Eyeing up the pandemic: A literature review of the ocular manifestations of COVID-19

*Ali Mardini,[1] Seemal Maqsood AbdulQadir,[1] Khaled Alhomsi[2]**

Abstract

Background Since the onset of SARS-CoV-2, this novel virus has been the focus of many studies seeking to improve the ability of healthcare systems to withstand pandemics against it. COVID-19 has pulmonary and cardiovascular implications, but its ocular effects remain a subject of debate.

Objectives The objective of our narrative review is to explore the ophthalmic manifestations of COVID-19, identify research gaps, and act as a guide for further research in the field.

Methods The literature search involved original studies published from January 1, 2020, up until August 20, 2021, on the PubMed database. Title and abstract screening and full text review were conducted by two independent researchers, with a third researcher resolving conflicts. Studies that met the set inclusion criteria were used for data synthesis.

Results The preliminary search generated 59 articles, with 25 being data extracted. Conjunctivitis, epiphora and ocular irritation were consistently stated anterior segment manifestations. Posterior segment implications were mostly subclinical, including cotton-wool spots and retinal nerve-fiber layer thinning, but some cases were more detrimental, such as central retinal vein occlusion, posterior segment inflammation, retinal hemorrhages, and fungal infiltration. RT-PCR tests were unreliable in detecting SARS-CoV-2 infection in ocular tissues, potentially due to methodological limitations.

Conclusion Anterior segment findings were significant manifestations of the novel coronavirus, but a clear resolution of posterior segment findings is yet to be made. In the absence of reliable COVID-19 ocular sample tests, all links made to SARS-CoV-2 etiology remain tentative; further research must be directed to the field with modified testing strategies.

Keywords: Anterior Segment; COVID-19; Ocular; Posterior Segment; Retina; SARS-CoV-2

(J Med J 2022; Vol. 56 (2):115- 133)

Received	Accepted
October, 9, 2021	*December, 8, 2021*

1. Introduction

On 31 December, 2019, the first cases of SARS-CoV-2 were reported in Wuhan, a city in mainland China, as new cases of a mysterious pneumonia began to emerge. The first lockdown to prevent the spread of this novel coronavirus was instated in Wuhan on 23 January, 2020 and many countries followed suit as the disease evolved into a pandemic [1].

Research on the virus was in full swing as healthcare systems were overwhelmed with high infection rates and COVID-19 patients filled wards. With the medical workforce and resources overstretched, many aspects of patient care were deferred as this new form of pneumonia took precedence. Social distancing measures and lockdowns were put in place to limit infection and alleviate the pressure on hospitals; as researchers gained more knowledge of the virus, health workers became

1. School of Medicine, Royal College of Surgeons in Ireland – Medical University of Bahrain, Busaiteen, Bahrain
2. Al-Sham Private University, Damascus, Syria
* Correspondence: k.a.foph@aspu.edu.sy

better equipped to manage the disease.

By October, 2020, more than 87,000 papers on COVID-19 had been published, validating the clinical implications of the virus and identifying new ways for prevention and treatment [2]. As of now, there are established views on the effects of COVID-19 on pulmonary and cardiovascular health, but data on the ocular manifestations of the virus remains a subject of controversy which implicates disease management overall. We will be exploring the literature on the transmission and pathology of the novel coronavirus from an ophthalmic perspective. Our appraisal provides an overview of currently available research as of 20 August, 2021, highlighting research gaps to suggest further research areas that should be explored.

Methods

The literature search was carried out on the PubMed database and involved studies published between 1 January, 2020 and 20 August, 2021. A language restriction was set to only include studies published in English. The search combination used to identify relevant articles was: “Eyes” AND “Ocular” AND “Retina” AND “SARS-CoV-2”. Title and abstract screening, full text review and data extraction were carried out by two independent researchers, with any conflicts being settled by a third researcher.

Inclusion Criteria: English publication, participant age ≥18 years, peer-reviewed article, detailed methods and results, open access full text.

Exclusion criteria: Commentary, editorial, opinion piece, incomplete research/research in progress, unavailability of full text.

Results

The initial search generated 59 articles, of which 25 were found to meet the inclusion criteria for data extraction. These 25 articles included eight cross-sectional studies and seven literature reviews, among which there were: a systematic review, five case reports, three case series, and two cohort studies. Tables 1–5 summarize the findings from these articles for the purposes of synthesizing the data for our narrative review data. These studies are related to a range of ocular aspects of COVID-19, such as transmission, infection etiology, and acute and chronic visual health effects.

In the form of ophthalmic findings, the review provided insight into common ocular manifestations observed in COVID-19 patients, the duration of symptomatic presentation after diagnosis or recovery, and the association between accompanying co-morbidities and the severity of disease burden. Concomitantly, the proposed immunopathogenesis of COVID-19 in terms of its biochemistry and systemic associations was explored.

Mechanism of Infection

ACE2 is a key element in the enabling of the adverse effects of SARS-CoV-2, and so the eyes were investigated for expression of ACE2 to determine whether ocular infection with the virus was viable. The literature highlighted that ACE2 was more ubiquitous in the corneal epithelium and the superficial conjunctiva, with decreased expression in the retina as well as ocular vessels [3]. The review article we found additionally identified an alternative integrin-mediated pathway of infection compatible with all ophthalmic tissue, in which a spike (S) protein initially binds to integrin rather than ACE2 [4]. Investigations for these receptors were conducted using immunohistochemical staining and Western Blot.

Anterior Segment Findings

Conjunctival manifestations were among the more established manifestations of ocular involvement. These included conjunctivitis and increased lacrimation, with some patients contrastingly experiencing dry eyes persisting 30-days after infection. The frequency of these findings was more common among mild-to-moderate systemic COVID-19 cases [5]. In the wake of the pandemic, conjunctivitis should thus be added to the myriad list of presentations for COVID-19.

Posterior Segment Findings

Retinal signs of the virus were subclinical and included cotton wool spots (CWSs) and retinal nerve fiber thinning. A retrospective cohort study compared the thickness of retinal layers in recovered COVID-19 patients with non-infected individuals; it found that 19 out of 32 recovered patients demonstrated a thinner retinal nerve-fiber layer compared to 36 of the control group. The visual implications of this finding were inconclusive but the thinning was more pronounced amongst patients complaining of associated ocular pain rather than being asymptomatic [6].

