DOI: https://doi.org/10.53350/pjmhs22162321

ORIGINAL ARTICLE

Risk factors for development of covid associated pulmonary aspergillosis in ICU population. An observational study from a large tertiary care hospital

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ABSTRACT

Background: Covid associated pulmonary aspergillosis is a serious life-threatening infection which is increasingly being identified in severe covid pneumonia. There are multiple factors which predispose to this infection, still lot of research is needed to explore more about this infection

Objective: Our aim of study was to find out risk factors associated with development of CAPA in severe covid pneumonia.

Materials and methods: We prospectively enrolled 698 cases of severe covid pneumonia and aimed to identify risk factors associated with development of CAPA. We included only those who were PCR confirmed cases severe covid pneumonia requiring ICU admission with at least 48 hours of ICU stay. Infectious disease experts decided candidacy of Tocilizumab. CAPA cases were diagnosed according to ISHAM criteria for diagnosis of CAPA.

Results: Out of 678 participants, 17.4% developed CAPA. Out of 17.4% cases of CAPA, 83.9% did not survive. Median ICU stay was 10 days. NUTRIC score and ICU days were identified as statistically significant risk factors for CAPA (OR: 2.1,1.2 p= 0.006, <0.001). Median NUTRIC score was 3. Tocilizumab prevents development of CAPA (OR: 0.09, p=< 0.001).

Conclusion: We concluded that NUTRIC score and ICU days are predisposing factors for CAPA in severe covid pneumonia. Tocilizumab has role in reducing CAPA infection in severe covid pneumonia.

Keywords: Pneumonia, CAPA, aspergillus, mortality

INTRODUCTION

Severe covid pneumonia is a fatal condition requiring ICU admission due to Acute respiratory failure. Danger associated molecules are released which provide a permissive environment for the growth of aspergillus in severe covid pneumonia leading to invasive pulmonary infection (1). Invasive pulmonary aspergillosis in covid is now termed as covid associated pulmonary aspergillosis (CAPA) and was first described in 2020 in small case series (2-4). Since then, CAPA has been a focus of research and increasingly being recognized as a life-threatening entity in ICU population. Its incidence varies in different studies (3%-33%) (5, 6)due to different level of awareness and diagnostic tools and diagnostic criteria (7).

Recently proposed criteria to define CAPA provide more uniformity in identification of CAPA and is based on clinical conditions, radiological infiltrates, and microbiological evidence of aspergillus (8). Several risk factors have been identified for CAPA which include use of corticosteroids, tocilizumab and baseline pulmonary illnesses (9). Severe covid pneumonia has been recently identified as an independent risk factor for CAPA(2). However, there is a much need to identify risk factors which could help in adopting measures for early recognition of CAPA in severe covid pneumonia. for this purpose, European Confederation of Medical Mycology ECMM has initiated a multicenter prospective study to identify risk factors associated with CAPA and their potential impact on mortality.

Another single centered epidemiological study conducted at National level aimed to find out incidence of CAPA suggested that risk factors associated with development of CAPA should be identified to prevent or diagnose this serious infection. We conducted this prospective study to identify risk factors associated with development of CAPA in severe covid pneumonia (10)

METHODOLOGY

Study was conducted at Covid ICU of Shifa International Hospital from Ist October 2020 to 31st October 2021. Our hospital is a 50-bedded Medical ICU and one of the biggest research and academic institute of the country. Study protocol was approved by institutional review board committee. Informed consent was taken from all participants of the study. We included 18 years or above confirmed cases of severe covid pneumonia admitted requiring ICU admission due to respiratory failure and had an ICU stay of ≥ 48 hours at least. We excluded those who were less than 18 years; those who had negative PCR for covid pneumonia; those who didn't consent to participate in study and those who were transferred out or expired within 48 hours of admission.

