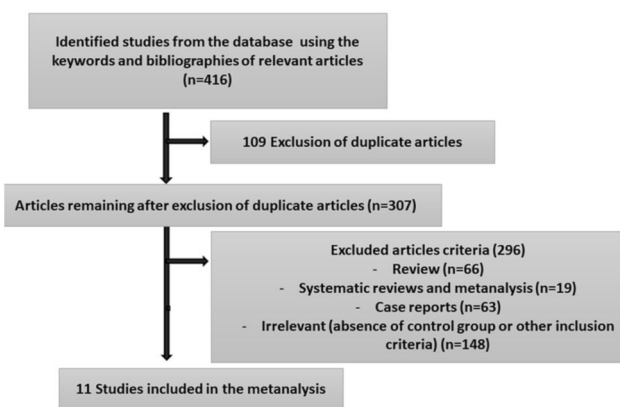


Fig. 1 Study selection flow chart

Odds Ratios (OR) and 95% confidence intervals (CIs) were calculated. Data were pooled and compared with a random-effect model. The presence of publication bias was evaluated using the Egger's test. Statistical heterogeneity was calculated by I^2 . The software Comprehensive Meta-Analysis (version 2.2.064, USA, 2011) supported the analysis. The presence of publication bias was explored using funnel plots of effect size against standard error.

We included studies in hospitalized patients with COVID-19 that assessed the severe (as severe pneumonia, mortality, ARDS, use of mechanical ventilation or intensive care units recovery) and non-severe forms of the disease and reported the incidence of conjunctivitis.

Eleven studies [3–13] including 2308 patients, assessed the clinical course of patients with COVID-19 and presence/absence of conjunctivitis (Fig. 1).

Clinical characteristics of the studies are reported in Table 1. Patients from Euro-Mediterranean area (Italy, Germany, Spain, Turkey, Egypt) and Asia (China) were included (Table 1). Compared to Asian studies, a higher incidence of conjunctivitis was observed in those of Euro-Mediterranean

area (severe COVID: 9% vs 16% and not-severe: 1.3 vs 7%, respectively). A significant increase of conjunctivitis in severe COVID-19 patients was observed in both ethnic groups (random model, Asian population: O.R. 2.5; 95% C.I. 1.1–6.0; $p=0.03$; Euro-Mediterranean population: O.R. 2.3; 95% C.I. 1.1–4.9; $p=0.02$) (Fig. 2).

The overall rate of conjunctivitis was 5.9%; it was 12.7% and 4.1% in severe and non-severe COVID-19 patients, respectively. The overall meta-analysis showed that patients with severe COVID-19 infection had an increased incidence of conjunctivitis (random model, O.R. 2.4; 95% C.I. 1.4–4; $p=0.002$) (Fig. 2). Moderate heterogeneity among trials was observed ($I^2=32%$); the publication bias was not statistically significant (Egger's test, $p=0.395$).

This meta-analysis provides evidence that conjunctivitis, in a multi-ethnic population, is associated with a more severe form of COVID-19; this difference remains also when the subgroups analysis for ethnic groups was performed.

The close relationship between conjunctivitis and COVID severity could be very important for clinicians to recognize a possible critical evolution of the patient early. In this regard, we recently demonstrated [13] in patients admitted to the medical wards for COVID pneumonia that when conjunctivitis appears the prognosis becomes poor with an increase of intensive care admissions or mortality rate. An interesting hypothesis is if conjunctivitis is related not to the route of entry of the virus in the human body but to the manifestation of a systemic disease. Thus, conjunctivitis could represent a sign of a systemic disease and a warning sign of poor outcome consequent to the systemic inflammation. This hypothesis may be supported by the multisystem inflammatory syndrome in young with COVID-19, where conjunctivitis has been described as a sign of a storm of cytokines and inflammatory molecules [14, 15].

Another important message that comes from this meta-analysis is the high incidence (approximately 13%) of conjunctivitis in multi-ethnic patients with severe COVID.

