

Clinical Profile of COVID Patients During Recovery Phase at Tertiary Eye Care Centre in South India

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Abstract: BACK GROUND: Though Corona virus -19 first reported in china, Indian population in urban as well as rural areas were badly effected during second wave with involvement of various ocular structures, some patients lost vision due to retinal vascular occlusions, some patients required enucleation and orbital exenteration due to fungus infections of the eye. Patients reported with different ocular disorders were documented and intervened, were included in this study. We tried to understand whether these manifestations were due to Corona Virus or due to immune compression because of systemic disorders in Corona patients treated with oral steroids and unsterile oxygen support. Aim: Purpose is to study the various clinical manifestations noted in COVID-19 patients during second wave after treatment while recovering from the acute illness. Methods: Retrospective interventional study done at tertiary eye care centre. Duration of the study is 3months from April 2021 to June 2021.500 patients were presented to our tertiary eye care centre with various clinical manifestations. All patients underwent detailed systemic and ocular examination. Patients after treatment for COVID-19 at various hospitals across the country were presented to our institute with many opportunistic infections. Apart from history BCVA, Slit Lamp examination, fundus examination, OCT, Fundus Fluorescein Angiography and B Scan done in patients where media was hazy, documentation done in all cases. Systemic examination and other investigation like RT PCR for corona virus was done in all patients. Patients presented with orbital involvement were advised CT Scan orbit. Results: Most of the patients were badly effected with many ocular complications, very few patients could maintain normal visual acuity. Many patients developed diabetes mellitus, probably they were pre diabetics manifested after use of oral steroids. Conclusion: Second wave in India increased the mortality and also effected the quality of the life in survivors. Fatality was high due to various ocular complications in all individuals irrespective of age and immune status.

Keywords: COVID-19, Crao, Cotton Wool Spots, Vitritis, Retinitis, Endophthalmitis, Panophthalmitis, RBN, AION

1. Introduction

Coronavirus disease 2019 (COVID-19) is a new viral infection affecting both the upper and lower respiratory tracts through aerosols, faeces and contaminated surfaces. Fatality is due to severe acute respiratory syndrome (SARS) [1]. Highly contagious RNA virus termed as SARS coronavirus 2 (SARS-CoV-2), with rapid mutation rates compared to DNA viruses. Whole world is badly affected and suffering due to various complication occurred in most of the patients. Patients with comorbidities were highly effected and showed many ocular manifestation during recovery phase.

Coronavirus Disease 19 (COVID-19) was first reported in

Wuhan, China in December 2019 and is now pandemic all over the world [2]. India is badly affected during second wave of the Pandemic. First wave was less severe compared to second wave, elderly people and patients with comorbidities were effected during first wave. Health infra structure was not planned in many states of India for second wave, that is the reason why many middle aged group of people suffered from COVID-19 complications.

SARS-CoV-2 is transmitted mainly through aerosols or close contact. The ocular surface is exposed to the outside environment, is a main source for the organisms to invade the human body. ACE 2 has also been detected in the retina, retinal pigment epithelium choroid and cornea and

conjunctival epithelia [3]. ACE 2 is a cellular receptor for SARS-CoV-2 [4]. The most common symptoms are fever, cough and fatigue and diarrhoea [5]. SARS-CoV-2 is transmitted mainly through aerosols or close contact. The ocular surface is exposed to the outside environment, is a main source for the organisms to invade the human body.

AIM: Purpose is to study the various clinical manifestations noted in COVID19 patients during second wave after treatment while recovering from the disease.

2. Materials and Methods

Retrospective interventional study done at tertiary eye care centre. Patients presented with various clinical manifestations were examined and treated. Patients who presented between April to June month were included in this study. Patients of different age group were presented. Males were predominantly reported. Females were also presented, ratio of M: F was 4:1. Age group was between 25 to 75, maximum number of patients age group in both males and females was 40 to 50 years. All patients underwent detailed examination, BCVA, Slit Lamp examination, indirect ophthalmoscopy, B Scan, FFA (Fundus fluorescence angiography), OCT and documentation done. All patients after treatment during recovery period from COVID with COVID test negative or positive were included in the study. Rapid antigen test was done in all patients.