Ocular vessels were implicated in infection, and findings were accentuated in cases with greater disease severity. An increase in the arterial and venous diameter of ophthalmic vessels was a statistically significant manifestation depicted in a cross-sectional study, in which 21 out of 54 COVID-19 patients had larger retinal vessel diameters compared to a control group of 133. A negative correlation between mean retinal venous diameter and time since symptom onset was also established by the study. These findings were evaluated within 30 days of presentation with COVID-19 [7].

Although not encountered as frequently as other posterior segment findings, central retinal vein occlusion (CRVO) was still noted in two studies, with a total of five patients presenting with these findings [8–9]. Four out of the five patients discussed had associated macular edema and were managed by steroid therapy which resolved symptoms. Central retinal arterial occlusion (CRAO) was also noted across the literature in four patients, two of whom had associated paracentral acute middle maculopathy (PAMM) [8]. Another common manifestation was retinal hemorrhaging. In four studies, such retinal findings were noted in 23 patients. Retinal hemorrhages can variously present as flame hemorrhages, peripheral retinal hemorrhages, macular hemorrhages, microhemorrhages, or peripapillary hemorrhages [7-8, 10-11]. In most of these cases, CWSs were a common co-existing finding [7, 10].

Three studies recognized fungal infiltration of the eyes as a complication in patients suffering from severe COVID-19. Endogenous endophthalmitis was the most emphasized fungal manifestation, followed by posterior uveitis, and candida retinitis. Patients requiring intensive medical attention upon infection with SARS-CoV-2 often have additional pre-disposing factors to these opportunistic manifestations, such as diabetes, hypertension, and immunosuppression. When coupled with a prolonged hospital stay and glucocorticoid therapy warranted for COVID-19 treatment, the risk for systemic fungemia is substantially increased [12–14].

Neurotropism

Based on two case reports and accounts of retinal nerve-fiber thinning in other studies, our literature analysis supports the possibility of SARS-CoV-2 having the propensity to directly infect neural tissue. The first proposed case report concerns an anesthetist who developed scotomas in the left eye. Corresponding hyperreflective lesions were detected on optical coherence tomography (OCT), involving the inner plexiform layer and ganglion cell layer of the retina. OCT was key in aiding the diagnosis, demonstrating its importance in the ophthalmic evaluation of COVID-19 [15]. Another unique case report described a 51-year-old woman having SARS-CoV-2 atypical pneumonia; two days after presentation, she complained of ocular pain accompanied by diminished visual acuity. Bilaterally dilated pupils were noted on inspection and COVID-19 was credited as the cause of her Adie's tonic pupils after any other etiology was disproven. Nasopharyngeal swab for the virus was negative, but chorioretinopathy was detected on OCT and a positive serology test supported the diagnosis [16].

Discussion

The literature search highlighted several pathways for SARS-CoV-2 optical tissue infection. All mechanisms required the virus' S protein to bind to complementary transmembrane cellular receptors, followed by endocytosis.

There are two main mechanisms by which infection occurs, namely an integrin pathway and a transmembrane enzyme-mediated pathway. In the integrin pathway, the S protein directly binds to integrins on the cellular surface via its RGD (Arginylglycylaspartic acid) motif. Integrins are found in the cornea, conjunctiva, lens, and retina, implicating these ocular tissues as possible sites of COVID-19 contagion [4]. As for the transmembrane enzyme-associated pathway, the S protein is first cleaved by TMPRSS2 (transmembrane serine protease 2). This makes it complementary to ACE2 and CD147, which act as receptors to the newly activated virus. A cell could co-express TMPRSS2 and ACE2/CD147, thus facilitating viral adhesion, or the virus could just be primed by one cell that has TMPRSS2 and then cling to another cell that has ACE2/CD147 [17]. ACE2 is abundant in the superficial cornea and conjunctiva, with TMPRSS2 being concomitantly expressed in the conjunctiva [3, 18]. ACE2 is also found in the endothelium of ophthalmic vessels and the retina, but its retinal presence is much lesser. CD147 is prominently demonstrated in retinal tissue, however, making it potentially susceptible to SARS-CoV-2. Following endocytosis, Cathepsin L (an endosomal lysozyme) breaks down the virus, allowing the release of its single-stranded RNA into the cytosol, which results in infection [17].

Several anterior segment findings were commonly cited in the literature, including conjunctivitis, conjunctival hyperemia, epiphora, chemosis, and dry eyes [5]. In addition to ocular pain, these aspects would sometimes be among the first signs and symptoms for patients acutely contracting COVID-19 before any complaints of shortness of breath or fever. Conjunctivitis with conjunctival injection was the most common ocular manifestation of the virus, and may be attributable to greater expression of the aforementioned infective agents in the conjunctiva relative to other parts of the eye [11, 14].

RT-PCR tests have been the gold standard for COVID-19 diagnosis since the pandemic's onset, and so several studies have utilized this technology to identify whether the novel virus truly infects ocular tissue. The results were variable in patients who demonstrated characteristic SARS-CoV-2 ophthalmic findings, such as conjunctivitis, even when all other causes of ocular pathology were ruled out. In the studies included in our review, an average of only 35–45% of ocular swabs would test positive in patients with evident optical COVID-19 involvement [14–15, 19–23]. This may be attributed to the RT-PCR testing techniques not being tailored to the eye and this is thus a subject for further research.

Posterior segment findings, on the other hand, demonstrated central retinal arterial occlusion, central retinal vein occlusion, retinal hemorrhages, and cotton wool spots. Studies attempting to evaluate the pathophysiological changes surrounding these findings demonstrated coagulopathy, endotheliopathy, and vasculitis [8, 24].

A citation of Adie's syndrome in a case report suggested SARS-CoV-2 as the most likely culprit of Cranial Nerve (CN) 3 compromise [16], and several other articles highlighted retinal lesions and retinal nerve-fiber layer thinning as commonalities in COVID-19 patients. Together with the described CN 3 and CN 2 damage, our review suggests that the novel coronavirus might also exhibit neurotropism.

Dilatation of retinal arteries and veins was also cited in SARS-CoV-2 patients. The diameter of retinal veins was particularly observed to be linked to the severity of COVID-19, with more severe cases demonstrating a larger increase in venous diameter. This was related to increased blood supply due to an inflammatory response and poor venous drainage resulting from coagulopathy [7]. In another article, an interesting revelation surrounding ocular manifestations was the lack of SARS-CoV-2-RNA detected in the vitreous and retinal samples of deceased COVID-19 patients on postmortem examination [23]. However, immunohistological analysis in a further subset of deceased COVID-19 patients demonstrated fibrin microthrombi in the larger choroidal vessels, and retinal and ciliary body vessels, alluding to a picture of vasculitis due to endothelial damage [21].

