Correlation of ocular manifestations with severity of systemic disease and conjunctival SARS-CoV-2 in COVID-19 Positive patients

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DOI:10.56018/20230617

Abstract
Background: Ocular manifestations of SARS-CoV-2 and the associated risk factors require a comprehensive analysisincludingConjunctival swab (CS) RT-PCR results irrespective of ocular involvement. **Aims**: To study the correlation of ocular manifestations & systemic COVID-19 status with clinical risk factors, during first & second outbreaks (FO & SO) of COVID19 pandemic in western India. CS RT-PCR results of diagnosed COVID-19 patients with positive nasopharyngeal swab (NPS) RT-PCR with or without ocular manifestations to be evaluated. **Material and Methods:** Prospective study conducted with confirmed COVID-19 cases with positive NPS RT-PCR during FO & SO of COVID-19 pandemic in year 2020 & 2021 in western India. Ocular manifestations & CS RT-PCR results were evaluated with systemic COVID-19 status. CS was collected within 48 hours of admission for RT-PCR analysis with repeat test within 72 hours upon increasing severity of COVID-19 stage. **Result:** Thirty-two (20.51%,13 FO,19 SO) patients had uniocular complaints, redness being the commonest during both the outbreaks. Out of 32 patients with ocular symptoms (OS), 87.5% had refractive error, 75% had diabetes & 53.1% had moderate COVID-19, (*P=<0.0001,* significant). 25% & 18.8% patients with OS had history of use of protective eye gears & covid vaccine respectively. 103 & 80 CS from 103 & 53 patients of FO & SO respectively were tested. All primary (183) & repeat (93) CS were negative for RT-PCR.**Conclusion:** Ocular involvement in diagnosed COVID-19 cases is variable. SARS-CoV-2 presence in conjunctival samples is inconsistent irrespective of systemic severity, probably due to intermittent shedding of virus.
Keywords: COVID-19 ocular manifestations, first outbreak, second outbreak, CS RT-PCR

Introduction

Coronavirus disease 2019 (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic since its emergence in December 2019. Ophthalmologists are one of most vulnerable medical sub specialists at risk of becoming infected, because of the proximity to the mucosal surfaces during evaluation of the patients with ophthalmic equipment.[1] There have been several reports of COVID-19 with involvement of unprotected eyes in medical & paramedical staff with nosocomial transmission of the SARS-CoV-2 as a potential route.[2,3] Among the ocular manifestations of COVID-19, conjunctivitis is the most prevalent manifestation with or without presence of viral RNA in conjunctival specimens unrelated to viral RNA from nasopharyngeal swab (NPS) orthroat swabs.[4,5,6]
The present study from western India aims to evaluate ocular manifestations & systemic COVID-19 status with clinical risk factors during first & second outbreaks (FO & SO) in year 2020 & 2021.Conjunctival swab (CS) RT-PCR results of diagnosed COVID-19 patients with positive NPS RT-PCR with or without ocular symptoms will be correlated.

Material and Methods

This prospective study was conducted at a dedicated tertiary covid care center in western India after institutional ethical committee clearance (ECR/72/Inst/GJ/2013/RR-2019) during FO (September to December 2020) & SO (April to July 2021).[7]

COVID-19 patients with positive NPS RT-PCR report admitted in the covid care hospital for the same & willing to be part of study were included. Suspected or indeterminate COVID-19 and confirmed cases of COVID-19 managed as outdoor patients for home isolation were excluded. Also, patients with history of ocular/extraocular surgery within 6 months of covid diagnosis were not included.

Data were collected in form of demographic details, systemic COVID-19 stage details, risk factors & comorbidities during the period of admission. Presence of COVID-19 was confirmed by NPS positivity with or without symptoms of severe respiratory distress & characteristic chest imaging (radiograph and computed tomographic scan with ground glass opacification) with clinical covid status graded as per guidelines by Ministry of Health and Family Welfare (e.g., mild, moderate & severe).[8] History of COVID-19 vaccination amongst the infected was considered during second outbreak.