Patients treated with oral steroids, oxygen, injection Remidesevir, Tab Fabi flu, injection heparin based on SO2 and D-timer levels and patients who were not hospitalised and only isolated at home were also included in the study.

Patients presented with pain, protrusion of eye ball, redness, watering, diminished vision in the involved eye, retro orbital pain and restricted eye movements. Few patients had only vision impairment in the involved eye. Patients presented with fungal infections involving sinuses and orbit underwent functional endoscopic sinus surgery (FESS), maxillectomies, orbital exenterations, enucleation, intra orbital amphotericin b, intravitreal amphotericin, Tab Posoconazole and symptomatic treatment done. Treatment was done based on the clinical presentations and also most of the procedures in ophthalmology done after FESS by ENT surgeons. Patients underwent fundus examination before and after FESS. Many patients had vision in the involved eye when they presented but after FESS and intra orbital amphotericin b they became blind. Dose of intra orbital amphotericin b given was 3.5 micro grams every day for continuous 5 days.

3. Results

Outcome in almost 70 percent of the patients was poor. Patients with comorbidities were badly affected, patients between 40 to 55 were lost vision in the involved eye before the treatment. Involvement of the eye in post recovery was noted in almost all patients who were treated with or without steroids. Hospitalised patients treated with oxygen support were badly affected with involvement of cavernous sinus when compared to patients who were only isolated at home.

4. Discussion

The pathogenesis and tissue tropism of SARS-CoV-2 relates to the binding of the viral spike protein to its cognate receptor on human host cells— the angiotensin-converting enzyme 2 (ACE-2) receptor [6]. Efficient cell entry requires cleavage by protein transmembrane serine protease 2 (TMPRSS2). ACE-2 is expressed primarily on respiratory mucosal and alveolar epithelial cells and other tissues like the gastrointestinal tract, kidney, vascular endothelial cells, immune cells, and even neurons. Virulence is due to direct cellular invasion and death and the cause of widespread is cytokine mediated inflammation and vascular leakage [7]. The prevalence of ophthalmic manifestations among COVID-19 patients ranges from 2-32% [8]. The cause is exactly not known, whether direct invasion of virus is responsible for the ophthalmic manifestations or the immune privilege is lost or complement system is impaired due to virus and causing the opportunistic infections.

Anterior segment and posterior segment manifestations were noted in most of the patients with and without comorbidities. During first wave patients were commonly presented with conjunctivitis, keratitis, anterior uveitis, intermediate uveitis, retinitis, Optic nerve involvement and few patients with vascular events like CRAO and CRVO.

Positive patients without respiratory distress who were treated with only anti pyretics showed ocular manifestations like conjunctivitis, anterior uveitis, keratitis and meibomitis. Meibomitis was common in elderly individuals with comorbidities. Keratitis was noted in young and middle individuals. These patients presented with pain and irritation in the eye, unilateral involvement noted, most of them presented 2 to 3 weeks after recovery from COVID-19.

The incidence of serious complications of endoscopic sinus surgery has been reported as 0.5% or less [9]. The complications include cerebrospinal fluid leak, nasolacrimal duct injury, carotid injury, and orbital damage. The clinical sequel of orbital injuries is eye pressure, pain, retro bulbar haemorrhage, and restricted extraocular muscle movement with sequential binocular diplopia to blindness. Anatomically, the eyes and paranasal sinuses are near structures. The eyeball, orbit, and parts of the Sino nasal areas share the same vascular supply from the ophthalmic artery. The central retinal artery, long posterior ciliary arteries, and short posterior ciliary arteries emerge from the ophthalmic artery and supply the orbit and ocular structures. The venous drainage of the orbit and ocular structures are via the central retinal vein and the vortex vein; the former drains into the superior ophthalmic vein and the latter drains into the inferior ophthalmic vein [10]. Raise of episcleral venous pressure due to body position and procedure can cause increase in the intra ocular pressure which can lead to vascular events in eye. Procedure also has risk to cause damage to the lacrimal system and cause epiphora. Patients after FESS presented with no PL (Perception of light), possibility of trauma to the vascular structures at the time of procedure, clinically most of the

patients presented only with RAPD (Relative afferent pupillary defect), no other changes in the fundus.

Table 1. Anterior segment manifestations in COVID-19 patients.

