External Ocular Manifestations among Patients Diagnosed with Coronavirus Disease 2019 in a Referral Center in the Philippines

Alyssa Louise B. Pejana-Paulino, MD,[1] Aramis B. Torrefranca Jr., MD,[1,2]
Nilo Vincent dG. Florcruz, MD[1] and Ma. Dominga B. Padilla, MD[3]

[1]*Department of Ophthalmology and Visual Sciences, Philippine General Hospital, University of the Philippines Manila, Manila, Philippines*
[2]*Department of Ocular Health, Governor Celestino Gallares Memorial Medical Center, Bohol, Philippines*
[3]*St. Luke's Medical Center, Bonifacio Global City, Taguig, Philippines*

ABSTRACT

Background and Objectives. The global pandemic caused by Coronavirus Disease 2019 (COVID-19) has affected millions, with growing evidence of the potential role of ocular tissues in viral transmission. At the time of writing, local data regarding the phenomenon was limited. This study investigated external ocular manifestations in patients with COVID-19 at a referral center in the Philippines, examined correlations between demographics, systemic manifestations, and laboratory results with ocular manifestations, and determined their timing relative to systemic symptoms.

Methods. This single-center, descriptive cross-sectional study was carried out from December 8 to 18, 2020 at the adult COVID-19 wards of the Philippine General Hospital involving 72 participants. Data collection involved relevant clinical history taking and performing gross eye examination. The prevalence of ocular manifestations was described with 95% confidence intervals. Correlations between ocular manifestations and quantitative variables were analyzed with point-biserial correlation, and associations with qualitative variables were tested using chi-square or Fisher's exact tests.

Results. Among participants, 31.9% presented with ocular manifestations with foreign body sensation as the most prevalent ocular symptom (11.1%) and conjunctival hyperemia as the most prevalent ocular finding (19.4%). The median age of patients with ocular manifestations was 41 years old with a higher prevalence in the male population (73.9%, CI=95%, p=0.001). No significant correlation was observed between presence of external ocular manifestations and the different systemic and ocular co-morbidities as well as with COVID-19 clinical classification. Among those who experienced symptoms, majority (29.2%) of the patients experienced systemic symptoms prior to the onset of ocular symptoms. Ocular complaints may present as the sole manifestation (13.9%). Several laboratory parameters were measured and only temperature and AST levels showed a low positive correlation with the presence of ocular manifestations.

Conclusion. Ocular manifestations occur in roughly one third of patients with COVID-19 based on this study population. With some individuals presenting with ocular signs or symptoms as the initial and sole manifestation, healthcare practitioners must exercise caution and remain vigilant in managing patients who present as such. At the time of writing, this is the first

Paper presentation – Asia-Pacific Academy of Ophthalmology Virtual Congress, September 2021, online platform.

eISSN 2094-9278 (Online)
Published: January 15, 2026
https://doi.org/10.47895/amp.vi0.12187

Corresponding author: Alyssa Louise B. Pejana-Paulino, MD
Sentro Oftalmologico Jose Rizal
Department of Ophthalmology and Visual Sciences
Philippine General Hospital
Taft Avenue, Ermita, Manila 1000, Philippines
Email: abpejana@gmail.com
ORCiD: https://orcid.org/0000-0002-8423-9064

local study investigating the different external ocular manifestations in patients with COVID-19. There is a need to pursue more robust studies and conduct more local investigations which will guide both ophthalmologists and other practitioners in strengthening existing guidelines regarding precautionary practices, clinical diagnosis, and management of COVID-19 patients.

Keywords: SARS-CoV-2, COVID-19, ocular manifestation, Philippines

INTRODUCTION

Coronavirus is a positive-sense single-stranded enveloped ribonucleic acid virus that can be transmitted among humans. The disease spectrum of the virus can range from infections causing common cold to infections causing past epidemics and pandemics such as the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003.[1]

In early December 2019, a series of pneumonia cases of unknown etiology emerged in Wuhan, China. The pathogen was later identified as a novel enveloped RNA coronavirus which is phylogenetically similar to SARS-CoV. The causative agent was later officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) officially named the infection as coronavirus disease 2019.[1-3] On March 11, 2020, the WHO declared the disease as a pandemic as the number of infected cases and mortalities continue to rise globally.[4] As of September 8, 2021, there is a total of 219 million laboratory-confirmed cases and 4.5 million deaths worldwide.[5] In the Philippines, confirmed cases have already reached 2.12 million with 34,498 mortalities.[6] In one of the largest COVID-19 referral centers in the country, 1,597 health care workers have already been infected as of September 8, 2021.[7]

Based on the rapid spread of the virus, reports have suggested that human-to-human transmission occurs primarily via direct contact with mucous membranes or inhalation of respiratory droplets from an infected individual.[8] Several studies have reported that the pathophysiology of the disease mainly affects the lower respiratory tract with some involvement of the gastrointestinal system.[1] The most common symptoms associated with the viral infection are fever and non-productive cough but some studies have reported the incidence of sore throat, dyspnea, myalgia, headache, diarrhea, nausea, and vomiting.[1,9] Current advancements in the knowledge of the clinical spectrum of COVID-19 have shown evidence supporting the possible involvement of the ocular tissue in its disease process.[10,11]

To date, there is limited local data on the ocular manifestations associated with COVID-19. Studies on its local prevalence will likely prove beneficial and further guide both ophthalmologists and other practitioners in the management of the disease.

