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ORIGINAL RESEARCH

STUDY OF CD4/CD8 AMONG COVID AND POST COVID PATIENT WITH FUNGAL INFECTION

Amit Kumar[1], Jyoti Kumar Dinkar[2], Kamal Kumar[3], Sudhir Kumar[4], Prity Kumari[3], Naresh Kumar[5]

[1]Senior Resident, [2]Assistant Professor, [3]Junior Resident, [4]Professor, [5]Professor and Head, Department of General Medicine, IGIMS, Patna, Bihar, India

Corresponding author
Dr. Sudhir Kumar, Professor, Department of General Medicine
IGIMS, Patna, Bihar, India
Email id: sudh75@gmail.com

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ABSTRACT

Background: A secondary condition arising in India is a large number of post-COVID fungal infections. The present study was conducted to study CD4/CD8 among covid and post covid patients with fungal infection.

Material & methods: The present prospective observational study was conducted among 50 patients admitted under COVID unit, IGIMS, Patna over a period of 6 months. 5ml of venous blood was drawn with aseptic precautions from patients. Then the serum was separated which was used for estimation of CD4+ and CD8+ count. Mean, standard deviation and confidence interval was calculated and the same represented by tables and graphs.

Results: Mean CD4/CD8 ratio according to orbital/facial pain, orbital/facial edema, ptosis, proptosis, loss of vision was 1.46. Mean CD4/CD8 ratio according to nasal block, nasal discharge, orbital/facial pain, orbital/facial edema, ptosis, loss of vision was 1.74. The p value of CD4 count was 0.322, p value of CD8 count was 0.885 which was non-significant. The p value for CD4/CD8 ratio was 0.869 which was non-significant. According to final outcome among study subjects, the p value for was non significant for CD4, CD8 and CD4/CD8 ratio. According to final outcome if regressed among study subjects the p value was non significant for CD4, CD8 and CD4/CD8 ratio. According to severity of COVID symptoms among study subjects the p value was non significant for CD4, CD8 and CD4/CD8 ratio. According to species identified among study subjects, the p value was non significant for CD4, CD8 and CD4/CD8 ratio. According to primary management among study subjects, the p value was non significant for CD4, CD8 and CD4/CD8 ratio.

Conclusion: The present study concluded that CD4/CD8 among covid and post covid patients with fungal infectionaccording to final outcome, According to final outcome if regressed, the p value was non significant. According to severity of COVID symptoms, According to species identified, According to primary management, the p value was non significant for CD4, CD8 and CD4/CD8 ratio.

Keywords: CD4/CD8, covid, post covid, fungal infection.

INTRODUCTION

At the end of May 2021, India reports more than 20 million confirmed cases of SARS-COV-2 with 300 thousand deaths.[1] India is now in the midst of two epidemic after government declare Mucormycosis, as notifiable disease. Mucormycosis a fungal infection is being reported in in COVID-19 patients during or post recovery, as per Press information bureau india reports more than 11thousand cases of mucor.[2] SARS-COV-2 infection may dysregulate T lymphocytes particularly CD4+ and CD8+ T cells which play a role in the pathogenesis of COVID-19 infection.[3] A study conducted in previous SARS patients found decrease in CD4+ an CD8+ count and the ratio of CD4/CD8 in the early acute phase of SARS, in contrast to other viruses such as HIV-1,CMV, or EBV which shows a specific immune pathology response to coronavirus.[4] CD4+T and CD8+T play a vital role in maintaining immune function and viral clearance in the body.[5] Prozenza et al also described the role of Mucorales specific T cell (CD4+ & CD8+) as a diagnostic marker of invasive Mucormycosis. Study was conducted in, Haematological malignancy group at risk of invasive Mucormycosis, they also correlated Mucorales specific T cell (CD4+ & CD8+) with clinical condition of patient.[6] The significant reduction of T cells and lymphocytes, over expression of inflammatory cytokines and impaired cell mediated immunity in COVID-19 associated with worst outcome and expose greater threat and susceptibility of developing opportunistic infection.[7,8] It is important to notice that COVID-19 patients can develop fungal infections during middle and latter stages of this disease especiallyseverly ill ones.[9] Looking back on SARS in 2003,it was found that incidence of fungal infection in SARS patients accounts for 14.8-27% which was even higher in severly ill ones, upto 21.9-33%, meanwhile fungal infection was the main cause of deaths for SARS patients (25-73.7%).[9] COVID-19 patients with trauma, diabetes mellitus, glucocorticoids use are more likely to develop Mucor mycosis.[10] In fungal infection both CD4+ and CD8+ cell participate in the elimination of fungal pathogens.[11] CD4+ cells differentiate into TH1 and TH17 helper T cells to fight against invading fungi.[11] Upon recognition of fungal particles presented by APC, CD8+ T cells differentiation which contribute in killing of fungal infected host cell.[12] The present study was conducted to study CD4/CD8 among covid and post covid patients with fungal infection.