After consent and meeting inclusion criteria, participants were enrolled in study. Standard treatment protocol was given to all participants. Use of Steroids was part of standard care. Infectious diseases expert of the hospital decided candidacy of Tocilizumab and remdesivir. A preformed structured questionnaire was used to record demographic and clinical data like age, gender, comorbid conditions. At enrollment, clinical severity scores like APACHE II, NUTRIC and SOFA scores were calculated for all patients. Variables like use of vasopressors, remdesivir or/and Tocilizumab, ICU days were recorded by resident physician. Outcome variables like discharge from ICU or death within ICU were also recorded. Mortality was defined as death during treatment in ICU and survival was defined as discharge-e from ICU.

Participants were tested for CAPA when they had clinically evident respiratory deterioration in terms of increased oxygen demand or ventilatory settings. Chest X-Rays were performed to detect any radiological infiltrates and serum samples were sent for galactomannan levels. All samples were tested using Platelia™ Aspergillus kit (Bio-Rad Laboratories, Hercules, CA). Serum value > 0.5 was taken as cut-off. Tracheal aspirate was sent for fungal cultures. We diagnosed probable CAPA as suggested by European Confederation of Medical Mycology /International Society for Human and Animal Mycology (ECMM/ISHAM) (8). Oral Voriconazole was administered to confirmed cases of CAPA.

Statistical analysis: Statistical analysis was done with SPSS version 26. Continuous variables were tested for Normality by using Shapiro-wilk test. P value < 0.05 suggested non-normal distribution of the data and was presented in median and IQR. Chi square test was used for categorical data. Mann-Whitney U test was used to find out distribution of APACHE II, NUTRIC, SAPS,

SOFA and ICU days amongst Cohorts with CAPA and without CAPA. Binary logistic regression analysis was used to identify risk factors associated with increased mortality of CAPA in ICU population. P Value < 0.05 was taken as statistically significant.

RESULTS

We enrolled 678 participants during study period (Fig 1). Out of 678, 57.8% were males and 42.1% were females. Median age of our study participants was 60 (IQR: 54-67) years. Out of total study participants, we identified 118 cases of CAPA (17.4|%). We did not find any statistically significant difference between CAPA and both genders (P=0.28). Similarly, distribution of age was not statistically significant different amongst cohorts with CAPA and without CAPA (p=0.83) as given in table 2. Malignancy and cirrhosis were the most common comorbid conditions associated with CAPA (p= < 0.001 each).

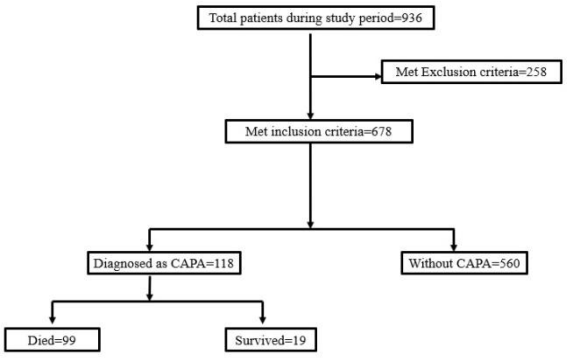

Figure 1: Flow diagram of study participants

Table 2: characteristics of both groups

	CAPA (n=118)	Without CAPA (n=560)	P value
Demographic data			
Age (Mean rank)	342.9	338.7	0.83
Gender Male:female	65:53	327:233	0.28
Smoking history (n=147)	30 (25.4%)	117 (20.9%)	0.16
Comorbidities			
DM (n=498)	83 (70.3%)	415 (74.1%)	0.61
HTN (n=332)	56 (47.4%)	276 (49.3%)	0.39
Cirrhosis (n=9)	8 (6.8%)	1 (0.18%)	<0.001
Malignancy (n=23)	16 (13.6%)	7 (1.2%)	< 0.001
Clinical severity scores			
APACHE II (Mean Rank)	394.8	327.8	0.001
SAPS (Mean Rank)	392.9	328.2	0.001
SOFA (Mean Rank)	387.5	329.3	0.003
NUTRIC (Mean Rank)	398.8	327	<0.001
Treatment			
ICU days (Mean Rank)	553.2	294.4	<0.001
Tocilizumab (n=70)	65 (55.1%)	5 (0.89%)	<0.001
Remdesivir (n=441)	52 (44.1%)	389 (69.4%)	<0.001
Vasopressors (n=220)	66 (55.9%)	154 (27.5%)	<0.001
Need for IMV (n=318)	89 (75.4%)	229 (40.9%)	<0.001
Outcome			
Mortality (n=342)	99 (83.9%)	243 (43.4%)	<0.001