Such cumulative findings increasingly point to the involvement of a direct inflammatory response in the posterior segment. Due to the contrasting data denoted in both studies, further histopathological analyses may lead to a more definitive conclusion.

Hospitalized COVID-19 patients tend to have other predisposing comorbidities, including diabetes, hypertension, and immunosuppression. This is further exacerbated by infection and glucocorticoid therapy which leaves patients particularly susceptible to fungal diseases. Studies in this regard include a case-series which reported that three patients developed endogenous endophthalmitis [12], and another in which a patient presented with fungal-induced unilateral chorioretinitis [14]. The prevalence of these complications in severe COVID-19 warrants more investigation to guide therapeutics.

Follow-up parameters can vary significantly in terms of detecting the ocular manifestations of SARS-CoV-2 after diagnosis or recovery from COVID-19. Although patients may present with ocular manifestations within the acute phase, some studies have shown findings to present predominantly within the convalescent phase. A prospective study attempting to identify the emergence of retinal changes due to COVID-19 infection was unable to detect any retinal findings within the acute phase. However, in the convalescent phase, five patients out of 93 presented with retinal findings such as CWSs and retinal hemorrhages between 22–44 days from diagnosis [10]. These findings align with a consecutive case series retrospectively assessing the retinal manifestations of COVID-19 at a tertiary care hospital in Southern India. Out of the seven cases studied, most presented with findings within the convalescent stage or after recovery, approximately 2–4 weeks after diagnosis, with the maximum duration being four months after recovery. One case that presented six weeks after a diagnosis of COVID-19 had concomitant systemic aspergillosis, and thus the retinal findings could be attributed to an amalgamation of the two illnesses [13]. The timeline of the afore-mentioned findings is complicated by underlying factors such as the immunopathogenesis of the virus and the accompanying condition of the host. Systemic comorbidities, the duration before which a patient presents to the hospital, and adequate in-place protocols for timely identification of ocular manifestations all contribute to determining the onset of symptoms after contracting the virus.

Physicians should be on the lookout for ocular manifestations of SARS-CoV-2 infection during diagnosis and follow-up, especially in light of the pandemic. Anterior segment findings are sometimes amongst the first findings for the virus. Catching such signs early-on could help limit the spread of the virus and guide therapeutic treatment for relevant cases. Further research is required to establish posterior eye segment implications of the virus, and a more procured ophthalmic sample COVID-19 test should be adopted in future studies.

Conclusion

Our article has brought to light a consensus on the current knowledge regarding the ocular manifestations of COVID-19. Conjunctivital injection, watery eyes, chemosis, and dry eyes are among the early findings of SARS-CoV-2 infection, of which doctors must be vigilant. Chronic visual effects involving the posterior eye were rare and only demonstrable in severe cases involving opportunistic optic fungal infection or ophthalmic vessel compromise. The validity of SARS-CoV-2's ocular tropism from the cited studies is inconclusive since ophthalmic RT-PCR tests showed variable results. Future research is required to establish the novel virus's posterior segment complications, utilizing enhanced testing methods for ophthalmic tissue.

Funding

None.

Conflicts of interest

None declared.

Acknowledgements

We are thankful to Dr. Ahmad Mardini of the University of Sharjah and Asher Khan of RCSI-Bahrain for their unwavering support and guidance throughout the research project.

Tables and Figures

Table 1: Cross-Sectional Studies

Title	Authors	Sample Size (If Available)	Study Setting and Main Results
COVID-19 retinal microangiopathy as an in vivo biomarker of systemic vascular disease? [25]	Landecho, M. F. Yuste, J. R. Gándara, E. Sunsundegui, P. Quiroga, J. Alcaide, A. B. García-Layana, A.	27	27 patients that were hospitalized for COVID-19 were evaluated for ophthalmic manifestations. All 27 patients were prophylactically administered low molecular weight heparin prior to check up when receiving care for infection. 22% (6 patients) were found to have developed cotton wool spots with no signs of vasculitis, retinitis, or other vascular pathology. The cotton wool spots showed the same elliptical morphology as those characteristic of non-proliferative diabetic retinopathy, which may be suggestive of similar pathophysiology. Such spots act as markers for vascular disease severity in other conditions which might also apply for SARS-CoV-2 patients.
Fundus evaluation in COVID-19 positives with non-severe disease [26]	Bypareddy, R. Rathod, B. L. S. Shilpa, Y. D. Hithashree, H. R. Nagaraj, K. B. Hemalatha, B. C. Basumatary, J. Bekal, D. Niranjan, R. Anusha, P. G.	138	Of 138 non-severe COVID-19 patients with no ocular comorbidities, ophthalmic examination showed no significant findings. There was only one case of a splinter hemorrhage that appears to be coincidental and unrelated to COVID-19. Based on these results, SARS-CoV-2 appears to have no effect on the eyes of healthy patients with non-severe infection.
Ocular findings among patients surviving COVID-19 [5]	Costa Í, F. Bonifácio, L. P. Bellissimo-Rodrigues, F. Rocha, E. M. Jorge, R. Bollela, V. R. Antunes-	64	Patients underwent ophthalmic examinations with at least a 30-day interval since the emergence of COVID-19 symptoms. Visual acuity deficits and dry eyes were demonstrated to be statistically significant findings among patients with the association more pronounced in groups who had severe COVID-19. 15.6% of subjects reported either the onset or worsening of blurry vision following SARS-CoV-2 infection with only 1 out of 64 reporting worsening of eye pain since acquiring the virus. Only 2 patients showed white-yellow