In this research, the authors determined and described external ocular signs and symptoms in patients with COVID-19 at a referral center in the Philippines. Additionally, the authors correlated the demographics, systemic manifestations, systemic laboratory results, and COVID-19 severity with the external ocular manifestations. The authors also described the chronological relationship between the onset of ocular symptoms relative to the onset of systemic symptoms.

MATERIALS AND METHODS

This study was a single-center, observational, descriptive, cross-sectional study carried out from December 8 to 18, 2020 at Philippine General Hospital. The target population was sampled using total population sampling. The sample size was determined using Cochran's equation, with a 17.5% prevalence estimate, 95% confidence level, and 5% precision, yielding 222 participants. Applying finite population correction based on an estimated 106 weekly COVID-19 inpatients, the final sample size was adjusted to 72. This adjustment ensured that the sample remained statistically valid while accounting for the limited pool of eligible participants.

This study included admitted patients of both sexes with ages 18 years old and above, diagnosed with COVID-19 infection, as confirmed by reverse transcription polymerase chain reaction (RT-PCR) results of nasopharyngeal swab and/or oropharyngeal swab. Patients who have previously undergone or are currently undergoing treatment for COVID-19 infection as well as patients diagnosed with ocular comorbidities were also included in the study. All participants accomplished informed consents that were properly explained by the investigator and understood by the patient or the legal authorized representative. The institutional ethics review board approved the conduct of the study. Patients classified as suspected and probable cases of COVID-19 were not included in the study. For patients who developed ocular signs and symptoms after the initial visit, only the data gathered during the initial examination were included.

Relevant clinical history taking and gross ocular examination were conducted, with findings recorded in data collection forms. Photodocumentation was performed using a Xiaomi Redmi 8 camera-equipped phone with 1 to 1.5x magnification. As much as possible, interaction between the participant and the investigator were kept to a sufficient minimum. In charity wards, history taking were done in person while maintaining the recommended physical distance between two individuals, which is at least six feet apart. In instances that there was difficulty in communication with the participants due to limitations brought about by the physical barriers of Personal Protective Equipment (PPE), the investigator used the prepared empty sheets of paper to legibly write their statements and inquiries for the patient. In the pay wards, the investigator contacted the participants from outside of their rooms to obtain the history and other relevant information from the participants, through their designated

room telephones. Ocular examination was limited to gross observation of both eyes. Investigators used a 20-diopter binocular indirect ophthalmoscopy lens for magnification of the external ocular surface and a transilluminator for better visualization. Since ophthalmologic examination was limited to the ocular surface, no instrument was used to visualize the posterior segment of the eye. No ocular medications, such as anesthetic drops and dyes, were instilled.

The following were noted during gross eye examination: chemosis, watery secretion, conjunctival hyperemia, and other gross ophthalmologic findings. Conjunctival hyperemia was graded based on the Japan Ocular Allergy Society's (JOAS) conjunctival hyperemia severity grading system.[12] It is a standardized tool for assessing conjunctival hyperemia, categorizing it into four grades (none, mild, moderate, severe) based on vessel dilation using reference images. Its utilization in this study ensured objective, reproducible assessment, minimizing inter-observer variability, and standardizing documentation.

To investigate the correlation between external ocular manifestations and COVID-19 severity, the investigators utilized the clinical classification outlined in the Philippine Society for Microbiology and Infectious Diseases (PSMID) March 2020 guidelines.[9] This classification aligns with the clinical pathway used by the Philippine General Hospital for managing confirmed COVID-19 cases. Participants were categorized into four groups: (A) Adults under 60 years old with stable or no comorbidities and uncomplicated upper respiratory tract infection; (B) Adults over 60 years old with stable or unstable comorbidities and mild pneumonia; (C) Adults with severe pneumonia, severe sepsis, or septic shock, managed as Community-Acquired Pneumonia–High Risk; and (D) Adults with Acute Respiratory Distress Syndrome (ARDS).

The clinicodemographic profile of participants, including age, sex, systemic and ocular comorbidities, and COVID-19 disease severity, was obtained through chart review and summarized using descriptive statistics. Stratified analysis was performed to compare findings across subgroups and multivariate regression analysis was performed to adjust for significant confounding factors. Clinical and laboratory data were fully collected through comprehensive medical record review and standardized data collection, ensuring a complete dataset with no missing values. Consequently, no cases were excluded from the analysis.

Quantitative variables were described as median and interquartile range; qualitative variables were described as counts and proportions. Data analysis was performed using Stata version 15.1 (StataCorp). The prevalence of external ocular manifestations was expressed as point-estimate with 95% confidence interval. Correlation between presence of at least one external ocular manifestations and the different quantitative variables were assessed by point-biserial correlation; association between presence of at least one external ocular manifestations and the different qualitative variables were assessed by chi-square or Fisher exact test of association, as appropriate.