Anterior segment manifestation	No of the patients
Meibomitis	21
Conjunctivitis	25
Exposure Keratitis	21
Keratitis	11
Anterior Uveitis	11

Table 2. Posterior segment manifestations in COVID-19 patients.

Posterior segment manifestations	No of the patients
MULTIPLE COTTON WOOL SPOTS	61
CRAO	51
CRVO	21
AION	21
PAPILLITIS	18
RETROBULBAR NEURITIS	18
PANOPTHALMITIS	18
PAMM	10
VITRITIS	9
RETINITIS	9
ENDOPHTHALMITIS	8
SUBRETINAL ABSCESS	5
INTERMEDIATE UVEITIS	5
HERPES ZOSTER OPHTHALMICUS	2
CENTRAL SEROUS CHORIORETINOPATHY	2
RETINAL VASCULITIS	2
MULTIFOCAL CHOROIDITIS	2
LOCALISED CHOROIDAL ABSCESS/THICKENING	1

Vascular Changes Noted in Patients During Recovery
Phase 12.2% of the patients showed isolated or multiple

cotton wool spots (Figures 1a and b) near the arcades due to disturbed axonal transport, congested vessels, few retinal haemorrhages like blotch or flame shape haemorrhages in one or two quadrants. These findings suggest that there is acute ischemia related to severe COVID-19 infection or embolism caused by vascular changes. Microvascular thrombosis is due to extensive alveolar and interstitial inflammation [11].

CRAO (Figure 2) was commonly noted in most of the patients. Many mechanisms are responsible for the retinal vascular occlusions in COVID-19, common mechanism is inflammation itself, other mechanisms could be thromboembolic episodes, microvascular injury mediated by complement pathways and hematologic disorders like hypercoagulability due to COVID-19 [12]. Patients with under perfused retina showed pale, white retina due to oedema of neurosensory retina. The effects of COVID-19 inflammatory and pro-coagulant state over the retinal vascular system have not been investigated yet.

Two male patients with comorbidities presented with bilateral simultaneous CRAO. In these cases, possibility is due to more vascular damage, may be the duration of infectious period and viral load was highly responsible for the simultaneous presentation. Patients CT chest showed complete lower lobe of both lungs ground glass appearance, CT Chest scoring was 18. Relationship of CT Scan chest score to the severity of ocular complications need to be studied in detail. CT chest findings are they really biomarkers which can predict the severity of ocular manifestations like CRAO need to be evaluated [13].

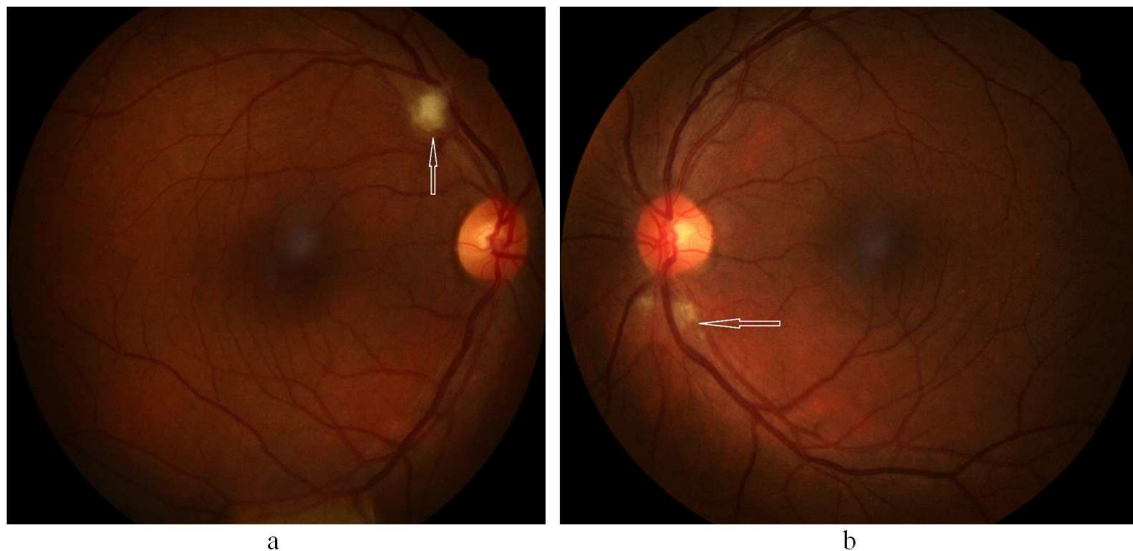


Figure 1. a and b: Colour fundus images white arrows depicting Cotton wool spot near the arcade.