MATERIAL & METHODS

The present prospective observational study was conducted among 50 patients admitted under COVID unit, IGIMS, Patna over a period of 6 months. The study was conducted after obtaining ethical clearance from the Institute Ethics committee, IGIMS, PATNA. Written informed consent was obtained from all the patients before enrolling them for the study**.** All patients of COVID or post COVID with fungal infection (diagnosed on the basis of microbiological study / culture or radiological evidence), Patients age more than 18 years of age of either sex. and Patient who gave consent to participate were included in the study. All patient of COVID or post COVID without evidence of fungal infection, Patients who refused to participate in the study were excluded from the study. 5ml of venous blood was drawn with aseptic precautions from patients (fromlarge peripheral veins) and put into a plain vacutainer and subjected forcentrifugation. Then the serum was separated which was with the help of flowCytometry used for estimation of CD4+ and CD8+ count. The history of theonset, progression, duration of various symptoms, drugs and diet history was noted. Clinical examination of patients was done for signs of fungal infection. Mean, standard deviation and confidence interval was calculated and the same represented by tables and graphs**.**

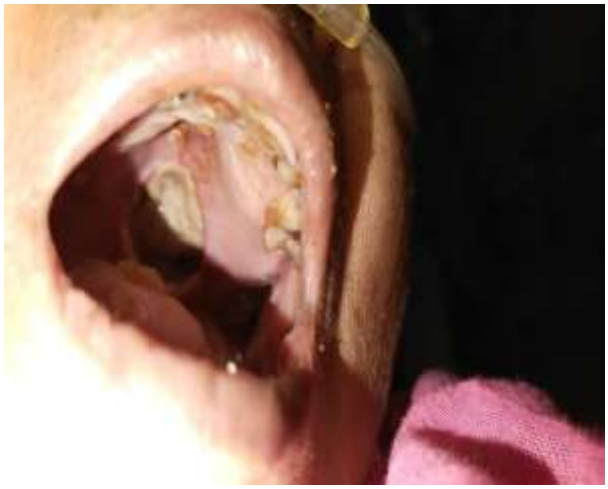


Figure 1: A case of palatal mucormycosis

Figure 2: A case of rhino orbital mucormycosis

Figure 3: A case of rhino orbital cerebral mucormycosis

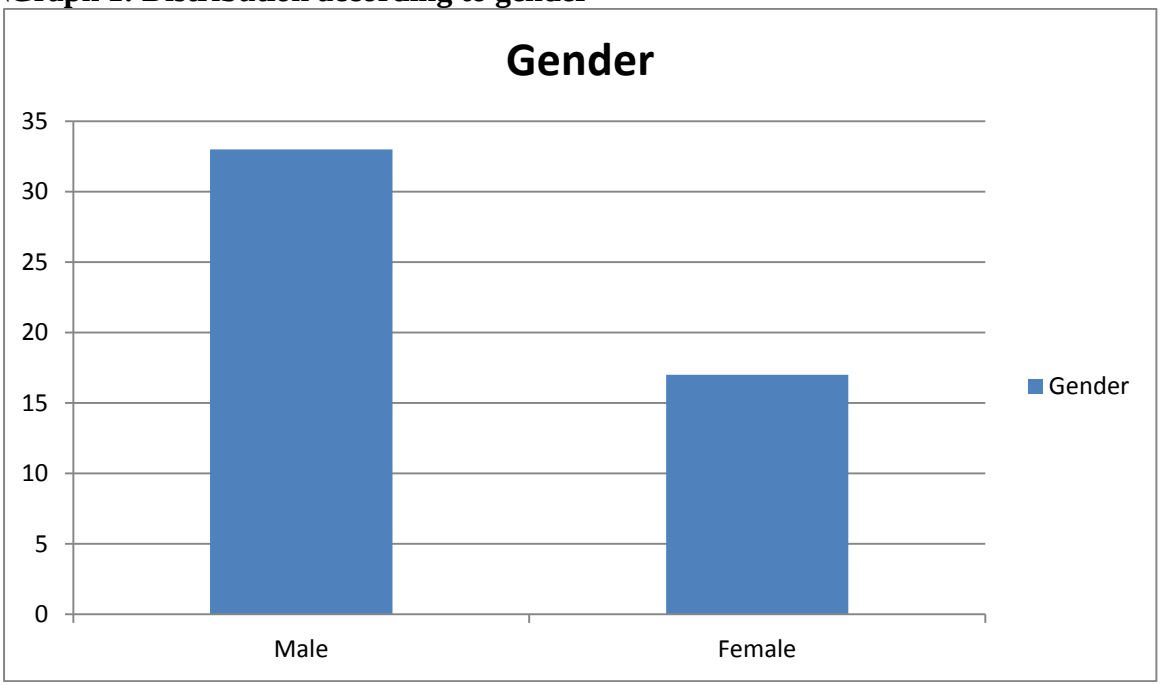
Figure 4: A case of rhino maxillary mucormycosis