RESULTS

The study included 72 participants confirmed to have COVID-19 infection. Of these patients, 33 (45.9%) were male and 39 (54.1%) were female. Upon analysis, sex is associated with presence of external ocular manifestations where a significantly higher proportion of males (73.9%) with external ocular manifestations was observed than those without. The median age among all participants was 43 (19-80) years old and 41 (19-68) years old for those with ocular manifestations. There is negligible correlation between age and presence of external ocular manifestations. The clinicodemographic characteristics of the included subjects are summarized in Table 1.

Systemic comorbidities observed among the participants included hypertension, diabetes mellitus, bronchial asthma, nonspecific pulmonary co-infection, and other diseases such as cervical cancer, bile duct disease, liver disease, hyperthyroidism, appendicitis, heart failure, and blood dyscrasia. Among these conditions, hypertension was observed to have the highest prevalence (13.9%) among all the participants while nonspecific pulmonary co-infection (50%) has the highest prevalence among subjects with ocular manifestations. Ocular comorbidities were also noted among the participants with the majority presenting with presbyopia (12.5%), error of refraction (11.1%), and cataract (11.1%). Some of the other conditions noted were scleral perforating injury, corneal foreign body, glaucoma, orbital cellulitis, and pterygium.

Clinical classification of patients with confirmed COVID-19 infection based on the PSMID guidelines were also taken into account with the majority (77.8%) of the subjects falling under the Category A, which includes patients with age less than 60 years old without comorbid illness and with mild nonspecific symptoms such as fever, cough, sore throat, nasal congestion, headache, muscle pain or malaise.[9] A higher proportion of patients with ocular manifestations were also classified under Category A (65.2%). There was no sufficient evidence to conclude that there is association between presence of external ocular manifestations with the different systemic and ocular co-morbidities, and COVID-19 clinical classification.

Potential confounders based on the clinicodemographic data were identified and analyzed. Sex was found to be significantly associated with the presence of external ocular manifestations (p=0.001). Given this significant difference, stratified analysis was conducted to examine the effect of sex separately, and it was determined that sex was the only major confounder, while other demographic and clinical factors did not significantly influence the presence of ocular manifestations. To assess the impact of sex on the presence of external ocular manifestations, multivariate regression analysis was performed and results showed that sex is a

Table 1. Clinicodemographic Profile of the Participants and its Association with Presence of External Ocular Manifestations

	All Participants (n = 72)		According to External Ocular Manifestations				
			With (n = 23)		Without (n = 49)		*p*-value/ Point-biserial correlation*
	Median/ Count	IQR/ Proportion	Median/ Count	IQR/ Proportion	Median/ Count	IQR/ Proportion	
Age, years	43	30	41	28	44	33	-0.118*
Sex							0.001
Male	33	45.93%	17	51.52%	16	48.48%	
Female	39	54.18%	6	15.38%	33	84.62%	
Systemic comorbidities							
Hypertension	10	13.89%	3	30.00%	7	70.00%	1.000
Diabetes mellitus	7	9.72%	3	42.86%	4	57.14%	0.673
Bronchial asthma	5	6.94%	–	–	5	100.00%	0.170
Pulmonary co-infection	8	11.11%	4	50.00%	4	50.00%	0.257
Others	14	19.44%	9	64.29%	5	35.71%	–
Ocular comorbidities							
Presbyopia	9	12.50%	1	11.11%	8	88.89%	0.255
Error of refraction	8	11.11%	3	37.50%	5	62.50%	0.704
Cataract	8	11.11%	3	37.50%	5	62.50%	0.704
Others	9	12.50%	5	55.56%	4	44.44%	–
Current medications							1.000
Ferrous sulfate + folic acid	1	1.39%	–	–	1	100.00%	
None	71	98.61%	23	32.39%	48	67.61%	
COVID Clinical classification							0.111
A	56	77.78%	15	26.79%	41	73.21%	
B	15	20.83%	8	53.33%	7	46.67%	
C	1	1.39%	–	–	1	100.00%	
D	–	–	–	–	–	–	

Table 2. Prevalence of the External Ocular Manifestations of the Participants

Ocular Manifestations	Count	Prevalence	
		Point-estimate	95% Confidence Interval
Presence of any symptoms or signs	23	31.94%	[21.44%, 43.99%]
Symptoms			
Eye redness	6	8.33%	[3.12%, 17.26%]
Eye pain	4	5.56%	[1.53%, 13.62%]
Tearing	7	9.72%	[4.00%, 19.01%]
Foreign body sensation	8	11.11%	[4.92%, 20.72%]
Pruritus	2	2.78%	[0.34%, 9.68%]
Others	7		
Signs			
Conjunctival hyperemia	14	19.44%	[11.06%, 30.47%]
JOAS Grade 1	10		
JOAS Grade 2	2		
JOAS Grade 3	1		
Pertaining to trauma	1		
Chemosis	2	2.78%	[0.34%, 9.68%]
Watery secretion	2	2.78%	[0.34%, 9.68%]
Others	7		

significant independent predictor of external ocular manifestations (OR=5.38, p=0.002), meaning males are 5.38 times more likely to develop ocular symptoms than females. Age, systemic comorbidities, ocular comorbidities, and COVID-19 severity are not significant predictors (p>0.05).