DM: Diabetes Mellitus, HTN: Hypertension, APACHE II: Acute Physiology And Chronic Health Evaluation II, NUTRIC: Nutrition Risk in Critically ill, SAPS: Simplified Acute Physiology Score, SOFA: Sequential organ failure score, IMV: Invasive mechanical ventilation

Other comorbid conditions like diabetes mellitus, hypertension did not have any statistically significant impact on development of CAPA (p=0.69,0.39). Median scores of APACHE II, SOFA, NUTRIC AND SAPS were 14, 4, 3 and 33 respectively. Cohorts with CAPA were sicker as compared to those who did not develop CAPA as indicated by mean ranks of APACHE II, SOFA, SAPS and NUTRIC scores amongst both groups (P=0.001, 0.003, 0.001, <0.001 respectively). Median ICU stay was 10 days (IQR: 4-19). Out of 678 participants, 46.9% required need for invasive mechanical ventilation. Out of 46.9%, 27.9% developed CAPA. however. Amongst 118 cases of CAPA 75.4% had received invasive mechanical ventilation (p=<0.001) and 55.9% required vasopressor support (p=<0.001). Length of stay was also more in those who developed CAPA as compared to those who did not (p=< 0.001). Tocilizumab was given to 55.1% participants and 44.1% received remdesivir. Observed mortality in cohorts with CAPA was 83.9 % as compared to 43.4% in those who did not have CAPA and there was statistically significant difference in both cohorts (p=<0.001).

Risk factors of CAPA were identified after adjustment of confounding factors. Amongst many other variables, we identified that those who had higher NUTRIC scores at presentation had more risk of developing CAPA with an odd of 2.1 (p=0.006). Similarly, those who had more prolonged stay in ICU also had an increased risk of developing CAPA with an odd of 1.2 (p=<0.001).

Table 3: risk factors for CAPA

Variable	Odds ratio	P value
Age	1.1	0.84
DM	1.6	0.9
HTN	1.1	0.73
Smoking history	0.79	0.58
APACHE II	1.0	0.85
NUTRIC	2.1	0.006
SAPS	0.12	0.97
ICU Days	1.2	<0.001
Remdesivir	1.8	0.09
Tocilizumab	0.09	< 0.001
Need for invasive mechanical ventilation	0.54	0.13
Vasopressors	0.66	.84

DM: Diabetes Mellitus, HTN: Hypertension, APACHE II: Acute Physiology And Chronic Health Evaluation II, NUTRIC: Nutrition Risk in Critically ill, SAPS: Simplified Acute Physiology Score