Many diabetic patients did not show any progression in retinopathy after using steroids at the time of acute illness, diabetes can cause immunosuppression and increase in the blood glucose levels can worsen the retinopathy, according to literature there should be complement mediated microangiopathy because COVID-19 will target vascular pericytes

expressing ACE-2, infection could lead to complement-mediated endothelial cell dysfunction, microvascular damage, and thus ocular circulation involvement [14]. During first wave limited number of cases presented with CRAO and CRVO but in second wave maximum number of cases were CRAO. Patients with de nova history of diabetes showed

microangiopathy features whereas diabetic patients with poor glycaemic control presented with CRAO. Viral infection has definitely increased the thromboembolic events and affected the ocular vascular circulation in survivors.

Two Z positive patients presented with unilateral CRAO (Figures 3a and 3b). CD4 count in both the patients was above 300 cells per cubic millimetre. HIV retinopathy will cause micro vascular changes that mimics diabetic retinopathy, CRAO in Z positive patients is very rare, usually large vessel involvement occurs in HIV patients associated with comorbidities but in these cases the co-existing COVID-19 may be responsible for the major vascular occlusions. COVID-19 systemic infection is prone to endothelial insult with vasculitis tendency, in which bilateral CRAO would not be unusual [15]. MRI of diffusion weighted images in patients with CRAO showed retinal hyper signal diffusion of the papilla or scattered diffusion restriction over the retina.

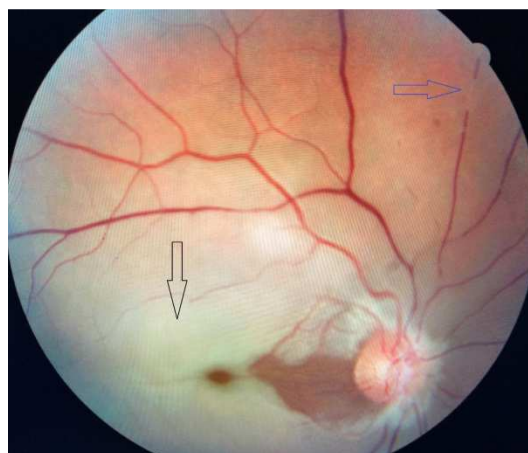


Figure 2. Colour Fundus image white arrow depicting pale retina in posterior pole, blue arrow depicting segmentation of blood column in the vessel.

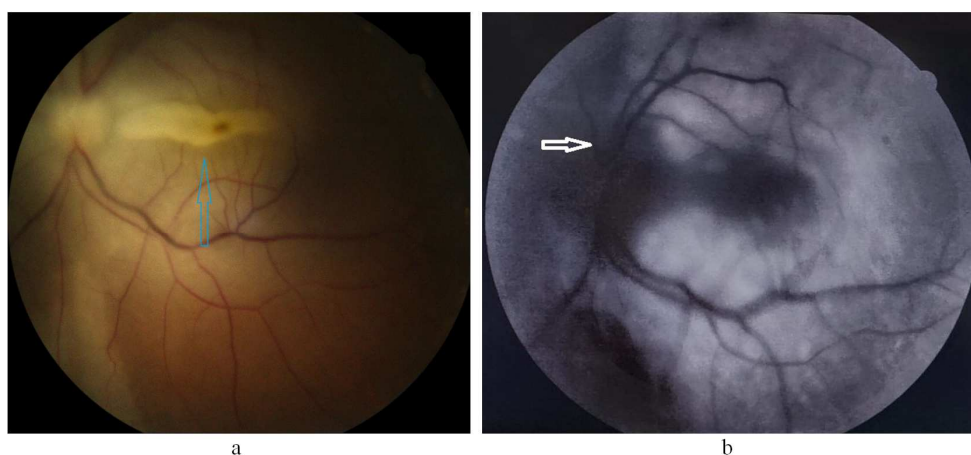


Figure 3. a. Colour fundus image of CRAO blue arrow depicting pale retina in posterior pole with dry macular fold; b. FFA image showing hypo fluorescence of retinal vessels arrow depicting vessel filling defect..