Ocular history included details of ocular manifestations (e.g., redness, itching, foreign body sensation, mucoid discharge etc.), history of refractive errors, use of any eye protection devices for COVID-19 & history of hand-eye contact. Bedside torch light eye examination of lids, conjunctiva & cornea were performed for both eyes.

A conjunctival swab (CS) was taken within 48 hours of admission with or without ocular manifestations after obtaining a well-informed consent. An alternate eye in absence of ocular involvement & affected eye in case of ocular involvement was considered for sample collection in FO. Both eye samples individually were considered during SO to improve detection in either eye of individual patient. The sample for CS was collected without topical anaesthesia from lower fornix, with sweeping motion of sterile swab stick for few seconds with minimum discomfort to the patient by trained ophthalmic resident posted for covid duty. The swab stick was kept in dedicated vial for transport to microbiology laboratory located in same campus for further processing as per the manufacturer's instructions of the kit. [9]. Use of personal protective equipment (PPE) during entire process of examination of patients, collection & transportation of sample was ensured. Repeat CS sample were collected in similar manner after 72 hours of first CS collection in co-operative patients upon systemic covid severity progression.

Positive & negative results for presence or absence of SARS-CoV-2 respectively were provided. The database was maintained using excel sheet. Statistical analysis was done using SPSS version 26 (Chi-square test for categorical variables. Independent t-test and ANOVA for continuous variables). A P value of <0.05 was considered to be statistically significant.

Results

Demographic details, details of comorbidities & COVID-19 status & other information collected are as per table 1 for both the outbreaks. Hypertension (75,72.8 %) was the most common co-morbidity in FO (statistically significant, P< *.0001*) & diabetes (20,37.7%) in the SO (P= *.5964*, non-significant). Ten out of 53 (18.9%) patients presented with clinical signs of rhino-orbital mucor-mycosis as presenting features of COVID-19 during SO. None of the patient was health personnel in the present study.

Out of 32 patients with ocular complaints ,17(53.1%) had moderate COVID -19 stage & 24 (75%) patients had diabetes as most associated co-morbidity. (*P=<0.0001,* significant). Presence of systemic complaints of COVID-19 at the time of collection of CS was statistically significant (P=*.0003*) in OS group however presence of fever at time of collection of samples was not found to be significant (4,12.5%patients, P= *.7859*). History of refractive error in 28(87.5 %) patients of OS group compared to 70(56.5 %) in ONS group was statistically significant (P < *.0001*). Other information for OS & ONS group are as per table 2.

All involved eyes were having unilateral presentation. Six out of 19 (31.58%) patients in-spite of using protective eye gears developed ocular symptoms during SO (P=*.0139*, significant). Also 6 out of 19 patients during SO with ocular complaints had history of covid vaccination (first dose of Covishield™). During FO, 3 patients (tablet oseltamivir phosphate 75 mg twice daily) & during SO, 8 patients (injection remdesivir 200 mg as per schedule) received systemic antiviral therapy for COVID-19. Other observations of OS patients for FO & SO are as per table 3.

Table 1. Details of patients from first & second outbreaks (FO & SO).

Variables		**FO N (%) 103(66.02)**	**SO N (%) 53(33.97)**	**P-Value**	**Total**
Age (years)		57.83 ± 14.70	51.21 ± 14.44	0.008	55.57
Gender	Female	32 (31.1)	22(41.5)	0.2163	54 (34.6)
	Male	71(68.9)	31(58.5)		102(65.4)
Systemic co-morbidities: Diabetes Hypertension Hyperthyroidism Rhino-orbital mucor-mycosis Ischemic heart disease		 34 (33) 75(72.8) 0(0) 0(0) 2(1.9)	 20(37.7) 10(18.9) 2(3.8) 10(18.9) 0(0)	 0.5964 <0.0001 - - -	 54(34.6) 85(54.5) 2(1.3) 10(6.4) 2(1.3)
Systemic covid status	Mild	30(29.1)	32(60.4)	<0.0001	62(39.7)
	Moderate	18 (17.5)	16(30.2)		34(21.8)
	Severe	55(53.4)	5(9.4)		60(38.5)
CS collected	Unilateral	103(100)	26 (49.05)	<0.0001	129(82.69)
	Bilateral	0(0)	27 (50.94)		27(17.4)
Ocular Symptoms present		13 (12.6)	19 (35.8)	<0.0001	32(20.5)
Refractive Error		62(60.2)	36 (67.9)	0.3850	98(62.8)
Systemic symptoms at time of CS collection		28(27.2)	24(45.3)	0.0310	52(33.3)
Average duration of systemic disease at time of first CS collection		7.31 ± 2.81	6.42+/-2.1	0.3140	7.769+/- 2.29
Fever at time of CS collection		17(16.5)	7(13.2)	0.6470	24(15.4)
Ventilator Patient		55(53.4)	5(9.4)	<0.0001	61(39.1)
Repeat CS		46(44.7)	47(88.7)	<0.0001	93(59.6)
Mortality		33(32)	12(22.6)	0.2650	45(28.8)
Vaccination		0(0)	25(47.2)	-	25(16)
Exposure of Covid Patient		59(57.3)	25(47.2)	0.2410	84(53.8)