Title	Authors	Sample Size (If Available)	Study Setting and Main Results
	Foschini, R		lesions in the posterior poles of the eyes. The results of this study may not be truly representative of COVID-19's ocular manifestations since many patients were already presenting with ophthalmic pathology prior to infection, potentially confounding the data.
Ocular pathology and occasionally detectable intraocular SARS-CoV-2 RNA in five fatal COVID-19 cases [21]	Reinhold, A. Tzankov, A. Matter, M. Mihic-Probst, D. Scholl, H. P. N. Meyer, P.	8	The study involved 5 patients who died of COVID-19 and 3 others who died of other causes. For all COVID-19 subjects, all ocular pathologies were consistent with age-related changes and comorbidities unrelated to SARS-CoV-2, such as diabetes and hypertension. The cornea, neural tissue, iris, and conjunctiva showed no signs of COVID-19 related inflammation. Endothelial damage of choroidal vessels was observed and linked to COVID-19 since caspase 3 and fibrin microthrombi were detected on immunohistochemical staining of COVID-19 subjects, while no similar findings were identified in the control. RT-PCR was positive for ocular samples, but viral load was found to be much lower than in the lungs of the same patients. ACE2 was found to be expressed in the conjunctiva, retina, and the endothelium of ophthalmic vessels, highlighting their potential for infection by and transmission of the novel coronavirus.
Retinal findings in patients with COVID-19: Results from the SERPICO-19 study [7]	Invernizzi, A. Torre, A. Parrulli, S. Zicarelli, F. Schiuma, M. Colombo, V. Giacomelli, A. Cigada, M. Milazzo, L. Ridolfo, A. Faggion, I. Cordier, L. Oldani, M. Marini, S. Villa, P.	187	54 patients admitted to a hospital for COVID-19 were enrolled into a study examining the effects of COVID-19 on the eye and compared with a non-infected group of 133. 27.7% of COVID-19 patients complained of ocular symptoms, with retinal hemorrhage (9.25%) and cotton wool spots (7.4%) showing up on ophthalmic evaluation. Drusen was observed in 6 patients. 21 patients were found to have ocular vessel abnormalities as increased mean arterial diameter (MAD) and mean venous diameter (MVD) were statistically significant findings in this cohort compared to control. This relationship was more pronounced in patients who had more severe infection, and MVD additionally showed a negative correlation with time since symptoms onset. The pathophysiology behind retinal findings was not investigated, but it was speculated to be linked to SARS-CoV-2 mediated inflammation, decreased

Title	Authors	Sample Size (If Available)	Study Setting and Main Results
	Rizzardini, G. Galli, M. Antinori, S. Staurenghi, G. Meroni, L.		venous drainage, decreased blood O_2 and/or increased blood CO_2. Infected patients with established retinal pathology prior to the study were excluded, but comorbidities such as hypertension and diabetes could have skewed the results since they could implicate ocular health.
Retinal involvement and ocular findings in COVID-19 pneumonia patients [14]	Pirraglia, M. P. Ceccarelli, G. Cerini, A. Visioli, G. d'Ettorre, G. Mastroianni, C. M. Pugliese, F. Lambiase, A. Gharbiya, M.	43	Patients hospitalized for COVID-19 conducted ophthalmic appraisal in an Italian teaching hospital. All patients showed no posterior segment findings except for one with unilateral posterior chorioretinitis arising due to opportunistic fungal infection (SARS-CoV-2 was excluded as the direct cause in aqueous humor analysis and blood workup). No findings of ocular vascular compromise were detected; however, this could be confounding since all patients were treated with heparin. Only 3 patients (7%) had anterior segment findings which included conjunctivitis and conjunctival hyperemia, but ocular samples tested negative for COVID-19 on RT-PCR in contrast to positive results for nasopharyngeal swab.
Retinal Involvement in COVID-19: Results from a Prospective Retina Screening Program in the Acute and Convalescent Phase [10]	Bansal, R. Markan, A. Gautam, N. Guru, R. R. Lakshmi, P. V. M. Katoch, D. Agarwal, A. Singh, M. P. Suri, V. Mohindra, R. Sahni, N. Bhalla, A. Malhotra, P. Gupta, V. Puri, G. D.	235	A prospective study detecting retinal involvement in both the acute and convalescent phase of COVID-19 infection. 142 patients were examined in the acute phase while 93 patients were examined in the convalescent phase. In the acute phase, pre-existing retinal changes were present and could be attributed to conditions such as diabetic and hypertensive retinopathy rather than COVID-19 infection. Retinal assessment in the convalescent phase, however, revealed 5 patients as having CWSs with/without retinal hemorrhages. Although these patients had pre-existing comorbidities (e.g., hypertension, diabetes mellitus, chronic kidney disease), prior to COVID-19 infection, they had no background features of retinopathy. The mean age of the 5 patients was 65.8 years, compared to the mean age of the 88 patients without findings (mean age = 39.72 years).
Severe acute respiratory Syndrome-Coronavirus-2: Can it be detected in the retina? [23]	Bayyoud, T. Iftner, A. Iftner, T. Bartz-	10	A study carried out in Germany aimed to assess the possibility of ocular reserves of COVID-19 infection in deceased patients by performing histopathological analysis and quantitative (q)RT-PCR-testing for SARS-CoV-2 RNA

Title	Authors	Sample Size (If Available)	Study Setting and Main Results
	Schmidt, K. U. Ziemssen, F. Bösmüller, H. Fend, F. Rohrbach, J. M. Ueffing, M. Schindler, M. Thaler, S.		on retinal and vitreous tissue postmortem. 10 postmortem cases were assessed. All 10 patients, while battling COVID-19, had extensive organ system involvement, ranging from the respiratory to the urogenital system. Three of the patients had multi-organ dysfunction syndrome, and all patients eventually progressed to acute respiratory distress syndrome (ARDS) and kidney failure. Postmortem histopathological assessment was carried out by an enucleation team, with RNA extraction and quantitative reverse transcription-polymerase chain reaction carried out to allow for intra-ocular tissue assessment. Postmortem assessment demonstrated that no SARS-CoV-2 RNA was detectable in retinal and vitreal tissues. Normal extra- and intra-ocular morphology was noted, without any detectable retinal inflammation or vascular occlusion.