Among the participants included in the study, 23 subjects (31.9%) presented with external ocular manifestations as listed in Table 2. Foreign body sensation was noted to be the most observed ocular symptom (11.1%) while conjunctival hyperemia was the most prevalent ocular finding (19.4%). Figure 1 shows photographs of ocular findings observed in patients with COVID-19, including conjunctival hyperemia, chemosis, and watery discharge.

Systemic manifestations were also noted among all participants as shown in Table 3, including cough (29.2%), fever (23.6%), sore throat (9.7%), dyspnea (12.5%), diarrhea (6.9%), malaise (8.3%) and other symptoms (19.4%) such as anosmia, headache, abdominal pain, and bipedal edema. Among patients with ocular manifestations, cough (33.3%) was noted to have the highest prevalence. However, on analysis, there is no sufficient evidence to conclude that there is association between presence of external ocular manifestations with the different initial clinical presentation of the COVID-19 disease.

The onset of systemic and ocular manifestations was taken into account (Table 4). Among the participants who

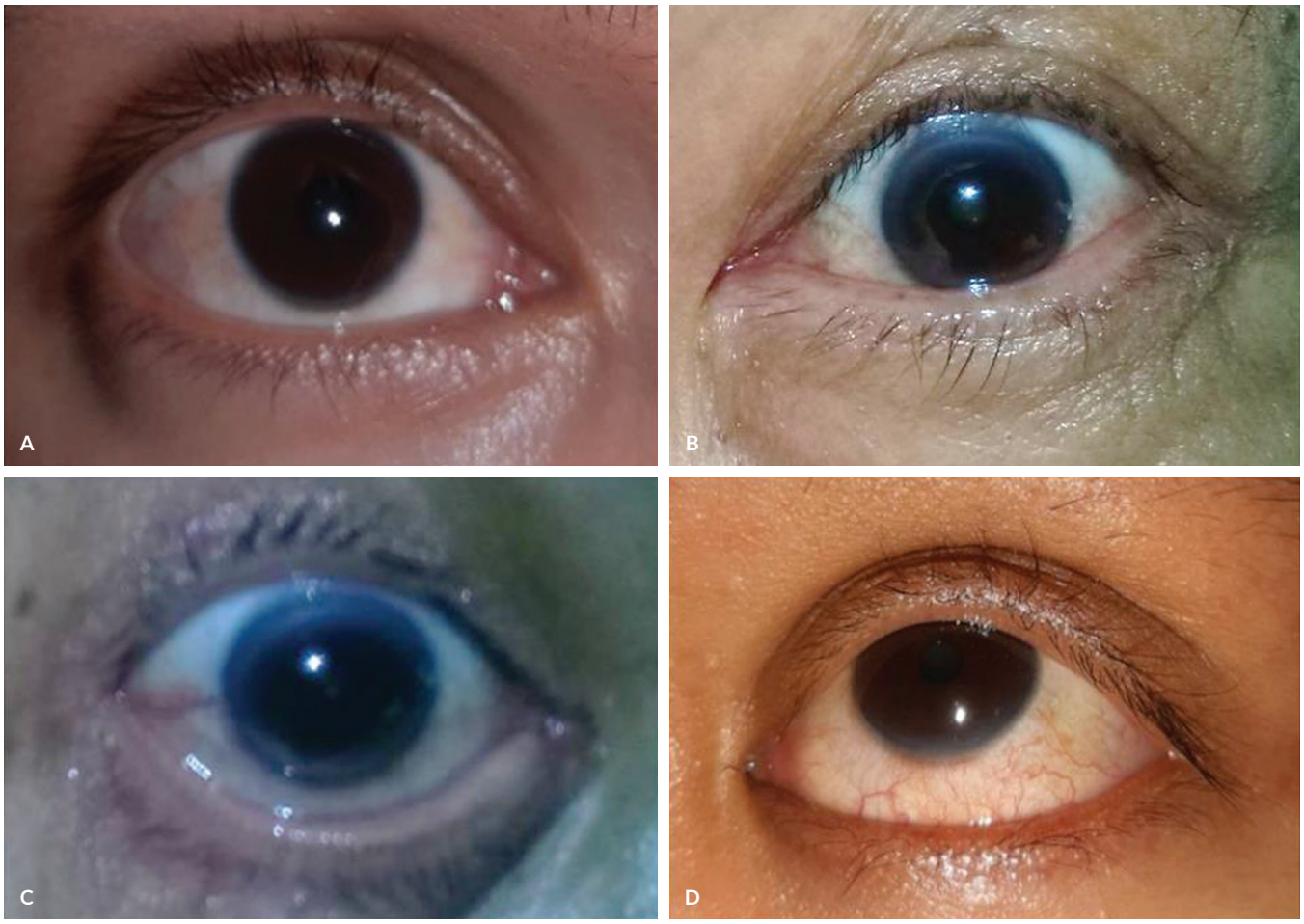

Figure 1. Representative photographs of ocular findings observed in patients with COVID-19. **(A)** Right eye showing conjunctival hyperemia of the inferior half of the bulbar conjunctiva. **(B)** Left eye showing conjunctival hyperemia of the inferior half of the bulbar conjunctiva. **(C)** Right eye showing conjunctival hyperemia and chemosis of the inferior half of the bulbar conjunctiva with watery discharge. **(D)** Left eye showing diffuse conjunctival hyperemia of the bulbar conjunctiva.