All patients had onset of ocular complaints post systemic covid manifestations. They received artificial tear substitutes (carboxy methyl cellulose 0.5 % QID or higher if required) &Fluoro-metholone 0.1% eyedrops QID with tapering of frequency as per clinical response in an individual. All survivors (24) of COVID-19 patients during admission showed improvement in symptoms & signs clinically with topical regime. Details of ocular symptoms are as per table 4.

Number of CS collected were 103 during FO from 103 patients. Number of CS collected were 80 during SO from 53 patients as in 27 patients, collection was from both eyes & rest of the patients not consented for contralateral collection of CS after first sample. Repeat CS were collected in total 93(59.6%) patients to corelate CS results with increasing severity of systemic disease with viral load. Repeat NPS were restricted for comparison with repeat CS in this study due to local discharge policy for COVID-19 cases. (Repeat NPS was done for severe COVID-19 cases only before discharging them after stable clinical recovery which otherwise would not match the timing of repeat CS in present study). Results of all the CS were available within 36 hours of CS collection. All the primary & repeat CS samples were negative for both ocular symptomatic & non-symptomatic group. Other details of repeat CS are as per table 5.

Table 2. Details of ocular symptomatic (OS) & non-symptomatic (ONS) patients.

Variable		**OS N/% 32/20.5**	**ONS N/% 124/79.48**	**P-Value**	**Total (%)**
Age (mean years)		57.83 ± 14.70	51.21 ± 14.44	0.008	55.577
Gender	Female	11 (34.4)	43(34.7)	1.0000	54(34.6)
	male	21(65.6)	81(65.3)		102(65.4)
Systemic co-morbidities: Diabetes Hypertension Hyperthyroidism Rhino-orbital mucor-mycosis Ischemic heart disease		 24 (75) 12(37.5) 1(3.1) 10(31.3) 0(0)	 30(24.2) 73(58.9) 1(0.8) 0(0) 2 (1.6)	 <0.0001 0.0450 0.3690 - -	 54(34.6) 85(54.5) 2(1.3) 10(6.4) 2(1.3)
Systemic covid status	Mild	7(21.9)	55(44.4)	<0.0001	62(39.7)
	Moderate	17(53.1)	17(13.7)		34(21.8)
	Severe	8(25)	52(41.9)		60(38.5)
CS collected	Unilateral	29(90.6)	100 (80.6)	0.2890	129 (82.69)
	Bilateral	3 (9.4)	24(19.4)		27(17.4)
Systemic symptoms at time of CS collection		18(56.3)	34(27.4)	0.0003	52(33.33)
Fever		4(12.5)	20 (16.1)	0.7859	24 (15.38)
Ventilator Patient		8(25)	53(42.7)	0.0716	61 (39.10)
Mortality		8(25)	37(29.8)	0.6660	45(28.8)
Repeat Sample		29(90.6)	64(51.6)	<0.0001	93 (59.61)
Vaccination		6(18.8)	19(15.3)	0.599	25(16)
Exposure to Covid Patient		17(53.1)	67 (54)	0.2410	84(53.8)
Refractive Error		28(87.5)	70(56.5)	<0.0001	98 (62.82)
Use of eye protective gears		8(25)	17(53.1)	1.0000	25(16)
History of systemic antiviral medication		11(34.4)	43(34.7)	1.0000	54(34.6)