Table 1 Clinical characteristics of the population included in the meta-analysis

Study	Period	Patients	Country	Age (median)	Males/females
Xia	January 26 to February 9, 2020	30	China	54	21/9 (70%/30%)
Wu	February 9 to 15, 2020	38	China	65.8	25/13 (66%/34%)
Guan	December 11, 2019 to January 29, 2020	1099	China	47	637/ 462 (58%/42%)
Hong	January 19 to February 29, 2020	56	China	48	31/25 (55%/45%)
Savastano	March 26 to April 21, 2020	50	Italy	69.6	36/14 (59%/23%)
Pirraglia	April 24 to May 24, 2020	46	Italy	70	25/21 (58%/42%)
Oncul	May 1 to June 30, 2020	359	Turkey	58.5	197/162 (55%/45%)
Guemes	2020	301	Spain	72	180/ 121 (60%/40%)
Dutescu	April, 2020	18	Germany	66.3	9/9 (50%/50%)
Mahmoud	May 18 to 28, 2020	28	Egypt	51.8	15/13 (54%/46%)
Loffredo	February 2020 to January 2021	218	Italy	61	122/96 (56%/46%)

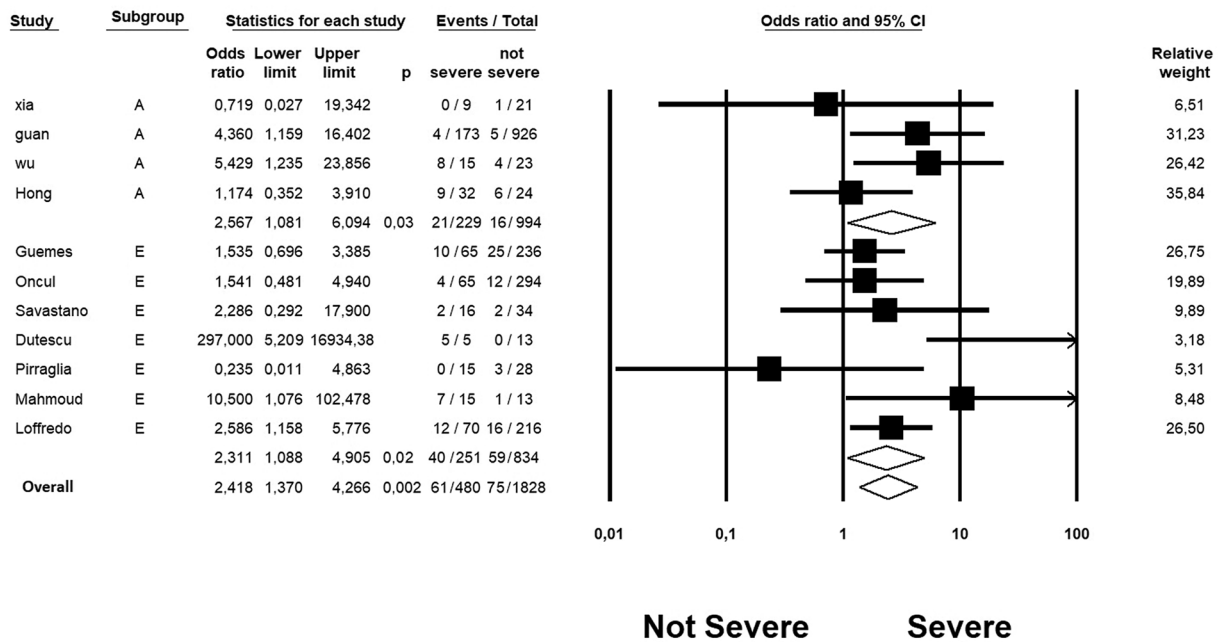


Fig. 2 Meta-analysis of conjunctivitis in patients with severe vs non-severe COVID-19 disease. A Asian population, E Euro-Mediterranean population

Although a higher incidence of conjunctivitis has been observed in the Euro-Mediterranean studies, no definitive conclusions can be drawn as further targeted studies, aimed at comparing this ocular sign in the European and Asian COVID population with a large sample and with similar clinical features, should be done. In any case, this meta-analysis shows that conjunctivitis is a frequent manifestation in both COVID areas and that this clinical sign should be carefully considered for its poor prognosis.

This meta-analysis has the following limitations:

- Composite events were analyzed; there are currently few studies [8, 13] that analyzed single events, such as mortality and ICU admission. Future studies need to evaluate the association among these single outcomes, COVID and conjunctivitis.
- The prognostic value of the conjunctivitis cannot be fully elucidated. We cannot exclude that conjunctivitis occurred following environments that favored its appearance such as that of intensive care. The predictive role of conjunctivitis was analyzed in our previous study [13] in which the diagnosis was done at admission and we found an association of conjunctivitis with increased mortality and ICU admissions. However, further longitudinal studies are needed to confirm this association.