Table 3. Systemic Manifestations of Participants with COVID-19 and its Association with Presence of External Ocular Manifestations

	All Participants (n = 72)		According to External Ocular Manifestations				
			With (n = 23)		Without (n = 49)		*p*-value
	Count	Proportion	Count	Proportion	Count	Proportion	
Fever	17	23.61%	5	29.41%	12	70.59%	0.798
Cough	21	29.17%	7	33.33%	14	66.67%	0.871
Sore throat	7	9.72%	1	14.29%	6	85.71%	0.418
Dyspnea	9	12.50%	2	22.22%	7	77.78%	0.709
Diarrhea	5	6.94%	–	–	5	100.00%	0.170
Malaise	6	8.33%	1	16.67%	5	83.33%	0.657
Others	14	19.44%	4	28.57%	10	71.43%	1.000

experienced symptoms, 21 (29.2%) developed systemic manifestations alone, 10 (13.9%) developed ocular manifestations alone, and 13 (18.1%) participants developed both ocular and systemic manifestations. It can be noted that among those who developed both systemic and ocular manifestations, a majority of the participants (69.2%) developed systemic manifestations first (15 ± 7 days interval) prior to the onset of ocular manifestations. Only one participant developed ocular manifestations prior to the onset of systemic manifestations wherein eye redness, eye pain, tearing, foreign body sensation,

Figure 2. Patient diagnosed with preseptal cellulitis presenting with right lower lid swelling and abscess formation, conjunctival hyperemia, chemosis, and mucopurulent discharge.

Table 4. Initial Clinical Presentation of the COVID-19 Disease of the Participants and its Temporal Relationship with Presence of Ocular Manifestations

Symptoms	Count	Proportion	Interval
Asymptomatic	28	38.89%	
Systemic only	21	29.17%	
Ocular only	10	13.89%	
Both systemic and ocular	13	18.06%	
Presented together	3	23.08%	–
Systemic before ocular	9	69.23%	15 ± 7 days
Ocular before systemic	1	7.69%	2 days

and lid swelling with abscess formation (Figure 2) were noted two days prior to the development of cough and fever, and he was later diagnosed with preseptal cellulitis.

Physical examination and laboratory findings of the patients were also documented. While acute phase reactants such as CRP and ferritin were noted to be elevated in patients with ocular manifestation, the differences in these parameters were not statistically significant. Among the observed parameters, a low positive correlation between presence of external ocular manifestations and Temperature and AST was observed. There is negligible correlation between presence of external ocular manifestations and the rest of the parameters measured.

DISCUSSION

Investigations in the ocular involvement in the disease process of COVID-19 have been conducted. Few studies have documented the presence of coronavirus in the tear samples of humans.[10,11] However, the detection rate of SARS-CoV-2 from conjunctival swabs is generally low.[13,14] In a literature review by Peng et al., the rate of viral detection from conjunctival swabs ranged from 0-8%.[13] In another meta-analysis by Lawrenson et al., the pooled estimate for the detection of SARS-CoV-2 in conjunctival swabs was 3%.[14]

Rates of detection of SARS-CoV-2 were noted to be low from studies but does not necessarily equate to the prevalence of ocular manifestations in affected patients. Many studies have shown that ocular manifestations can occur in infected patients regardless of the viral prevalence in conjunctival swabs.[11,13,14] In the same literature review by Peng et al. involving twelve studies, the prevalence of ocular manifestations ranged from 0-32% with the most common ocular manifestation grouped into signs and symptoms consistent with conjunctivitis.[13] In a systematic review by Inomata et al., 11.2% of the sample presented with ocular manifestations.[15] Findings of conjunctivitis such as hyperemia, pruritus, foreign body sensation, and epiphora were also the leading symptoms (86.4%). Moreover, aside from external ocular manifestations, some case reports have also detailed occurrence of panuveitis, optic neuritis, vitreous hemorrhage, and macular neuroretinopathy in a few patients.[16-18]

Prevalence of ocular manifestations in patients with COVID-19 (31.9%) reported in this study was within the range (0-32%) reported by Peng et al.[13] Foreign body sensation was noted to be the most prevalent ocular symptom (11.1%) while conjunctival hyperemia was the most prevalent ocular finding (19.4%). The rest of the ocular symptoms observed were eye redness, eye pain, tearing, pruritus, blurring of vision, mucopurulent discharge, and lid swelling while the rest of the ocular signs observed were chemosis, watery secretion, subconjunctival hemorrhage, periorbital edema, and lid swelling. Several studies have reported similar ocular findings with varying prevalence. Two prospective cross-sectional studies by Zhou et al. and Hong et al. detailed the ocular symptoms in adult patients with COVID-19 in China.[19,20] Out of 121 recruited subjects, eight (6.6%) presented with ocular symptoms with pruritus (62.5%) as the most common ocular symptom while the other study showed a higher prevalence (26.8%) of patients with ocular symptoms with dryness (33%) and eye redness (33%) as the most common ocular symptoms. Three studies conducted in Italy, Iran and Turkey by Abrishami et al., Cavalleri et al., and Öncül et al., respectively, aimed to investigate both ocular signs and symptoms observed in patients with COVID-19.[17,21,22] Prevalence of ocular signs and symptoms ranged from 4.5% - 64.8% with hyperemia (25% - 87.5%) as the most common ocular manifestation. In the previous studies, the mean age of participants ranged from 48-63 years old with a higher male to female ratio (1.41) that ranged from 1.3-3. In this study, the mean age was 41 years old (19-68), with a higher male to female ratio (2.83) as well. There were no significant differences in the ocular manifestations between males and females but the higher prevalence in the male population was suggested in some studies to be attributed to the biological differences in immune responses to SARS-CoV-2.[23] According to a study by Conti et al., women are less susceptible to viral infections than men based on innate immunity, higher load of antibody

production, steroid hormones, and factors related to sex chromosomes.[23]