Table 3. Details of ocular symptomatic patients for first & second outbreaks (FO & SO)

Variable		**FO N/% 13/12.62**	**SO N/% 19/35.84**	**P Value**
Age		56.77 ± 11.71	53.32 ± 16.36	0.518
Gender	Female	5 (38.5)	6 (31.6)	0.7210
	Male	8 (61.5)	13 (68.4)	
Systemic co-morbidities Diabetes Hypertension Hyperthyroidism Rhino-orbital mucor-mycosis Ischemic heart disease		 8 (61.5) 7 (53.8) 0 (0) 0 (0) 0 (0)	 16 (84.2) 5(26.3) 1 (5.3) 10 (52.6) 0(0)	 0.2190 0.1500 - - -
Systemic covid status	Mild	4 (30.8)	3 (15.8)	<0.0001
	Moderate	1 (7.7)	16 (84.2)	
	Severe	8 (61.5)	0 (0)	
CS collected	Unilateral	13 (38.5)	16(36.8)	0.3090
	Bilateral	0 (0)	3 (15.8)	
Systemic symptoms at time of CS collection		4 (30.8)	14 (73.7)	0.0290
Refractive Error		9(69.2)	19 (100)	0.0200
Fever		2 (15.4)	2 (10.5)	1.000
Mortality		3 (23.1)	5(26.3)	1.000
Vaccination		0 (0)	6 (31.6)	-
Exposure of Covid Patient		7 (53.8)	10 (52.6)	1.000
Use of eye protective gears		2(15.3%)	6(31.58%)	0.0139
Systemic antiviral therapy		3(23.07%)	8(42.10%)	0.2656

Table 4. Details of Ocular symptoms for first & second outbreaks. (FO & SO)

Ocular symptoms N/% (32 out of156 patients/20.51)	**FO N/% (13/ 40.62)**	**SO N/% (19/59.37)**	**P-Value**	**Mean ± SD Duration since onset (days)**
Onset (days)	2.62 ± 1.12	3.16 ± 1.50	0.2770	
Lid swelling 10/6.41	02(15.38) 4±1.42	08(42.11) 3.5±1.86	0.1149 0.4197	 3.6± 1.72
Foreign Body Sensation 11/7.05	03(23.07) 3.34±1.53	08(42.11) 3.63±1.93	0.2733 0.6542	 3.55±1.76
Redness 30/19.23	11(84.62) 2.37±0.93	19(100) 3.17±1.55	0.0822 0.1068	 2.87±1.36
Itching 03/1.92	02(15.38) 3±0	1(5.26) 2±0	0.3423	 2.67±0.58
Mucoid discharge 26/16.66	08(61.54) 2.25±1.04	18(94.74) 3.23±1.52	0.0200 0.0525	 2.87±1.36

Table 5. Details of repeat conjunctival swabs

Repeat CS	FO (N/%)	SO (N/%)	P- value
OS (32) ONS (124)	10(21.73%) 36(78.26%)	19(40.4%) 28(59.57%)	0.05178
Systemic covid status Mild Moderate Severe	 13(28.26%) 6(13.04%) 27(58.69%)	 26(55.31%) 16(34.04%) 5(10.6%)	 0.00001

Discussion

Conjunctiva as an unprotected mucous membrane may act as both the entry and exit site of the virus, either due to direct inoculation by the infected droplets; & indirectly via the nasolacrimal duct as a migration route of the virus to the upper respiratory tract, or haematogenic infection of the lacrimal gland. [10,11]

In the present study, the authors found hypertension (65.4%) & diabetes (34.6%) as the commonest comorbidities similar to but higher than reported by other authors with or without any ocular manifestations. [12,13,14]. Diabetes was more common in OS patients & ocular symptoms as a spectrum of rhino-orbital mucor-mycosis in addition to other comorbidities during second outbreak was observed in present study. Also, in-spite of 60(38.5%) patients having severe COVID 19 (8, 25% patients in OS group) & 24(15.4 %) having fever at time of collection of CS, no CS was positive for RT-PCR in the current study similar to the study by Michele Cavalleri et al. [15] Absence of positive results can be due to low sensitivity of the kit used or low viral load in conjunctival samples or may be owing to intermittent viral shedding from tears during the disease course. [11] Simultaneously, late ocular manifestations & prolonged shedding of virus has been reported. [16,17] Subsequent serial CS sampling after second CS on worsening of systemic disease further was not available due to lack of consent from patients for the procedure.

