Risk factors for COVID-19 associated pulmonary aspergillosis in a high endemic setting and development of a bedside clinical risk prediction score

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Background

- India has a high burden of invasive fungal infections at baseline.
- The real-world data on the risk factors and outcome of COVID-19 associated pulmonary aspergillosis (CAPA) are limited.

AIM

To determine risk factors and clinical outcomes of CAPA and develop a prediction model for patient stratification

Method

- A retrospective, case-control study was conducted at a 1300-bed tertiary care academic center in South India. from June 1st, 2020 to May 31st, 2021.
- CAPA cases were defined by the 2020 ECMM/ISHAM consensus criteria. Age- and admission period- matched control group with COVID-19 but without aspergillosis was selected in a 1:1 ratio.
- A risk scoring stratification for CAPA was developed based on the significant CAPA risk factors by employing a logistic regression model.

Result

- 95 CAPA cases, of which 75(79%) were probable and 20(21%) possible, were diagnosed during the study period. (Table 1)
- The time from COVID-19 diagnosis to CAPA (in days) was (median, IQR) 13, 12. 40 (42.1%) of patients were on mechanical ventilation at CAPA diagnosis.
- Logistic regression analysis of risk factors showed neutropenia, use of steroids, broad-spectrum antibiotic use, fluconazole prophylaxis and absence of co-infecting pathogen to be significant factors associated with CAPA (p<0.05). (Fig 1)
- An optimal risk score of ≥10.00 predicted CAPA with a sensitivity of 84.2% and a specificity of 59% with an area under the curve of 0.77 (PPV=67.23%, NPV=78.87%)(AUC=0.77)(Fig 2).
- MV, NIV and hospital/ICU stay were significantly higher in CAPA patients compared to controls (Table 2).
- 28-day (41.1% vs 33.7%, p=0.13) and 6-week all cause-mortality (48.4% vs 37.9%, p=0.07) were higher, but not statistically significant, for CAPA.

Table 1: Baseline characteristics and Risk factors

Variables	Total (N=190)(%)	Case (N=95)(%)	Control (N=95)(%)	P value
Average age (Mean±SD)	55.3±15.7	56.03±15.2	54.70±16.3	0.563
Male	140 (71.8)	74 (77.9)	66 (69.5)	0.12
Severity of COVID-19				
Mild	48 (25.3)	11 (11.6)	37 (38.9)	<0.001
Moderate-Severe	142 (74.7)	84 (88.4)	58 (61.05)	
Disease classification				
Probable	75(39.4)	75(78.9)	NA	
Possible	20(10.5)	20(21.05)	NA	
Comorbidities				
New onset Diabetas Mellitus after admission	2 (1.05)	1 (1.1)	1 (1.1)	0.05
Diabetic Ketoacidosis during IP stay	5 (2.63)	1 (1.1)	4 (4.2)	0.105
Diabetes Mellitus at admission	82 (43.15)	33 (34.7)	49 (51.6)	0.019
Hypertension	81 (42.63)	37 (38.9)	44 (46.5)	0.153
Chronic Kidney Disease	46 (24.21)	24 (25.3)	22 (23.2)	0.36
Risk factors				
EORTC risk factors	46 (24.21)	37 (38.9)	9 (9.5)	<0.001
Lymphopenia	91 (47.89)	75 (78.9)	16 (16.8)	<0.001
Neutropenia	14 (7.36)	12 (12.6)	2 (2.1)	0.006
Hematologic malignancy	14 (7.3)	7 (7.4)	7 (7.4)	0.163
Transplant	5 (2.63)	3 (3.2)	2 (2.1)	0.32
Prolonged steroid use prior to admission	8 (4.21)	7 (7.4)	1 (1.1)	0.033
T-cells and B-cell immunosuppresants	3 (1.57)	2 (2.1)	1 (1.1)	0.28
Ibrutinib use	1 (0.52)	1 (1.1)	0	
Solid organ transplant/Allogenic Stem Cell Transplant	5 (2.6)	3 (3.2)	2 (2.1)	0.32
Broad-spectrum antibiotic use	155(81.6)	88 (92.6)	67(70.5)	<0.001
Fluconazole prophylaxis	55 (28.9)	37 (38.9)	18 (18.9)	0.002
Diabetic ketoacidosis on admission	5 (2.6)	2 (2.1)	3 (3.2)	0.32
Clinical Lab Parameters and Microbiology				
HbA1c	7.72±1.99	7.7±2.48	7.72±1.90	0.95
Absolute Lymphocyte Count at admission	153.86±210.359	125.83 ± 148.14	182.48 ± 256.67	0.06
Total Leucocyte count	11.02±7.660	10.68 ± 6.49	11.35±8.71	0.551
Co-infecting Pathogen	24 (12.6)	5(5.2)	19(20)	0.002
Bacteria	17(8.9)	2(2.1)	15(15.7)	<0.001
Fungi	7(3.6)	3(3.1)	4(4.2)	0.7