Ocular manifestations observed in this study were consistent with symptoms and findings of other known viral conjunctivitis, such as conjunctival hyperemia, discharge, foreign body sensation, and pruritus. A study by Güemes-Villahoz et al. detailed their observations regarding the clinical characteristics of conjunctivitis in COVID-19 as compared to adenoviral conjunctivitis.[24] The onset for both diseases were noted be abrupt but COVID-19 conjunctivitis was noted to be more self-limiting with a faster rate of improvement. Conjunctival hyperemia was noted to be milder in presentation with mild follicular reaction and no associated corneal infiltrates, membranes or pseudomembranes. Temporal pattern with onset of systemic symptoms was noted to be variable. In this study, the duration of ocular symptoms lasted for 5-12 days and spontaneously resolved without medical treatment, except for one participant who was diagnosed to have concurrent preseptal cellulitis and was treated with topical and oral antibiotics.

One of the proposed mechanisms in the infection process of SARS-CoV-2 is through the binding of the viral protein to human angiotensin-converting enzyme 2 (ACE2) receptors.[25] These receptors are expressed in the majority of human tissues in varying degrees, mainly expressed in the alveolar epithelial cells and with lower amounts on the nasopharynx, and oral and nasal mucosa. Although not well-established as of present, several studies have attempted to determine the expression of ACE2 receptors in ocular tissues, which can serve as a potential route in the transmission of the virus.[25-27] The presence of these receptors in the ocular tissues may also provide a possible explanation to the presence of ocular manifestations in patients with COVID-19.[13] In a study by Sungnak et al., multiple organs were examined to determine the expression of ACE2 receptors, these receptors were found to be expressed in the corneal epithelial cells as well.[26] In contrast to the cornea, expression of ACE2 receptors in the conjunctiva was observed to be lower.[28] This potential route of viral transmission through the ocular tissue can also serve as a possible conduit of transmission to the respiratory tract through its connection via the nasolacrimal duct. However, limited studies have been conducted to support this possibility.

Some studies have discussed the association of external ocular manifestations with the severity of COVID-19 infection. In this study, majority of the patients (77.8%) were classified under the mild category. However, there was no sufficient evidence to conclude that there is association between presence of external ocular manifestations and COVID-19 clinical classification. Several studies have varying results. In the study by Abrishami et al., the frequency of ocular finding was proportional to the severity of the disease (82.1%).[21] The odds of developing chemosis were higher in patients admitted to the intensive care unit. A systematic review and meta-analysis by Aggarwal et al. reported the occurrence of ocular manifestations in patients with severe pneumonia (pooled estimate: 6.91%).[29] However, in the study by Güemes-Villahoz et al., no correlation was found between the COVID-19 severity score and the presence of conjunctivitis.[24]

Chronological sequence of ocular manifestations relative to the systemic symptoms was noted in this study. A higher percentage of patients presented with systemic symptoms prior to the onset of ocular symptoms with an interval of 15 ± 7 days. Only one patient developed ocular symptoms as the initial complaint which presented two days prior to the onset of systemic symptoms. Some studies have reported ocular symptoms as the initial presenting symptoms in patients with confirmed COVID-19. In the similar study by Aggarwal et al., pooled estimate from five studies showed that ocular symptoms were the initial manifestation in 2.26% of patients.[29] In a systematic review by Inomata et al., 12.5% of patients developed ocular symptoms with an interval of three to five days prior to development of systemic symptoms.[15] In a case report by Ozturker, a patient presented with conjunctivitis as the sole manifestation of COVID-19.[30]

Correlation between external ocular manifestations and systemic laboratory parameters of patients with COVID-19 was also determined. In this study, CRP and ferritin levels were noted to be higher in patients with external ocular manifestations, however, these differences were not statistically significant. Similarly, in a study by Cavalleri et al., CRP and ferritin levels were noted to be higher in patients with ocular symptoms.[22] They believed, however, that these results were a consequence of a higher prevalence of patients with advanced disease wherein inflammatory markers are expected to be elevated.

This study had some limitations. Several confounders may have influenced the findings, including pre-existing ocular conditions and concurrent medications, which could contribute to conjunctival hyperemia independent of COVID-19. Disease severity may have also affected ocular findings, with more severe cases potentially exhibiting different manifestations. Additionally, hospital-related factors such as prolonged PPE use, mechanical ventilation, and ICU admission could cause ocular irritation and tear film changes. Demographic and systemic factors like age, sex, diabetes, hypertension, and autoimmune diseases may further impact inflammatory responses and ocular health. While some confounders, such as demographic and systemic factors, pre-existing ocular conditions, and COVID-19 severity, were analyzed, the effects of other potential confounders were not fully controlled. Moreover, the clinical and ophthalmologic evaluation did not include milder cases managed conservatively as outpatient, which limited the epidemiological findings to the hospitalized population only. Additionally, a comprehensive ophthalmologic examination to include the investigation of the intraocular condition was not performed in this study, owing to logistical challenges and additional risk to both the investigators and participants.