Optic nerve involvement in COVID patients was observed in many individuals. Ischaemic or inflammatory pathology noted in most of the patients. Few patients were suspected to have compressive optic neuropathy which was resolved after FESS. Young patients below 30 years' age showed papillitis, possibly post fever optic nerve inflammation, all these patients treated with systemic steroids, recovered vision after steroid therapy. Patients with AION were observed and advised to maintain glucose levels normal. Increased levels of cytokines due to inflammation may be responsible for the thrombogenesis. Non ischemic and ischemic optic neuropathies were noted in patients with comorbidities and also age group above 45 years, probability of micro emboli causing hypo perfusion of the optic nerve.

Neurological complications occur in approximately 32% of patients infected with beta coronavirus [16]. Neurological complications in Indian Variant B. 1.617.2, Delta were also reported with cerebellar changes and optic nerve involvement to our institute. Optic nerve is considered as one of source to reach the eye and cause changes in the inner retinal layers [17], as these changes were noted after 8 to 10 days 'of post infection, could be due to residual inflammation of acute

illness. Loss of taste and smell were other symptoms commonly reported probably associated with other cranial neuropathies.

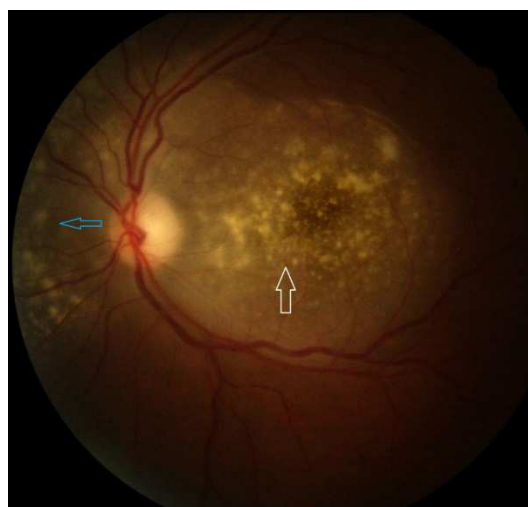


Figure 4. Colour fundus image white and blue arrow depicting ill-defined multiple, irregular and coalescent retinal infiltrates in the macular area and nasal to disc.

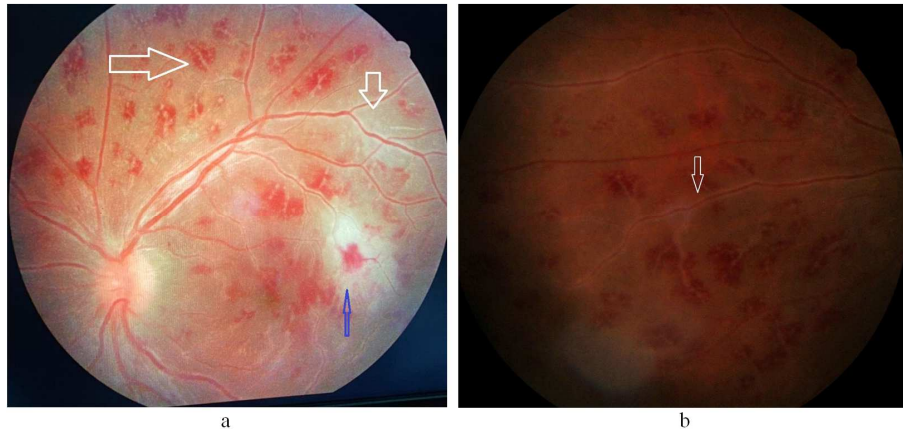


Figure 5. a. Fundus image showing broad big white arrow depicting frosted branch angiitis, small white arrow depicting elevated retina due to sub retinal fluid accumulation in superior temporal quadrant and blue arrow depicting active retinitis patch with overlying superficial retinal haemorrhage; b. Colour peripheral fundus image white arrow depicting the perivascular sheathing of the vessel.