Table 2: Cohort Studies

Title	Authors	Retrospective or Prospective	Sample Size (If Available)	Study Setting and Main Results
COVID-19: more than a respiratory virus, an optical coherence tomography study [6]	Dag Seker, E. Erbahceci Timur, I. E.	Retrospective	68	This study compared the thickness of different layers of the retina between 32 patients that had recovered from COVID-19 and 36 healthy patients that did not contract the virus. Through OCT, COVID-19 patients were shown to have thinning of the retinal layers when compared to the control group. The thinning was more pronounced among COVID-19 patients that had ocular pain rather than being asymptomatic. These subclinical findings' long-term implications are still not established. Patients did not have any other ocular findings such as cotton wool spots, which may be due to the infection cases being non-severe.
Ophthalmic Screening in Patients with Coronavirus Disease 2019: A	Papazoglou, A. Conen, A. Haubitz, S. Tschopp, M.	Prospective	50	50 COVID-19 patients of varying disease severity had regular ophthalmic check-ups upon enrollment into the study. 18% were found to have signs and symptoms of superficial ocular irritation in the acute phase of infection. Only 3

Title	Authors	Retrospective or Prospective	Sample Size (If Available)	Study Setting and Main Results
Prospective Cohort Study [11]	Guignard, V. J. Menke, M. N. Enz, T. J.			patients showed posterior segment lesions due to retinal and peripapillary hemorrhage, although these were most likely attributable to comorbidities. Based on the results, the article alludes that ocular surface manifestations of SARS-CoV-2 infection, such as conjunctivitis and conjunctival hyperemia, are established manifestations of the virus, but intraocular findings are intangible and likely linked to underlying prior pathology.

Table 3: Literature Reviews

Title	Authors	Study Setting and Main Results
Can SARS-CoV-2 infect the eye? An overview of the receptor status in ocular tissue [3]	Schnichels, S. Rohrbach, J. M. Bayyoud, T. Thaler, S. Ziemssen, F. Hurst, J.	Infection of cells with SARS-CoV-2 requires ACE2 as a receptor for virus binding, and TMPRSS2 (a transmembrane protease) to facilitate infection. Expression of these proteins in the cornea was more established than retinal expression with detection being variable among studies of the retina. Actual infection of eye structures seems feasible but whether it occurs was in-definitive, which could be attributed to different preservation and testing methods of eye samples for COVID-19.
Human coronaviruses: ophthalmic manifestations [18]	Abdul-Kadir, M. A. Lim, L. T.	This review cited multiple studies that examined ACE2 and TMPRSS2 tropism in the eyes as facilitating SARS-CoV-2 infection, detection of the virus in tears and conjunctival swabs, and ophthalmic pathology. The study concluded that, based on co-expression of ACE2 and TMPRSS2 in the conjunctiva along with positive RT-PCR tests for conjunctival swabs from COVID-19 patients, the conjunctiva is a plausible method of transmission and infection of the novel coronavirus. Conjunctivitis was the most common ocular manifestation, although ocular imaging of the eye demonstrated cotton wool spots and hyperreflective lesions as further ophthalmic implications of the virus. RT-PCRs of ocular tissue were not a viable testing method for COVID-19 due to the variability of results in which even patients that demonstrated SARS-CoV-2 related conjunctivitis showed negative results on swabs.
Integrins: An Important Link between Angiogenesis, Inflammation and Eye Diseases [4]	Mrugacz, M. Bryl, A. Falkowski, M. Zorena, K.	COVID-19 infects cells via the ACE2 and TMPRSS2 pathway as well as through integrins. Integrins are expressed on the cornea, conjunctiva, lens, and retina, and can act as possible methods of infection for the novel coronavirus. This occurs by binding of the RGD (arginylglycylaspartic acid) motif of the virus' S protein to complementary integrin subunits potentially

Title	Authors	Study Setting and Main Results
		facilitating infection.
The Ocular Manifestations and Transmission of COVID-19: Recommendations for Prevention [20]	Dockery, D. M. Rowe, S. G. Murphy, M. A. Krzystolik, M. G	This review articles listed several articles that highlighted the conjunctiva as a possible site for transmission and infection of the novel coronavirus. A Chinese study reported only 2 patients with positive conjunctival COVID-19 RT-PCRs out of 38 infected patients, of whom 12 had ocular symptoms. Another reference stated that only 3 patients' conjunctival samples tested positive from a sample of 67, with one patient having conjunctivitis but showing negative results for ocular SARS-CoV-2 RT-PCR. Other citations were of the same pattern, in addition an Italian case report of a patient sustaining positive COVID-19 test results for ocular swabs even days after nasopharyngeal swabs resolved to negative.
Potential of Ocular Transmission of SARS-CoV-2: A Review [17]	Barnett, B. P. Wahlin, K. Krawczyk, M. Spencer, D. Welsbie, D. Afshari, N. Chao, D.	TMPRSS2 (transmembrane serine protease 2), ACE2, CD147 and CTSL (Cathepsin L) were identified as key proteins for SARS-CoV-2 infection. TMPRSS2 acts as a primer for COVID-19 infection by cleaving the virus' S protein. Once cleaved, the S protein becomes complementary to both ACE2 and CD147, which are membrane proteins allowing the virus to cling onto cells. Either ACE2 or CD147 are needed at this stage of the process. CTSL, an endosomal lysozyme, further cleaves the virus after endocytosis facilitates endosomal membrane binding of the virus and RNA release into the cytosol. Based on the described mechanism, cells lacking TMPRSS2 can be infected if they have all other aforementioned proteins, since the virus will already be primed for infection by other cells that have TMPRSS2; this is only grounded in theory at the time of this review. CD147 is more abundant in the retina than ACE2, with CTSL coexisting in this tissue, but whether COVID-19 truly has retinal pathology requires more investigation. ACE2 and TMPRSS2 are co-expressed in the conjunctiva, which could explain the significant reporting of conjunctivitis in patients with severe COVID-19. These signs could be misleading since they could be attributed to ICU ventilation complications with positive RT-PCRs of ocular samples just being droplets containing the virus rather than actual infection of the eye or tears.
Retinal manifestations in patients with SARS-CoV-2 infection and pathogenetic implications: a systematic review [8]	Sen, S. Kannan, N. B. Kumar, J. Rajan, R. P. Kumar, K. Baliga, G. Reddy, H. Upadhyay, A. Ramasamy, K.	This is a systematic review aiming to determine the retinal manifestations of COVID-19, as well as its mechanism of action. Retinal changes such as retinal hemorrhages and CWSs, arterial and venous occlusion, vitritis, posterior uveitis, and vascular dilatation were taken into consideration. The most common ocular manifestations were flame hemorrhages, CWSs, and peripheral retinal hemorrhages, and most of these patients had accompanying raised D-dimer levels. Only 4 patients demonstrated central retinal vein occlusion (CRVO), and these patients were treated with either steroids or a combination of steroids plus Bevacizumab (anti-VEGF monoclonal antibody), having a