DISCUSSION

After literature search on PubMed using search terms (CAPA, Risk and COVID), we claim that this is the largest prospective study conducted at National level which provide insight into risk factors associated with development of CAPA. We included PCR confirmed cases of severe covid pneumonia requiring ICU care and had at least 48 hours stay in ICU. The rationale behind this inclusion criteria came for results of a systematic review which showed that time to CAPA diagnosis from ICU admission and need for invasive mechanical ventilation ranged from 3 to 8 days (11). Median age of our study participants was 60 years and those who had developed CAPA were clinically higher severity of illness as shown by APACHE II, SOFA and NUTRIC scores in table 1. In a study of 147 subjects conducted at National level identified median age of 71 years (10). This is an established fact that immunity decreases with age and increased age may predispose individuals with severe covid pneumonia to develop CAPA but we did not find any statistically significant difference in distribution of age between cohorts with CAPA and without CAPA. incidence of CAPA in our study participants remained 17.4% which is far less than 27.7% reported in a prospective study of 108 patients conducted on only mechanically ventilated patients(12). This difference is likely due to the different infection control practices in ICU and use of corticosteroids in treatment of severe covid pneumonia. Clinical severity scores were much higher in those who developed CAPA and amongst all severity scores, NUTRIC score had strongest association with development of CAPA (OR:2.1, P=0.006). Association of NUTRIC score with CAPA has not been well studied in existing literature since data on CAPA is very limited so far. NUTRIC score has been well studied as a risk factor for malnutrition in critically ill patients (13-15) but literature does not provide any evidence whether it is also a risk factor for CAPA in severe covid pneumonia. There is limited evidence on association of APACHE II and development of CAPA. A prospective

observational study showed that APACHE II is an independent risk factor for CAPA(16). Mean score of APACHE II in aforementioned study was 22 where as in our study median score of APACHE II was 14 and significantly higher in those who developed CAPA (Table 2). This study had a sample size of only 32 patients and so its results cannot be generalized. We did not find any association of APACHE II with CAPA amongst our 678 cases.

Interestingly, Tocilizumab did not show any association with development of CAPA (OR :0.09, p=<0.001). This is in contrast to rheumatology literature which shows that use of tocilizumab along with corticosteroids is associated with increased incidence of bacterial and fungal infections (17), however experience from literature showed that use of tocilizumab reduce inflammatory injury in severe covid pneumonia(18) and incidence of superadded fungal infections is only 3.3% (19). This may explain that use of tocilizumab may have protective role in development of CAPA. another explanation for this finding is that we did not make liberal use of Tocilizumab in our study cohorts. We involved Infectious disease experts to decide candidacy of tocilizumab.

Median ICU days in our study cohorts were 10 days and significantly higher in those who developed CAPA as compared to those who did not (P=< 0.001) Table 2 and found that ICU stay is a strong risk factor for development of CAPA (OR:1.2, p=<0.001). Studies have shown that risk of developing CAPA increases after ICU admission. A systematic review showed that time to development of CAPA in non-ICU population is 8 to 16 days and it reduced to 4 to 15 days after admission to ICU (11). This observation closely resembles the observations made for influenza associated invasive aspergillosis (20). Risk factors that predispose patients to development of CAAP include increased use of broad-spectrum antibiotics, corticosteroids, ARDS and disruption of normal mucosal barrier (1, 21). Despite use of antifungals, we observed much higher mortality in those who developed CAPA (83.9%) which is much higher than those reported in a systematic review (48.4%)(11). Another study reported an overall mortality of 60-70% in putative CAPA (18). Increased mortality of CAPA in our cohort was probably due to the reason that we administered antifungals only to confirmed cases of CAPA. Another explanation of increased mortality is that our CAPA cases were much sicker as compared to those who did not have CAPA.

There are few limitations of our study. First limitation was that it was single center study because it was difficult to monitor and standardize the study protocols amongst different centers of the country. Second limitation is that we did not get galactomannan levels in tracheal aspirate which has higher sensitivity as compared to serum (22). There are few strengths of our study also. First strength of our study is that its results can be generalized to larger population owing to its larger sample size. Second major strength of this study is its prospective design which reduces bias.

CONCLUSION

We concluded that CAPA is serious infection in ICU population and carries significant mortality. NUTRIC Score and ICU days are strong risk factors for development of CAPA. NUTRIC score measured at the time of admission and increasing ICU days should prompt the ICU physicians to conduct early testing for CAPA infection and more stringent surveillance criteria is needed to implement to reduce ICU mortality. When candidacy of tocilizumab is carefully decided, it doesn't pose any further risk for development of CAPA, rather it has protective effect.

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