Vitritis, retinitis (Figure 4) vasculitis, endophthalmitis and panophthalmitis were the intra ocular inflammation were noted in many patients. KOH stain revealed aspergillus fungus in most of the patients. Black fungus was the second common organism noted in our study and candida was the third most common organism noted. Endogenous endophthalmitis during recovery phase may be due to prolong hospitalisation causing nosocomial infections or immunosuppression due to diabetes or use of systemic steroids to reduce inflammatory markers, actually the reason is not known for these various ocular inflammation involving posterior pole. Vitritis, retinitis and vasculitis (Figures 5a and 5b) were unilateral and bilateral presentations noted in middle age patients where as endophthalmitis and panophthalmitis were unilateral presentation noted in patients age above 45 years. Vitritis, retinitis and vasculitis patients were treated with local steroids, posterior sub tenon injections of Triamcinolone acetanide 40mg/ml given, repeated after two weeks, totally three times given, vision was restored in these patients.

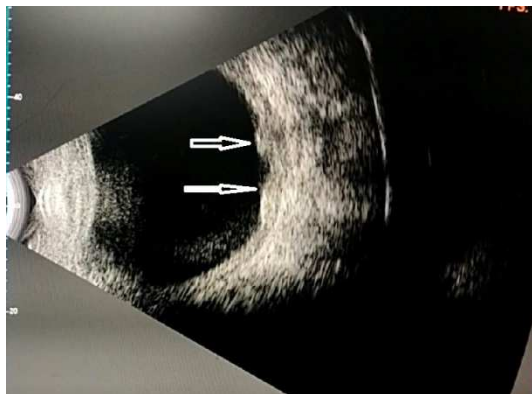


Figure 6. B Scan image white arrows depicting sub retinal abscess.

Sub retinal abscess (Figure 6), choroidal abscess (Figure 7) was also reported in few patients who presented after FESS to our institute. Patient had ocular pain and the choroidal thickening was nasal to disc, patient had good vision in that eye BCVA was 6/12. Local steroids were planned but not

given due to mucopurulent discharge from the eye. Choroidal abscess patient treated only with topical steroids showed good response after 4 weeks, choroidal abscess resolved. Patients with sub retinal abscess were almost in pre phthysical stage, topical steroids and cycloplegics were advised.



Figure 7. Colour fundus image of choroidal abscess yellow arrow depicting the cotton wool spot, blue arrow depicting the margin of elevated choroid.

Intermediate uveitis in few patients presented with clouding and vision impairment. Bilateral presentation was common. After complete uveitic workup, treated with topical and posterior sub tenon injections.

Two patients presented with central serous chorioretinopathy probably due to usage of steroids at the time of acute illness, explained regarding the condition and advised topical nonsteroidal anti-inflammatory drugs.

Herpes Zoster Ophthalmicus (HZO) seen during recovery phase without any abnormal changes in fundus, advised to consult dermatologist for the skin management.

Few patients who were already treated for ocular conditions before COVID infection like retinal vasculitis and ocular toxoplasmosis, suddenly presented with severe reactivity, severe vitritis, active inflammation and high body temperature, these patients were tested positive for COVID-19.

Ocular immunity which protects the eye from infections, innate immunity is lost due to the viral infection, complement system is activated and inflammatory markers released causing severe damage to the eye.

Few patients showed hypertensive retinopathy changes and the remaining patients fundus was normal. These patients though presented with sinusitis, presumed of fungal aetiology, with different fungal organisms like *Mucor*, *Aspergillus* and *Candida* on KOH stain, some patients did not show any organisms on stain and fundus was normal with normal visual acuity. We think viral load, immune status, hospital stay, oxygen support at hospital, uncontrolled glycaemic levels, associated cardiac and kidney dysfunctions, steroid use, environment, hygiene, exposure to aerosols, not properly wearing masks and long working hours all factors have badly affected the health and eye.

5. Conclusion

COVID-19 has caused devastating effects to the eye, need to plan to prevent and control the infection first, prevention is very important, education about the virus causing vision loss and other health problems is required in rural and urban areas to prevent the blindness. Quality of life in patients with complications after recovery was so miserable. Frequent testing, isolation, quarantine need to be followed strictly to protect ourselves from the COVID-19 infection. Limited study, need proper evaluation of each case and follow them regularly to detect the changes in fundus. Delta virus reducing the ocular immune status and affecting the eye with opportunistic fungal infections and causing vascular changes in eye due to vaso invasion of the organisms need further evaluation to see that how long these effects will last.

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