RESULTS

Table1. Demographic characteristics of study subjects

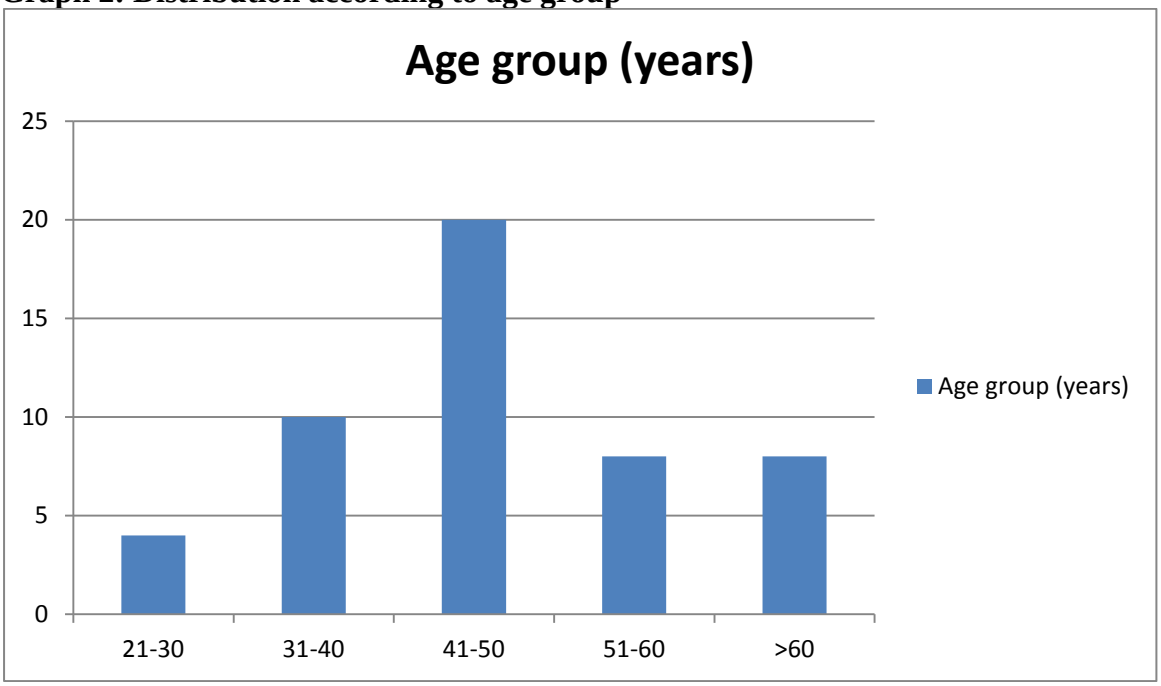
	Frequency	Percent
Age Group (Years)		
21-30	4	8.0
31-40	10	20.0
41-50	20	40.0
51-60	8	16.0
>60	8	16.0
Gender		
Male	33	66.0
Female	17	34.0
Occupation		
Job	5	10.0
Business/self employed	13	26.0
Farmer	11	22.0
Housewife	16	32.0
Labour/worker	2	4.0
Student	1	2.0
Retired	2	4.0

\Graph 1: Distribution according to gender



In this study, maximum participants were of age group 41-50yrs (40%) and 66% were males. Maximum participants were housewives (32%).