- The Asian studies included in this meta-analysis were performed in the first phase of the pandemic period (by February 2020) unlike the European ones performed in a later phase (after February 2020); this could have created a different infectious scenario due to the increase in COVID-19 variants and a different incidence among the populations studied.

In conclusion, the results of this meta-analysis show that conjunctivitis may represent a sign of severe COVID-19 infection associated with a poor outcome in Asian and Euro-Mediterranean patients.

Funding All the authors have no financial relationships relevant to this article to disclose.

Declarations

Conflict of interest All the authors have no conflicts of interest to disclose.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

References

1. Violi F, Pastori D, Cangemi R, Pignatelli P, Loffredo L (2020) Hypercoagulation and antithrombotic treatment in Coronavirus 2019: a new challenge. *Thromb Haemost* 120(6):949–956. <https://doi.org/10.1055/s-0040-1710317>
2. Loffredo L, Pacella F, Pacella E, Tiscione G, Oliva A, Violi F (2020) Conjunctivitis and COVID-19: a meta-analysis. *J Med Virol* 92(9):1413–1414. <https://doi.org/10.1002/jmv.25938>
3. Xia J, Tong J, Liu M, Shen Y, Guo D (2020) Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. *J Med Virol* 92(6):589–594. <https://doi.org/10.1002/jmv.25725>
4. Guan WJ, Ni ZY, Hu Y et al (2020) Clinical characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 382(18):1708–1720. <https://doi.org/10.1056/NEJMoa2002032>
5. Wu P, Duan F, Luo C et al (2020) Characteristics of ocular findings of patients with Coronavirus Disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmol* 138(5):575–578. <https://doi.org/10.1001/jamaophthalmol.2020.1291>
6. Hong N, Yu W, Xia J, Shen Y, Yap M, Han W (2020) Evaluation of ocular symptoms and tropism of SARS-CoV-2 in patients confirmed with COVID-19. *Acta Ophthalmol*. <https://doi.org/10.1111/aos.14445>
7. Guemes-Villahoz N, Burgos-Blasco B, Garcia-Feijoo J et al (2020) Conjunctivitis in COVID-19 patients: frequency and clinical presentation. *Graefes Arch Clin Exp Ophthalmol* 258(11):2501–2507. <https://doi.org/10.1007/s00417-020-04916-0>
8. Oncul H, Oncul FY, Alakus MF, Caglayan M, Dag U (2021) Ocular findings in patients with coronavirus disease 2019 (COVID-19) in an outbreak hospital. *J Med Virol* 93(2):1126–1132. <https://doi.org/10.1002/jmv.26412>
9. Savastano MC, Gambini G, Savastano A et al (2020) Evidence-based of conjunctival COVID-19 positivity: an Italian experience: Gemelli against COVID Group. *Eur J Ophthalmol*. <https://doi.org/10.1177/1120672120976548>
10. Dutescu RM, Banasik P, Schildgen O, Schrage N, Uthoff D (2021) Detection of Coronavirus in tear samples of hospitalized patients with confirmed SARS-CoV-2 from Oropharyngeal Swabs. *Cornea* 40(3):348–350. <https://doi.org/10.1097/ICO.0000000000002562>
11. Pirraglia MP, Ceccarelli G, Cerini A et al (2020) Retinal involvement and ocular findings in COVID-19 pneumonia patients. *Sci Rep* 10(1):17419. <https://doi.org/10.1038/s41598-020-74446-6>
12. Mahmoud H, Ammar H, El Rashidy A, Ali AH, Hefny HM, Mounir A (2020) Assessment of Coronavirus in the conjunctival tears and secretions in patients with SARS-CoV-2 infection in Sohag Province, Egypt. *Clin Ophthalmol* 14:2701–2708. <https://doi.org/10.2147/OPHTH.S270006>
13. Loffredo L, Oliva A, Parainfini A et al (2021) An observed association between conjunctivitis and severity of COVID-19. *J Infect*. <https://doi.org/10.1016/j.jinf.2021.06.006>
14. Loffredo L, Campana A, Olivini N et al (2021) Hypoalbuminemia and clinical adverse events in children with COVID-19. *J Med Virol*. <https://doi.org/10.1002/jmv.26856>
15. Faller EBR, O'Flynn O, Kearney P, Sadlier C (2021) Kawasaki-like multisystem inflammatory syndrome associated with SARS-CoV-2 infection in an adult. *BMJ Case Rep* 7(14):3. <https://doi.org/10.1136/bcr-2020-240845>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.