Title	Authors	Study Setting and Main Results
		drastic improvement in visual acuity. One patient, a 57-year-old woman, developed vitritis and a yellow macular lesion 12 days after her diagnosis, which persisted for 1 month before reducing in size. An 11-year-old patient positive for COVID-19, alongside developing chilblains, also demonstrated retinal vasculitis with perivascular infiltrates and retinal exudates in the left eye, further information about the patient's condition was not mentioned. Only a handful of patients till date have reported central retinal arterial occlusion, with accompanying paracentral acute middle maculopathy (PAMM) and acute macular neuroretinopathy (AMN). Two of the aforementioned patients presented with new onset paracentral scotoma. In another large-scale study, COVID-19 patients were shown to have greater retinal venous and arterial diameters in comparison to unexposed subjects. This change was thought to be attributed to rising inflammatory mediators released during the blood in early COVID-19 disease.
COVID-19: Limiting the Risks for Eye Care Professionals [19]	Sadhu, S. Agrawal, R. Pyare, R. Pavesio, C. Zierhut, M. Khatri, A. Smith, J. R. de Smet, M. D. Biswas, J.	Eye tissues have shown expression of ACE2, the membrane enzyme facilitating SARS-CoV-2 infection, which makes them a potential site for acquiring and transmitting the virus. The lacrimal gland, eyes and mouth are continuous with one another, making them accessible pathways for the novel coronavirus to enter the gastrointestinal and respiratory tracts, leading to infection. RT-PCR tests of ocular samples give variable results for COVID-19 detection even for patients with symptomatic conjunctivitis, but this does not obviate the possibility of transmission via the eyes and tears as this may be a limitation of testing strategies for viral load.

Table 4: Case Series

Title	Authors	Sample Size (If Available)	Study Setting and Main Results
A case series of presumed fungal endogenous endophthalmitis in post COVID-19 patients [12]	Shah, K. K. Venkatramani, D. Majumder, P. D.	4	Hospitalized COVID-19 patients tend to have comorbidities like diabetes, hypertension, and immunosuppression. Exposure in the hospital along with a compromised immune system leaves them susceptible to nosocomial fungal infections that manifested as endogenous endophthalmitis in this study, leading to visual losses. This condition could be misdiagnosed as COVID-19 retinitis resulting in inappropriate treatment, particularly since vitreal tests are inconsistent in detecting the fungus.
Retinal manifestations in patients following COVID-19 infection: A consecutive case series [13]	Goyal, M. Murthy, S. I. Annum, S.	7	This is a retrospective chart review of retinal manifestations associated with COVID-19 infection in a tertiary care hospital in Southern India. Varying ocular manifestations were seen, with a predisposition for unilateral eye involvement. The most common presenting complaint was a deterioration in visual acuity with symptoms that started during a diagnosis of COVID-19, or after recovery. On examination, some OCT findings included hyper-reflective lesions in the retina (suggesting acute macular neuropathy), serous detachment of the macula and paracentral and intraretinal hemorrhages. The cases ranged from mild to severe vision impairment. More serious manifestations were due to endogenous endophthalmitis, candida retinitis, tubercular choroidal abscess, and bilateral pre-foveal hemorrhages. In 3 of the cases, a focus of infection could not be identified, and patients were started on antifungals instead with significant visual improvement. These presentations could be due to immunosuppression caused by COVID-19 and its resulting management. A state of immunosuppression can also lead to the propagation of underlying comorbidities, while also predisposing patients to the acquisition of nosocomial infections. This was evident in the remaining cases, in which patients presented with reactivation of systemic tuberculosis, pseudomonas septicemia, and invasive systemic aspergillosis.

Title	Authors	Sample Size (If Available)	Study Setting and Main Results
			Visual changes due to voriconazole use, such as photopsia, blurred vision, and photophobia were witnessed in the management of invasive systemic aspergillosis requiring treatment discontinuation to alleviate the symptoms.
Presumed SARS-CoV-2 Viral Particles in the Human Retina of Patients With COVID-19 [22]	Araujo-Silva, C. A. Marcos, A. A. A. Marinho, P. M. Branco, A. M. C. Roque, A. Romano, A. C. Matuoka, M. L. Farah, M. Burnier, M. Moraes, N. F. Tierno, Pfgmm Schor, P. Sakamoto, V. Nascimento, H. de Sousa, W. Belfort, R., Jr.	3	This report discussed the optical findings of 3 patients who had died due to severe COVID-19. All subjects had comorbidities that could compromise ocular health, including diabetes and hypertension, among others. Prior to death, one patient underwent ophthalmic evaluation with findings being vitreous hemorrhage in the right eye and temporal subretinal hemorrhage in the left eye. No anterior segment abnormalities were detected. The 2 other patients could not do these tests as they died shortly after hospitalization, but they showed no signs of ophthalmic damage when analyzed post-mortem. Electron microscopy and immunocytochemistry confirmed the presence of virus particles in the retina and choroid of all 3 patients, but further research is required to determine whether any ocular pathology highlighted in the patients was directly related to viral infection of ophthalmic tissue or was secondary to systemic COVID-19 implications, such as microvascular compromise and/or immunological changes typical of the virus.

Table 5: Case Reports

Title	Authors	Study Setting and Main Results
Unilateral frosted branch angiitis in an human immunodeficiency virus-infected patient with concurrent COVID-19 infection: a case report [27]	Lim, T. H. Wai, Y. Z. Chong, J. C.	The case follows a 33-year-old Malay man with newly found AIDS and concurrent COVID-19 in October, 2020. In December, 2020, the patient presented with blurring of vision in his right eye; ophthalmic examination revealed generalized retinal vasculitis with sheathing of retinal vessels and mild vitritis, a classic presentation of Frosted Branch Angiitis (FBA). A CMV panel was carried out, with IgG and IgM positivity. During this time, the patient was still COVID-19 positive with a low cycle threshold value. To combat the FBA, the patient was started on IV ganciclovir, with massive improvement within 2 weeks. CMV can commonly be attributed to the development of FBA; however, this is the first time that FBA has been demonstrated in a patient with concomitant CMV