Graph 2: Distribution according to age group



Graph 3: Distribution according to occupation

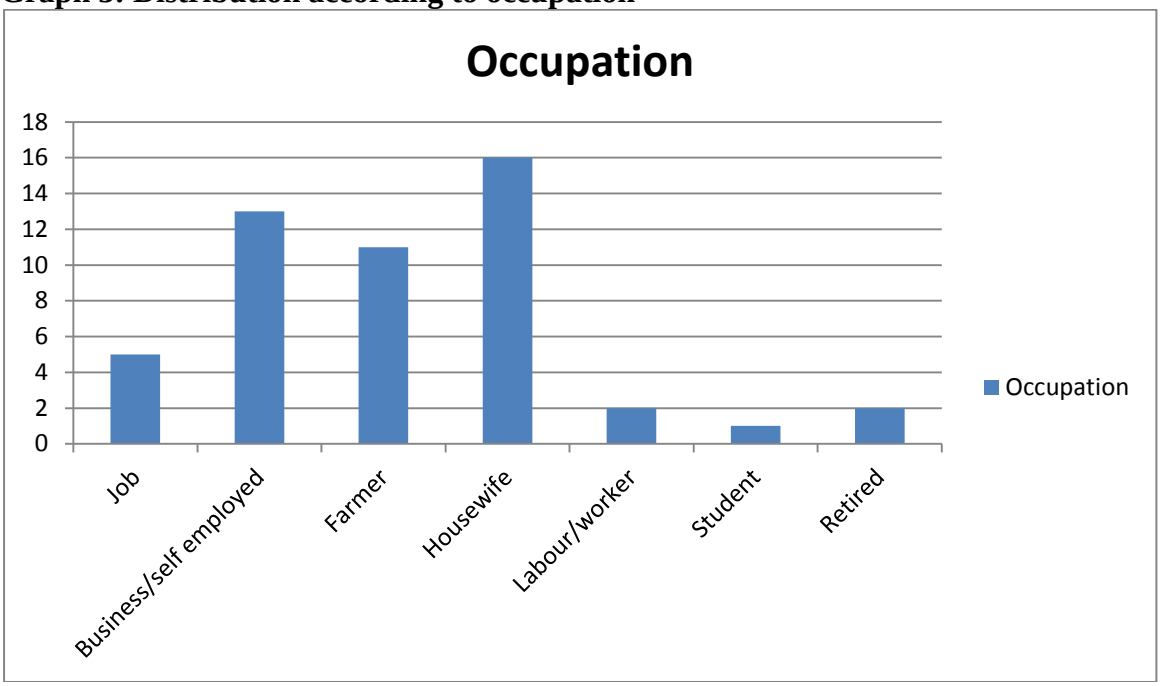


Table2. Mean of blood and immunological parameters overall among study subjects

Parameters	Minimum	Maximum	Mean	Std. Deviation
Hb	6.0	15.9	10.55	2.23
TLC	2770.0	14640.0	8068.84	2849.29
Neutrophil	52.0	89.0	74.70	7.96
Lymphocytes	3.6	41.8	18.98	8.02
CRP	3.0	80.0	31.08	13.55
Dimer	.12	3.22	0.86	0.57
S.ferritin	22.0	2000.0	580.44	414.40
RBS	88.0	722.0	270.16	124.87
HbA1c	4.4	15.3	8.62	2.76
CD4 HelperTCell (%)	18.0	63.2	38.53	10.26
CD8(%)	10.1	44.0	28.03	8.82
AbsoluteCD4HelperTCell	41.0	1374.0	535.14	325.10
AbsoluteCD8CytotoxicTCell	34.0	1359.0	416.58	329.51
AbsoluteCD4/CD8Ratio	.45	5.22	1.56	0.84

Mean Hemoglobin of participants was 10.55, mean TLC was 8068.84, mean neutrophils was 74.70, mean lymphocytes was 18.98, mean CRP was 31.08, mean dimer values was 0.86.S.ferritin was 580.44, RBS was 270.16, HbA1c was 8.62. CD4 Helper T cell % was 38.53, CD8 % was 28.03, Absolute CD4 Helper T Cell were 535.14, Absolute CD8 Cytotoxic T Cell 416.58, AbsoluteCD4/CD8 Ratio was 1.56.

Table3. Comparison of mean CD4, CD8 count and CD4/CD8 Ratio according to primary symptoms among study subjects

Parameters	Symptoms	Mean	Std. Deviation	F value	p value
CD4	**1346**	524.24	364.65	0.457	0.636
	34689	592.83	368.91		
	123469	482.36	219.03		
CD8	**1346**	399.35	359.61	0.533	0.59
	34689	483.83	358.94		
	123469	367.36	261.39		
CD4/CD8 Ratio	**1346**	1.49	0.78	0.505	0.607
	34689	1.46	0.61		
	123469	1.74	1.16		

1=nasal block2=nasal discharge3=orbital/facial pain4=orbital/facial edema5=orbital/facial discoloration6=ptosis7=diplopia8=proptosis9=loss of vision