Fig 1: Bedside clinical scoring for CAPA incidence

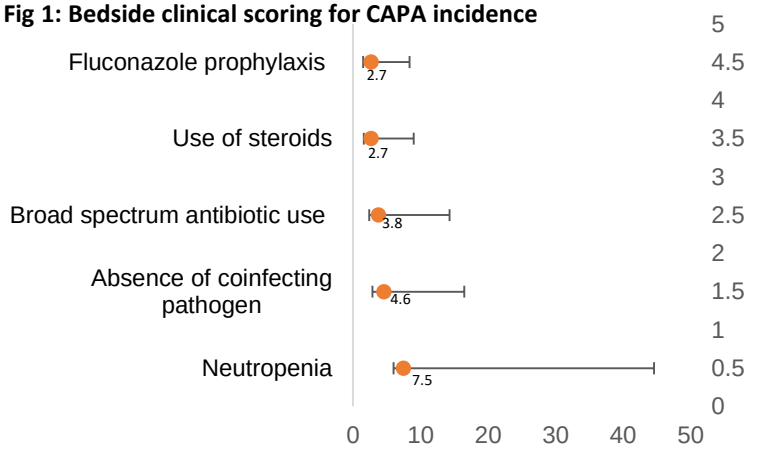

Table 2:Primary and Secondary outcomes

Variables	Total (Case+ Control) N=190(%)	Case n=95(%)	Control n=95(%)	RR	P value
Mortality					
28 Day mortality	71(37)	39 (41.1)	32 (33.7)	1.37	0.293
6 week mortality	82(43)	46(48.4)	36(37.9)	1.27	0.14
Clinical cure	108(57)	49(51.6)	59(62.1)	0.65	0.14
Mechanical Ventilation	82(43)	49(51.6)	33(34.7)	2	9
Non-Invasive Ventilation(Over the course)	98(51.5)	66(69.4)	32(33.6)	4.48	<0.001
Hospital stay					
Average length of stay	16.31±12.09	20 ± 12	13±11	–	0.0001
ICU stay	115(60.5)	66(69.5)	49(51.6)	2.14	0.011
More than 7 days of ICU stay	80(42.1)	52(54.7)	28(29.5)	2.89	<0.001

Conclusion

Risk factors of CAPA in India were similar to those reported previously in other countries.
CAPA can be seen in severe COVID-19 patients who are not mechanically ventilated.
A CAPA risk scoring system, that needs external validation, is a simple and feasible risk stratification tool for patients with suspected CAPA.

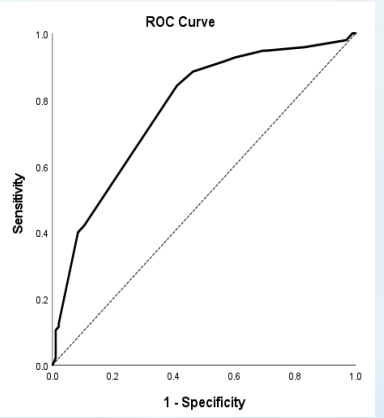

Figure 2: Receiving operating characteristic curve of CAPA incidence score for predicting CAPA in the study cohort

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