This study acknowledges potential sources of bias that may have influenced the findings. Selection bias may be present, as the study was conducted in a single COVID-19 referral center, which may not be representative of the general population; future multi-center studies are recommended. Recall bias may also be present but was minimized by using hospital records and standardized patient interviews. Observer bias was mitigated by using an objective grading system for documenting particular ophthalmologic manifestations. Finally, confounding bias, particularly sex, age, comorbidities, and disease severity, was managed through multivariate regression and stratified analysis. By implementing these strategies, the study aimed to improve the reliability of findings and reduce potential biases. However, future research should consider blinded assessments, larger sample size, and multi-center approaches to further improve the validity and generalizability of results.

CONCLUSION

Among the 72 participants in this study, all of whom were hospitalized for COVID-19, 31.9% presented with ocular manifestations; with foreign body sensation as the most prevalent ocular symptom (11.1%) and conjunctival hyperemia (19.4%) as the most prevalent ocular sign. The median age of patients with ocular manifestations was 41 years old with a higher proportion observed in the male population (73.9%). No significant correlation was observed between presence of external ocular manifestations and the different systemic and ocular co-morbidities as well as with COVID-19 clinical classification. Majority of the patients experienced systemic symptoms prior to the onset of ocular symptoms however, the latter can also be the initial complaint as observed in one patient. Ocular complaints can also present as the sole manifestation. Several laboratory parameters were measured and only temperature and AST levels showed a low positive correlation with the presence of ocular manifestations.

While not considered a main manifestation of COVID-19, findings of the study show that ocular manifestations occur in roughly one third of patients in this population of hospitalized COVID-19 patients, with some cases presenting ocular symptoms as the sole indication of infection. This suggests the possibility of the ocular surface as an entry point and a potential conduit for the transmission of the virus. It also serves as a cautionary reminder that conjunctivitis may indicate COVID-19. With some individuals presenting with ocular symptom as the initial and sole manifestation, healthcare practitioners must exercise caution and remain vigilant in managing patients who would present as such. To our knowledge, this is the first local study to explore external ocular manifestations in Filipino COVID-19 patients.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

The study was funded by the University of the Philippines – Philippine General Hospital Expanded Hospital Research Office (UPM-PGH EHRO).

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506. doi: 10.1016/S0140-6736(20)30183-5. PMID: 31986264. PMCID: PMC7159299.
2. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. doi: 10.1056/NEJMoa2002032. PMID: 32109013. PMCID: PMC7092819.
3. Auwaerter P. Coronavirus [Internet]. 2020 [cited 2020 Apr 1]. Available from: https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540143/all
4. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 [Internet]. 2020 [cited 2020 May 21]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
5. World Health Organization. Coronavirus disease (COVID-2019) situation reports [Internet]. 2021 [cited 2021 Sep 21]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
6. Department of Health. Updates on novel Coronavirus Disease (COVID-19) [Internet]. 2021 [cited 2021 Sep 8]. Available from: https://www.doh.gov.ph/2019-nCoV.
7. Philippine General Hospital - Hospital Infection Control Unit. COVID-19 Daily Report. Report, Philippine General Hospital, Philippines, 2021 September 8.
8. Chan W, Liu D, Chan P, Chong K, Yuen K, Chiu T, et al. Precautions in ophthalmic practice in a hospital with a major acute SARS outbreak: An experience from Hong Kong. Eye. 2006;20:283–289. doi: 10.1038/sj.eye.6701885. PMID: 15877099. PMCID: PMC7091695.
9. Philippine Society for Microbiology and Infectious Diseases. Interim guidelines on the clinical management of adult patients with suspected or confirmed COVID-19 infection. Report, PSMID, Philippines, 2020 March 31.
10. Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L, et al. Characteristics of ocular findings of patients with Coronavirus Disease 2019 (COVID-19) in Hubei Province, China. JAMA Ophthalmol. 2020;138(5):575–8. doi: 10.1001/jamaophthalmol.2020.1291. PMID: 32232433. PMCID: PMC7110919.
11. Xia J, Tong J, Liu M, Shen Y, Guo D. Evaluation of coronavirus in tears and conjunctival tears of patients with SARS-CoV-2 infection. J Med Virol.2020;1–6. doi: 10.1002/jmv.25725. PMID: 32100876. PMCID: PMC7228294.
12. Takamura E, Uchio E, Ebihara N, Ohno S, Ohashi Y, Okamoto S, et al. Japanese guidelines for allergic conjunctival diseases. Allergol Int. 2017;66:220–9. doi: 10.1016/j.alit.2016.12.004. PMID: 28209324.
13. Peng M, Dai J, Sugali C, Rayana N, Mao W. The role of the ocular tissue in SARS-CoV-2 transmission. Clin Ophthalmol. 2020; 14: 3017–24. doi: 10.2147/OPTH.S269868. PMID: 33061288. PMCID: PMC7537833.
14. Lawrenson J, Buckley R. COVID-19 and the eye. Ophthalmic Physiol Opt. 2020; 40:383–8. doi: 10.1111/opo.12708. PMID: 32627913. PMCID: PMC7361197.