Mean CD4 count according to nasal block, orbital/facial pain, orbital/facial edema, ptosis was 524.24. Mean CD4 count according to orbital/facial pain, orbital/facial edema, ptosis, proptosis, loss of vision was 592.83. Mean CD4 count according to nasal block, nasal discharge, orbital/facial pain, orbital/facial edema, ptosis, loss of vision was 482.36. Mean CD8 count according to nasal block, orbital/facial pain, orbital/facial edema, ptosis was 399.35. Mean CD8 count according to orbital/facial pain, orbital/facial edema, ptosis, proptosis, loss of vision was 483.83. Mean CD8 count according to nasal block, nasal discharge, orbital/facial pain, orbital/facial edema, ptosis, loss of vision was 367.36.Mean CD4/CD8ratio according to nasal block, orbital/facial pain, orbital/facial edema, ptosis was 1.49. Mean CD4/CD8ratio according to orbital/facial pain, orbital/facial edema, ptosis, proptosis, loss of vision was 1.46. Mean CD4/CD8ratio according to nasal block, nasal discharge, orbital/facial pain, orbital/facial edema, ptosis, loss of vision was 1.74.

Graph 4: Comparison of mean CD4, CD8 count according to final outcome among study subjects

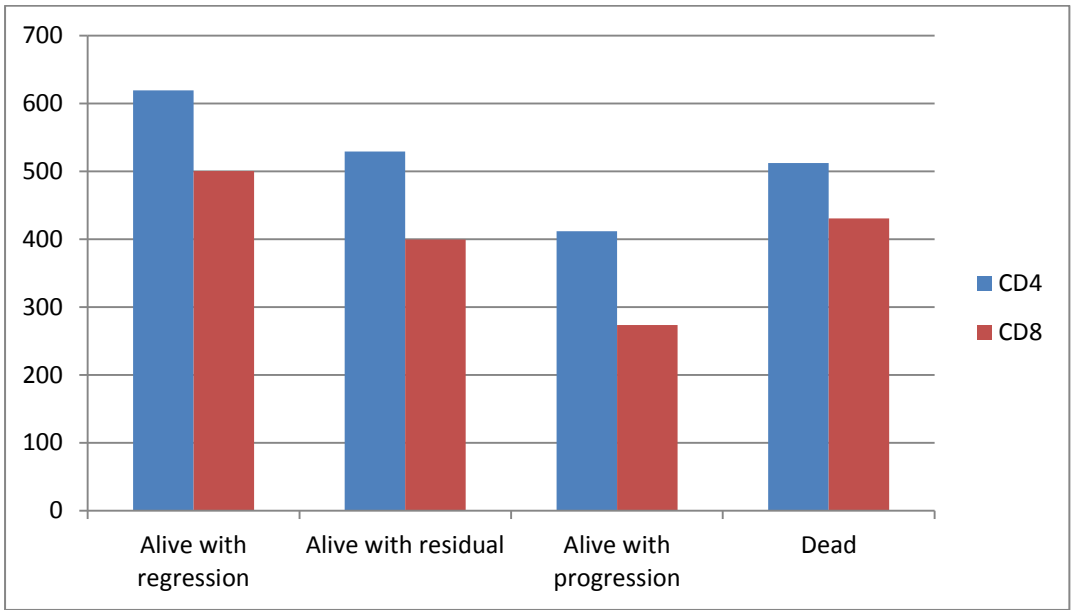


Table4. Comparison of mean CD4, CD8 count and CD4/CD8 Ratio according to primary signs among study subjects

Parameters	Signs	Mean	Std. Deviation	F value	p value
CD4	**135**	302.00		1.198	0.322
	235	275.00			
	1235	523.26	334.75		
	1359	134.00			
	2586	520.17	257.37		
	3689	1108.00			
	12356	915.00			
	12569	362.00			
	13569	287.50	205.77		
	135689	671.10	361.17		
	1235689	191.00			
CD8	**135**	237.00		0.492	0.885
	235	143.00			
	1235	437.37	371.35		
	1359	174.00			
	2586	389.08	306.95		
	3689	635.00			
	12356	485.00			
	12569	276.00			
	13569	222.00	74.95		
	135689	538.20	365.08		
	1235689	74.00			
CD4/CD8 Ratio	**135**	1.27		0.515	0.869
	235	1.93			
	1235	1.39	0.58		
	1359	0.78			
	2586	1.88	1.34		
	3689	1.74			
	12356	1.89			
	12569	1.31			
	13569	1.21	0.52		
	135689	1.53	0.72		
	1235689	2.57			