Various studies have reported unilateral or bilateral ocular manifestations mainly in moderate to severe status of disease with timing of symptoms & signs suggestive of conjunctivitis being common in first or second weeks similar to present study. [2,15,18,19]Sindhuja K et al., reported ocular complaints with conjunctival congestion in 6.29% (8/11) patients even with mild COVID-19 stage, although no conjunctival specimen was subjected for RT-PCR analysis in their study.[5]. Chawhan A et al., also did not find any positive CS results in ocular symptomatic patients.[13] Since no CS was positive, correlation of CS sensitivity with severity of ocular involvement was not possible in present study.

Methods of tear sample collection either with CS method or Schirmer paper strip or combination of both methods from unilateral eye or simultaneously from both eyes have been used with a positive concordance on the same day or within 2 days of NPS positivity. However positive RT-PCR results in conjunctival secretions have been observed with CS method (57.1% by Azzolini C et al, 28.5% by Mahmoud H et al., & 14.7% by Arora R et al), hence the authors in present study preferred the same, although it is not patient friendly in absence of topical anaesthesia. [12,18,20,21] In the present study none of samples was rejected for RT-PCR analysis for the inadequacy of sample material.

Repeat sampling was used in various studies to yield maximum positivity of CS sample correlated with systemic disease severity as viral load detected in nasal and throat swabs have been shown to be elevated for a period of approximately 2 weeks from the onset of COVID-19 symptoms. [2,6,22] The present study has covered the duration (within 72 hours of first CS sample upon systemic disease progression) during hospitalization for repeat sampling to ensure reliability for corelation, however no positive results were found even in repeat CS samples.

The present study has the limitation that It did not have results for CT (cycle threshold) value available for CS (all negative) & no viral culture was performed from any sample collected during study period. Type of virus strain has not been identified (facility not available during study period) although it is presumed to be of different variant for each outbreak.[23] Since repeat NPS was not performed due to local discharge policy, CT value of NPS on worsening of systemic disease could not be considered for corelation of presumed high

viral load with CS results or ocular manifestations either. The study neither co-relates other laboratory parameters of covid severity & ocular involvement with CS RT-PCR results. However, this is the only study with large sample of patients & CS (156 patients,276 CS including repeat samples) with possibility of CS testing on different strain during first & second outbreaks & corelation of ocular features with systemic covid status for both the outbreaks in western India. Also, this study includes CS results & ocular presentations among covid vaccinated patients who presented with positive NPS RT-PCR during second outbreak which no study has reported yet in literature as per authors' knowledge.

In the present study among the patients with OS, 28(87.5%) had refractive error with history of glasses (no use of contact lens) which may be potential cause of ocular involvement due to hand eye touch, however 8(25%) patients in spite of wearing protective eye gears developed ocular symptoms questioning conjunctiva as a sole source for covid infection. Hence, conjunctival transmission of coronaviruses remains debatable & requires further studies with serial sampling, if possible. [12,24] Present study noticed history of first dose of covid vaccine in 6(18.8 %) & systemic antiviral medication for systemic COVID-19 in 11(34.4%) patients among OS group. Presence of viral particles in ocular samples with serum antiviral antibody titre or significance of antiviral agent concentration in blood or ocular sample may be explored in future studies, for association of ocular manifestations in active COVID-19 patients.

Conclusion

Ocular involvement & detection of SARS-CoV-2 in conjunctival samples of diagnosed COVID-19 cases are variable irrespective of systemic covid-19 severity probably due to intermittent shedding of virus from conjunctival secretions. Diabetes is a major risk factor in OS patients. Since the corona virus strains are still mutating & pandemic is still on with possibilities of future outbreaks, precautions & safety measures need to be continued by health care personnel at risk while ocular or systemic examination of all the patients.

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