15. Inomata T, Kitazawa K, Kuno T, Sung, J, Nakamura, M, Iwagami M, et al. Clinical and prodromal ocular symptoms in coronavirus disease: A systematic review and meta-analysis. Invest Ophthalmol Vis Sci. 2020;61(10):1–4. doi: 10.1167/IOVS.61.10.29. PMID: 32797198. PMCID: PMC7441339.
16. Benito-Pascual B, Gegúndez J, Díaz-Valle D, Arriola-Villalobos P, Carreño E, Culebras E, et al. Panuveitis and optic neuritis as a possible initial presentation of the novel Coronavirus Disease 2019 (COVID-19). Ocul Immunol Inflamm. 2020;8:922–5. doi: 10.1080/09273948.2020.1792512. PMID: 32870739.
17. Öncül H, Öncül F, Alakus M, Çağlayan M, Dag U. Ocular findings in patients with coronavirus disease 2019 (COVID-19) in an outbreak hospital. J Med Virol. 2020;0–3. doi: 10.1002/jmv.26412. PMID: 32776614. PMCID: PMC7436579.
18. Gascon P, Briantais A, Bertrand E, Ramtohul P, Comet A, Beylerian M, et al. COVID-19-associated retinopathy: a case report. Ocul Immunol Inflamm. 2020;28:1293–7. doi: 10.1080/09273948.2020.1825751. PMID: 33021856.
19. Zhou Y, Duan C, Zeng Y, Tong Y, Nie Y, Yang Y, et al. Ocular findings and proportion with conjunctival SARS-COV-2 in COVID-19 patients. J. Ophthalmol. 2020;127:982–3. doi: 10.1016/j.ophtha.2020.04.028. PMID: 32359840. PMCID: PMC7194804.
20. Hong N, Yu W, Xia J, Shen Y, Yap M, Han W. Evaluation of ocular symptoms and tropism of SARS-CoV-2 in patients confirmed with COVID-19. Acta Ophthalmol. 2020;98(5):649-55. doi: 10.1111/aos. 14445. PMID: 32336042. PMCID: PMC7267628.
21. Abrishami M, Tohidinezhad F, Daneshvar R, Omidtabrizi A, Amini M, Sedaghat A, et al. Ocular manifestations of hospitalized patients with COVID-19 in northeast of Iran. Ocul Immunol Inflamm. 2020; 28:739-44. doi: 10.1080/09273948.2020.1773868. PMID: 32569494.
22. Cavalleri M, Brambati M, Starace V, Capone L, Nadin F, Pederzolli M, et al. Ocular features and associated systemic findings in SARS-CoV-2 infection. Ocul Immunol Inflamm. 2020;28:916–21. doi: 10.1080/09273948.2020.1781198. PMID: 32870738.
23. Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. J Biol Regul Homeost Agents. 2020;34(2):339-43. doi: 10.23812/Editorial-Conti-3. PMID: 32253888.
24. Güemes-Villahoz N, Burgos-Blasco B, García-Feijoó J, Sáenz-Francés F, Arriola-Villalobos P, Martinez-de-la-Casa J, et al. Conjunctivitis in COVID-19 patients: frequency and clinical presentation. Graefe's Arch Clin Exp Ophthalmol. 2020;258: 2501–7. doi: 10.1007/s00417-020-04916-0. PMID: 32860573. PMCID: PMC7455778.
25. Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care. 2020;24:422. doi: 10.1186/s13054-020-03120-0. PMID: 32660650. PMCID: PMC7356137.
26. Sungnak W, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med. 2020; 26:681–7. doi: 10.1038/s41591-020-0868-6. PMID: 32327758. PMCID: PMC8637938.
27. Zhou L, Xu Z, Castiglione G, Soiberman U, Eberhart C, Duh E. ACE2 and TMPRSS2 are expressed on the human ocular surface, suggesting susceptibility to SARS-CoV-2 infection. Ocul Surf. 2020;18:537-44. doi: 10.1016/j.jtos.2020.06.007. PMID: 32544566. PMCID: PMC7293510.
28. Lange C, Wolf J, Auw-Haedrich C, Schlecht A, Boneva S, Lapp T, et al. Expression of the COVID-19 receptor ACE2 in the human conjunctiva. J Med Virol. 2020;92:2081–6. doi: 10.1002/jmv.25981. PMID: 32374427. PMCID: PMC7267303.
29. Aggarwal K, Agarwal A, Jaiswal N, Dahiya N, Ahuja A, Mahajan S, et al. Ocular surface manifestations of coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. PLoS One. 2020;15(11). doi: 10.1371/journal.pone.0241661. PMID: 33151999. PMCID: PMC7643964.
30. Ozturker Z. Conjunctivitis as sole symptom of COVID-19: A case report and review of literature. Eur J Ophthalmol. 2021;31(2):161-6. doi: 10.1177/1120672120946287. PMID: 32703010. PMCID: PMC7383095.