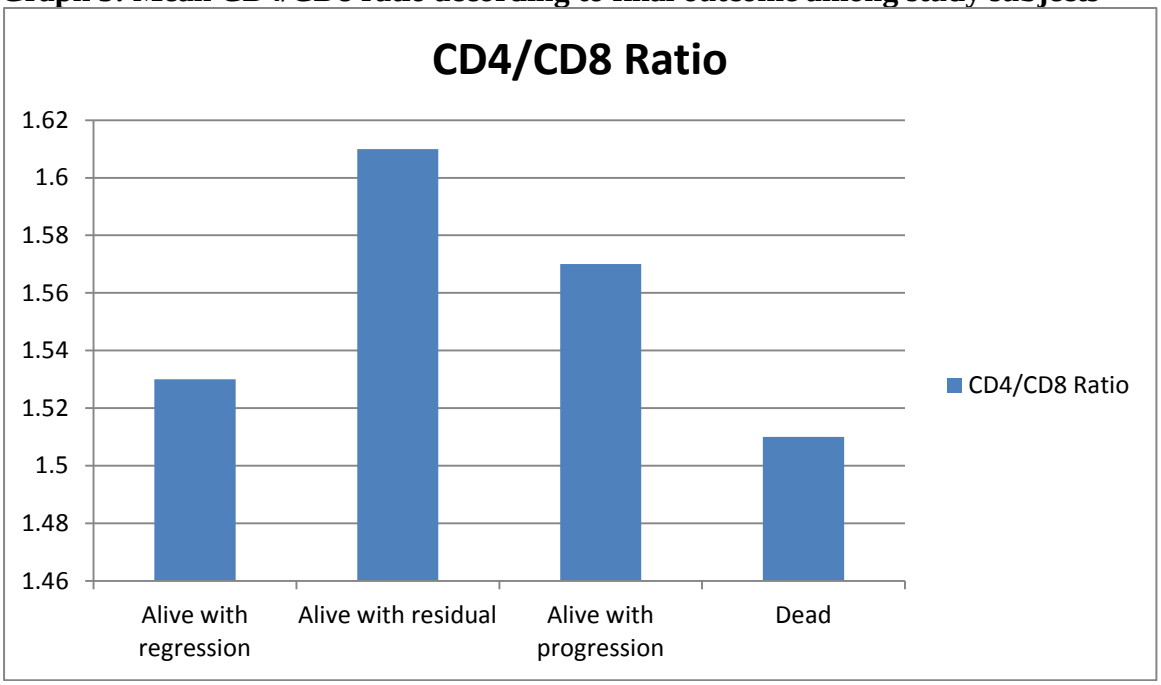
1=nasal ulcer/eschar2=nasal discharge3=periocular/facial edema4=periocular/facial discoloration5=periocular hypaesthesia6=ptosis7=diplopia8=proptosis9=loss of vision

The p value of CD4 count was 0.322, p value of CD8 count was 0.885 which was non-significant. The p value for CD4/CD8 ratio was 0.869 which was non-significant.

Table 5. Comparison of mean CD4, CD8 count and CD4/CD8 Ratio according to final outcome among study subjects

Parameters	Outcome	Mean	Std. Deviation	F value	p value
CD4	Alive with regression	619.15	313.44	0.581	0.631
	Alive with residual	529.24	299.65		
	Alive with progression	411.83	70.52		
	Dead	512.30	470.24		
CD8	Alive with regression	500.15	371.81	0.668	0.576
	Alive with residual	399.19	251.38		
	Alive with progression	273.33	67.76		
	Dead	430.40	489.02		
CD4/CD8 Ratio	Alive with regression	1.53	0.84	0.039	0.99
	Alive with residual	1.61	1.06		
	Alive with progression	1.57	0.52		
	Dead	1.51	0.55		

Graph 5: Mean CD4/CD8 ratio according to final outcome among study subjects



According to final outcome among study subjects, the p value for CD4 was 0.631, for CD8 was 0.576 and CD4/CD8 ratio was 0.039 which was non significant for all.

Table 6. Comparison of mean CD4, CD8 count and CD4/CD8 Ratio according to final outcome if regressed among study subjects

Parameters	Outcome	Mean	Std. Deviation	F value	p value
CD4	Exenteration	546.38	268.99	.132	.877
	Eye salvage	520.63	364.67		
	Vision Salvage	406.00			
CD8	Exenteration	407.75	290.32	.433	.652
	Eye salvage	438.75	275.28		
	Vision Salvage	155.00			
CD4/CD8 Ratio	Exenteration	1.64	0.95	1.135	.332
	Eye salvage	1.29	0.64		
	Vision Salvage	2.61			

According to final outcome if regressed among study subjects the p value for CD4 was 0.877, the p value for CD8 was 0.652, for CD4/CD8 ratio it was 0.332. The p value was non significant for all.