Title	Authors	Study Setting and Main Results
		and COVID-19 infection. Although COVID-19 cannot directly be linked to the patient's FBA, immunocompromised patients presenting atypically with ocular findings as opposed to systemic signs of COVID-19 should be assessed further before dismissal.
Central retinal vein occlusion with COVID-19 infection as the presumptive etiology [9]	Walinjkar, J. A. Makhija, S. C. Sharma, H. R. Morekar, S. R. Natarajan, S.	COVID-19 is established to have thrombotic pathology leading to thromboembolic events, such as pulmonary embolisms and strokes. Being an end-artery system, retinal circulation is particularly susceptible to ischemia. This case report details central retinal vein occlusion with subsequent retinal hemorrhage and macular edema in a 17-year-old girl due to thromboembolic complications of COVID-19. CXR showed pulmonary infiltrates due to infection, while RT-PCR swabs were negative for COVID-19 since the patient had recently recovered. The patient showed no marker of vasculitis, so the embolism could not be attributable to COVID-19-related vasculitis.
Non-arteritic anterior ischaemic optic neuropathy sequential to SARS-CoV-2 virus pneumonia: preventable by endothelial protection? [24]	Moschetta, L. Fasolino, G. Kuijpers, R. W.	A 64-year-old Caucasian man presented with visual deficits involving the right eye one month after hospitalization for COVID-19. The patient showed no sign of vasculitis alluding to arteritic ischemic optic neuropathy, since he had a normal ESR (erythrocyte sedimentation rate), normal C-reactive protein levels and no clinical features of giant cell arteritis. The vision loss was attributed to SARS-CoV-2-related endotheliopathy resulting in non-arteritic ischemic optic neuropathy (NAION). Endotheliopathy is a consequence of COVID-19 which causes reduced vessel compliance and thus compromises circulation, which in this case led to NAION.
Ophthalmic and Neuro-ophthalmic Manifestations of Coronavirus Disease 2019 (COVID-19) [16]	Ortiz-Seller, A. Martínez Costa, L. Hernández-Pons, A. Valls Pascual, E. Solves Alemany, A. Albert-Fort, M.	A 51-year-old woman presented to the hospital with typical COVID-19 symptoms, such as fever, fatigue, headache, and dry cough. Two days later, she developed ocular pain and decreased visual acuity. On optical examinations, she demonstrated bilaterally dilated pupils with white-yellowish retinal lesions with both eyes. Upon further assessment, bilateral Adie's syndrome was confirmed as the diagnosis with SARS-CoV-2 being enlisted as the most probable cause, since lab work-up for systemic hematologic, inflammatory, and infectious pathologies was negative. Areas of choroidal hypoperfusion were detected bilaterally on OCT in conjunction with retinal disruptions and thinning consistent with chorioretinopathy. This case report highlights the potential neurotropism of SARS-CoV-2.
Retinal imaging study diagnoses in COVID-19: a case report [15]	Ortiz-Egea, J. M. Ruiz-Medrano, J. Ruiz-Moreno, J. M.	A 42-year-old anesthetist working on COVID-19 patients presented with acute temporal relative scotoma in the left eye. On ophthalmic examinations, no signs of visual deficits were demonstrated, with the scotoma complaint not appearing during examination. OCT detected hyperreflective bands in the ganglion cell layer and inner plexiform layer, while no other parts of the retina had evident lesions. Fluoresceine angiography was insignificant for vascular compromise. Lab workup, thoracic imaging and blood pressure was normal. The only complaint at presentation was visual, and due to the high risk of viral

Title	Authors	Study Setting and Main Results
		exposure at work, SARS-CoV-2 tests were done. Nasopharyngeal swab was negative, but antibody tests for the virus were positive. Visual symptoms persisted 30 days since onset, with retinal lesions intensifying. This is a unique study highlighting the importance of OCT findings to confirm SARS-CoV-2 infection and manifestation.

References

1. Zhu H, Wei L, Niu P. The novel coronavirus outbreak in Wuhan, China. Glob Health Res Policy. 2020;5:6.
2. Cai X, Fry CV, Wagner CS. International collaboration during the COVID-19 crisis: autumn 2020 developments. Scientometrics. 2021:1-10.
3. Schnichels S, Rohrbach JM, Bayyoud T, Thaler S, Ziemssen F, Hurst J. Can SARS-CoV-2 infect the eye? An overview of the receptor status in ocular tissue. Ophthalmologe. 2021;118(Suppl 1):81-4.
4. Mrugacz M, Bryl A, Falkowski M, Zorena K. Integrins: An Important Link between Angiogenesis, Inflammation and Eye Diseases. Cells. 2021;10(7).
5. Costa Í F, Bonifácio LP, Bellissimo-Rodrigues F, Rocha EM, Jorge R, Bollela VR, et al. Ocular findings among patients surviving COVID-19. Sci Rep. 2021;11(1):11085.
6. Dag Seker E, Erbahceci Timur IE. COVID-19: more than a respiratory virus, an optical coherence tomography study. Int Ophthalmol. 2021:1-10.
7. Invernizzi A, Torre A, Parrulli S, Zicarelli F, Schiuma M, Colombo V, et al. Retinal findings in patients with COVID-19: Results from the SERPICO-19 study. EClinicalMedicine. 2020;27:100550.
8. Sen S, Kannan NB, Kumar J, Rajan RP, Kumar K, Baliga G, et al. Retinal manifestations in patients with SARS-CoV-2 infection and pathogenetic implications: a systematic review. Int Ophthalmol. 2021:1-14.
9. Walinjkar JA, Makhija SC, Sharma HR, Morekar SR, Natarajan S. Central retinal vein occlusion with COVID-19 infection as the presumptive etiology. Indian J Ophthalmol. 2020;68(11):2572-4.
10. Bansal R, Markan A, Gautam N, Guru RR, Lakshmi PVM, Katoch D, et al. Retinal Involvement in COVID-19: Results From a Prospective Retina Screening Program in the Acute and Convalescent Phase. Front Med (Lausanne). 2021;8:681942.
11. Papazoglou A, Conen A, Haubitz S, Tschopp M, Guignard VJ, Menke MN, et al. Ophthalmic Screening in Patients with Coronavirus Disease 2019: A Prospective Cohort Study. J Clin Med. 2021;10(5).
12. Shah KK, Venkatramani D, Majumder PD. A case series of presumed fungal endogenous endophthalmitis in post COVID-19 patients. Indian J Ophthalmol. 2021;69(5):1322-5.
13. Goyal M, Murthy SI, Annum S. Retinal manifestations in patients following COVID-19 infection: A consecutive case series. Indian J Ophthalmol. 2021;69(5):1275-82.
14. Pirraglia MP, Ceccarelli G, Cerini A, Visioli G, d'Ettorre G, Mastroianni CM, et al. Retinal involvement and ocular findings in COVID-19 pneumonia patients. Sci Rep. 2020;10(1):17419.
15. Ortiz-Egea JM, Ruiz-Medrano J, Ruiz-Moreno JM. Retinal imaging study diagnoses in COVID-19: a case report. J Med Case Rep. 2021;15(1):15.
16. Ortiz-Seller A, Martínez Costa L, Hernández-Pons A, Valls Pascual E, Solves Alemany A, Albert-Fort M. Ophthalmic and Neuro-ophthalmic Manifestations of Coronavirus Disease 2019 (COVID-19). Ocul Immunol Inflamm. 2020;28(8):1285-9.
17. Barnett BP, Wahlin K, Krawczyk M, Spencer D, Welsbie D, Afshari N, et al. Potential of Ocular Transmission of SARS-CoV-2: A Review. Vision

(Basel). 2020;4(3).