Table 7. Comparison of mean CD4, CD8 count and CD4/CD8 Ratio according to severity of COVID symptoms among study subjects

Parameters		Mean	Std. Deviation	F value	p value
CD4	None	673.00		2.132	0.069
	RT-PCR positive, asymptomatic	1374.00			
	Home care, ambulatory	439.80	223.92		
	Home care, needed assistance	850.00	487.90		
	Hospitalized, no oxygen	467.92	283.99		
	Hospitalized, oxygen - mask/prongs	517.44	291.27		
	Hospitalized, oxygen - on-invasive	664.67	414.21		
CD8	None	665.00		2.297	0.052
	RT-PCR positive, asymptomatic	530.00			
	Home care, ambulatory	263.60	191.11		
	Home care, needed assistance	903.00	644.88		
	Hospitalized, no oxygen	354.27	301.88		
	Hospitalized, oxygen - mask/prongs	344.89	209.86		
	Hospitalized,	699.17	409.01		

	oxygen - on-invasive				
CD4/CD8 Ratio	**None**	1.01		1.552	0.185
	RT-PCR positive, asymptomatic	2.59			
	Home care, ambulatory	2.21	1.83		
	Home care, needed assistance	1.01	0.18		
	Hospitalized, no oxygen	1.54	0.69		
	Hospitalized, oxygen - mask/prongs	1.72	0.59		
	Hospitalized, oxygen - on-invasive	1.00	0.31		

According to severity of COVID symptoms among study subjects the p value was non significant for CD4, CD8 and CD4/CD8 ratio.

Table 8. Comparison of mean CD4, CD8 count and CD4/CD8 Ratio according to species identified among study subjects

Parameters		**Mean**	**Std. Deviation**	**F value**	**p value**
CD4	**No Organism**	582.57	338.44	0.394	0.758
	Mucor	525.17	303.87		
	Rhizopus	524.44	359.60		
	aseptate irregular wideangle branched hyphae	711.75	381.52		
CD8	**No Organism**	487.86	408.35	0.123	0.946
	Mucor	454.56	335.33		
	Rhizopus	403.75	344.44		
	aseptate irregular wideangle branched hyphae	405.25	346.94		
CD4/CD8 Ratio	**No Organism**	1.42	0.63	2.609	0.064
	Mucor	1.40	0.50		
	Rhizopus	1.53	0.86		
	aseptate irregular wideangle branched hyphae	2.64	1.83		

According to species identified among study subjects, the p value was non significant for CD4, CD8 and CD4/CD8 ratio.

Table 9. Comparison of mean CD4, CD8 count and CD4/CD8 Ratio according to primary management among study subjects

Parameters		Mean	Std. Deviation	t value	p value
CD4	**Amphotericin B**	550.09	326.45	1.678	0.201
	Amphotericin B, Posaconazole	301.00	225.39		
CD8	**Amphotericin B**	431.68	333.01	1.668	0.203
	Amphotericin B, Posaconazole	180.00	142.17		
CD4/CD8 Ratio	**Amphotericin B**	1.56	0.86	0.01	0.917
	Amphotericin B, Posaconazole	1.61	0.54		

According to primary management among study subjects, the p value was non significant for CD4, CD8 and CD4/CD8 ratio.

Table10. Comparison of mean CD4, CD8 count and CD4/CD8 Ratio according to overall management among study subjects

Parameters	FESS done	Mean	Std. Deviation	F value	p value
CD4	**Yes**	522.13	342.71	0.819	0.447
	No	268.00	108.89		
	Open	568.48	316.79		
CD8	**Yes**	429.00	389.30	0.815	0.449
	No	124.00	70.71		
	Open	428.56	274.07		
CD4/CD8 Ratio	**Yes**	1.58	0.76	0.799	0.456
	No	2.28	0.42		
	Open	1.49	0.93		

According to severity of COVID symptoms among study subjects the p value was non significant for CD4, CD8 and CD4/CD8 ratio.

DISCUSSION

The possibility of opportunistic fungal infections in patients recovering from the COVID infection is now documented in the literature. Associated fungal infections are not just restricted to mucormycosis, but include a wide variety of organisms such as invasive aspergillosis, candidiasis, and cryptococcosis. It is essential to assess the risk factors, types of invasive mycosis, appropriate diagnostic methods, and the requirement for individual treatment protocols in COVID-19 patients.[13]

In this study, maximum participants were of age group 41-50yrs (40%) and 66% were males. Maximum participants were housewives (32%). Mean Hemoglobin of participants was 10.55, mean TLC was 8068.84, mean neutrophils was 74.70, mean lymphocytes was 18.98, mean CRP was 31.08, mean dimer values was 0.86.S.ferritin was 580.44, RBS was 270.16, HbA1c was 8.62. CD4 Helper T cell % was 38.53, CD8 % was 28.03, Absolute CD4 Helper T Cell were 535.14, Absolute CD8 Cytotoxic T Cell 416.58, Absolute CD4/CD8 Ratio was 1.56. Mean CD4/CD8 ratio according to nasal block, orbital/facial pain, orbital/facial edema, ptosis was 1.49. Mean CD4/CD8 ratio according to orbital/facial pain, orbital/facial edema, ptosis, proptosis, loss of vision was 1.46. Mean CD4/CD8 ratio according to nasal block, nasal

discharge, orbital/facial pain, orbital/facial edema, ptosis, loss of vision was 1.74. The p value of CD4 count was 0.322, p value of CD8 count was 0.885 which was non-significant. The p value for CD4/CD8 ratio was 0.869 which was non-significant. According to final outcome among study subjects, the p value for was non significant for CD4, CD8 and CD4/CD8 ratio. According to final outcome if regressed among study subjects the p value was non significant for CD4, CD8 and CD4/CD8 ratio. According to severity of COVID symptoms among study subjects the p value was non significant for CD4, CD8 and CD4/CD8 ratio. According to species identified among study subjects, the p value was non significant for CD4, CD8 and CD4/CD8 ratio. According to primary management among study subjects, the p value was non significant for CD4, CD8 and CD4/CD8 ratio.

FurongZent et al conducted a study at Hunan, China on "association of inflammatory marker with severity of COVID-19" and concluded that inflammatory markers are positively correlated with severity of COVID-19. [1]

Another study done by Feng Pan et al, in which various inflammatory marker was analysed in death event group and discharged patient. Study shows higher level of CRP, PCT, IL6, D-dimer, BNP in death event group compare to discharge patient group. [2]

Another retrospective study conducted in COVID designated hospital at Wuhan, China. In this hospital-based study, prognostic value of CRP level was evaluated, and concluded that CRP level well correlated with disease severity and it is the good predictor of outcome[3].

Desai N, et al showed that the frequency of proposed risk factors for COVID-19 associated mucormycosis (CAM) infection was diabetes mellitus (77%), recent history of steroid use (69%) and hypoxia during COVID-19 infection (52%). Iron metabolism was dysregulated in CAM patients with low TIBC and total iron. Further, CAM was accompanied with lymphopenia with drastic reduction in B cell counts; however, plasmablasts were not altered. Further, CAM patients had low immunoglobulin levels and antibodies specific to mucor peptide did not increase in CAM suggesting dysfunction in B-cell response. There was increase in activated effector cytotoxic CD8 T cells and NK cells in CAM compared with COVID-19 infection and healthy controls. Among T helper cells, Tregs were reduced and Th-1 frequency was increased in CAM compared with COVID-19 infection. A distinct cytokine signature was evident in CAM with increase in IL-1β, IFN-γ, IL-6, IL-22, IL-17A, IL-10, IL-2, IL-8, IL-7, IL-21 and GM-CSF.[14]

CONCLUSION

Our study aimed to investigate the CD4/CD8 ratio among COVID and post-COVID patients with fungal infection. Our results showed that the mean CD4 count was 535.14, mean CD8 count was 416.58, and the mean CD4/CD8 ratio was 1.56. The p values for CD4 count, CD8 count, and CD4/CD8 ratio were non-significant.

Our findings suggest that the CD4/CD8 ratio may not be a reliable marker for predicting the severity of fungal infection in COVID and post-COVID patients. However, further studies are required to confirm this result and explore other potential markers for fungal infection in COVID and post-COVID patients.

In conclusion, our study highlights the need for more research on the CD4/CD8 ratio as a potential marker for fungal infection in COVID and post-COVID patients. Although our study did not find a significant association between the CD4/CD8 ratio and fungal infection, it provides a valuable baseline for future investigations. Ultimately, better markers for fungal infection in COVID and post-COVID patients will help clinicians identify and treat these patients more effectively, improving their clinical outcomes.

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