18. Abdul-Kadir MA, Lim LT. Human coronaviruses: ophthalmic manifestations. BMJ Open Ophthalmol. 2020;5(1):e000630.
19. Sadhu S, Agrawal R, Pyare R, Pavesio C, Zierhut M, Khatri A, et al. COVID-19: Limiting the Risks for Eye Care Professionals. Ocul Immunol Inflamm. 2020;28(5):714-20.
20. Dockery DM, Rowe SG, Murphy MA, Krzystolik MG. The Ocular Manifestations and Transmission of COVID-19: Recommendations for Prevention. J Emerg Med. 2020;59(1):137-40.
21. Reinhold A, Tzankov A, Matter M, Mihic-Probst D, Scholl HPN, Meyer P. Ocular pathology and occasionally detectable intraocular SARS-CoV-2 RNA in five fatal COVID-19 cases. Ophthalmic Res. 2021.
22. Araujo-Silva CA, Marcos AAA, Marinho PM, Branco AMC, Roque A, Romano AC, et al. Presumed SARS-CoV-2 Viral Particles in the Human Retina of Patients With COVID-19. JAMA Ophthalmol. 2021.
23. Bayyoud T, Iftner A, Iftner T, Bartz-Schmidt KU, Ziemssen F, Bösmüller H, et al. Severe acute respiratory Syndrome-Coronavirus-2: Can it be detected in the retina? PLoS One. 2021;16(5):e0251682.
24. Moschetta L, Fasolino G, Kuijpers RW. Non-arteritic anterior ischaemic optic neuropathy sequential to SARS-CoV-2 virus pneumonia: preventable by endothelial protection? BMJ Case Rep. 2021;14(7).
25. Landecho MF, Yuste JR, Gándara E, Sunsundegui P, Quiroga J, Alcaide AB, et al. COVID-19 retinal microangiopathy as an in vivo biomarker of systemic vascular disease? J Intern Med. 2021;289(1):116-20.
26. Bypareddy R, Rathod BLS, Shilpa YD, Hithashree HR, Nagaraj KB, Hemalatha BC, et al. Fundus evaluation in COVID-19 positives with non-severe disease. Indian J Ophthalmol. 2021;69(5):1271-4.
27. Lim TH, Wai YZ, Chong JC. Unilateral frosted branch angiitis in an human immunodeficiency virus-infected patient with concurrent COVID-19 infection: a case report. J Med Case Rep. 2021;15(1):267.

ترقب الوباء: مراجعة للمؤلفات حول الظواهر البصرية لعدوى كوفيد–19

علي ماريني[1]، سيمل مقصود[1]، خالد الحمصي[2]

1. كلية الطب، الكلية الملكية للجراحين في أيرلندا – جامعة البحرين الطبية، بسيتين، البحرين
2. جامعة الشام الخاصة، دمشق، سوريا

الملخص

خلفية البحث منذ انتشار فيروس كورونا المستجد، بذلت جهود بحثية عظيمة حول هذه العدوى لتمكين المؤسسات الصحية من مواجهتها. قد أكدت الأدلة على تأثير كوفيد–19 في الجهاز التنفسي والقلبي الوعائي، ولكن ما زالت التأثيرات على الجهاز البصري نقطة نقاش.

الأهداف تهدف دراستنا إلى استكشاف ظواهر فيروس سارس–كوف–2 العينية، وإيجاد ثغرات في الأبحاث والدلالة على تكثيف الدراسات في هذا المجال.

منهجية البحث قمنا باستخدام قاعدة بيانات PubMed للبحث عن دراسات نشرت منذ 1 كانون الثاني 2020 إلى 20 آب 2021. فحصت العناوين والملخصات والمقالات بأكملها من قبل باحثين مستقلين وحسمت الخلافات بين الطرفين من خلال باحث ثالث، واستخدمت الدراسات المطابقة للشروط المسبقة لبحثنا لبناء محتوى هذا المقال.

النتائج نتج عن البحث الأولي 59 مقالا، ووظف منها 25 لاستخراج المعلومات. التهاب الملتحمة، إفراط في إفراز الدموع وتهيج العينين تكرر ذكرها في المقالات كعوارض تصيب الجزء الأمامي من العين. أما الجزء الخلفي فقد تضمن عوارض شبه سريرية منها نشوء بقع الصوف القطني في الشبكية وترقق طبقة الألياف العصبية الشبكية، ولكن وجدت حالات أكثر فتكا كانسداد الوريد الشبكي المركزي ونزيف الشبكية والتهاب باطن المقلة الفطري. أبدت فحوص الRT-PCR عدم جودتها في التحقق من إصابة الأنسجة البصرية بكوفيد–19، وقد يرجع هذا إلى قيود في منهجية إجراء ذلك التحليل على عينات العين.

الاستنتاج التأثيرات على الجزء الأمامي من أبرز ظواهر فيروس كورونا المستجد على العين، ولكن ما زالت تأثيرات العدوى على الجزء الخلفي غير واضحة مما يتطلب المزيد من الأبحاث. في ظل انعدام وجود اختبارات موثوقة لكشف إصابات كوفيد–19 البصرية، فإن كل الروابط بين عدوى سارس–كوف–2 والأمراض البصرية تبقى خاضعة للشك، لذلك لا بد من تطوير استراتيجيات تلك الفحوص ومواصلة الأبحاث حول الأعراض البصرية للفيروس.

الكلمات الدالة: الجزء الأمامي، كوفيد–19، الجزء الخلفي، الشبكية، سارس–كوف–2.