Risk Factors for COVID-19 Associated Pulmonary Aspergillosis (CAPA) in Severe COVID-19 and Impact of Airborne Fungal Contamination within Negative Pressure Isolation Room

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IDWeek 293

Background

COVID-19 increase the risk of invasive pulmonary aspergillosis. However, the risk factors and fungal origin of COVID-19 associated pulmonary aspergillosis (CAPA) is not fully defined yet. We aim to identify the risk factors for CAPA in severe COVID-19 and evaluate association between fungal contamination within the air of negative pressure rooms and diagnosis of CAPAs.

Methods

We performed a retrospective case-control study to identify risk factors for CAPA with 420 severe COVID-19 patients from March 2020 to January 2022 who admitted to a tertiary care hospital in South Korea. CAPA was defined with modified AspICU criteria. Control, matched by admission date and severity of COVID-19 at admission,.was selected for each case. Air sampling and fungal culture was done on Jan 2022 with a microbial air sampler (MAS-100NT) at 11 spaces in the COVID-19 designated isolation ward including 9 negative pressure isolation rooms (IRs). A cross-sectional comparison between rooms with and without airborne fungal contamination was performed.

Conclusion

Association between CAPA and airborne aspergillus contamination within the negative pressure room could not be demonstrated in this study. Rather than environmental factors, patient factors such as older age, ventilator care, and lymphopenia were found to be associated with CAPA diagnosis.

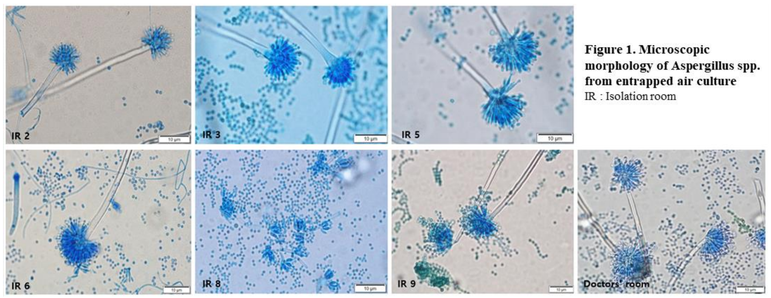

Figure 1. Microscopic morphology of Aspergillus spp. from entrapped air culture
IR : Isolation room

Results

A total of 420 COVID-19 patients were hospitalized during the study period, and 51 patients were diagnosed with CAPA (prevalence 12.14%, incidence 6.26 per 1000 patient•day). (Table 1) Multivariate analysis showed that older age (odds ratio [OR] 1.051, 95% confidence intervals [CI] 1.006-1.009, p=0.025), mechanical ventilator use (OR 2.692, 95% CI 1.049-6.911, p=0.04), and lymphopenia (OR 4.353, 95% CI 1.727-10.975, p=0.02) were independent risk factors for CAPA. (Table 2, 3) Aspergillus spp. was identified within the air from 7 out of 11 spaces including 6 IRs and 1 doctors' room. (Figure 1). All 6 IRs with positive aspergillus culture were being occupied by patients at least 8 days. Among 6 patients, 3 had already been diagnosed with CAPA whereas the other 3 were not diagnosed with CAPA through the observation period. Among 4 patients in isolation rooms without airborne aspergillus contamination, one patient had been diagnosed as CAPA before air sampling. (Table 4)

Table 1. Clinical data of CAPA in patients with severe COVID-19 (n=51)

CAPA diagnosis	51 (100%)
EORTC-MSG	
Proven	0
Probable	17 (33%)
Modified AspICU	
Proven	0
Putative	51 (100%)
CAPA prevalence, %	
Overall	12.14 (51/420)
Among severe COVID-19 patients	13.64 (51/374)
Among critically ill COVID-19 patients	18.18 (50/275)
CAPA incidence, per 1000 patient•day	6.26
Timing of CAPA diagnosis from COVID-19 diagnosis, days, Median [IQR]	7 [4-15]
Laboratory Findings	
Serum Aspergillus GM titer, Peak, Median [IQR]	2.23 [1.24-10.03]
Positive beta-D-glucan, n (%)	46 (90.2)
Treatment	
Interval, Diagnosis to Treatment, Median [IQR]	4 [2-10]
Anti-mold agent, n (%)	36 (70.6)
Voriconazole, n (%)	33 (64.7)
Echinocandin, n (%)	6 (11.8)
Amphotericin B, n (%)	1 (2.0)

CAPA : COVID-19 associated pulmonary aspergllosis, COVID-19 : Coronavirus Disease-19, IQR : Interquartile range, GM : galactomannan

Table 3. Multivariable analysis of potential conditions associated with CAPA diagnosis

Factors	Odds Ratio	95% Confidence Intervals	p-value
Age	1.051	1.006-1.099	**0.025**
Mechanical ventilator use	2.692	1.049-6.911	**0.04**
Steroid use, Mean dose > 0.5mg/kg/day	5.291	0.446-62.776	0.187
LDH	0.999	0.999-1.000	0.18
Lymphocyte<500	4.353	1.727-10.975	**0.02**

CAPA : COVID-19 associated pulmonary aspergllosis, LDH : Lactate dehydrogenase

Table 4. Data of Entrapped Air Culture Result and the Patients who occupied the Room

	Negative-pressure Aisle	Doctor's Room	IR 1	IR 2	IR 3	IR 4	IR 5	IR 6	IR 7	IR 8	IR 9
Result of Entrapped air Culture	No growth	Asp spp.	No growth	Asp spp.	Asp spp.	No growth	Asp spp.	Asp spp.	No growth	Asp spp.	Asp spp.
Patient in Occupancy at air culture	—	—	—	Occupied	Occupied	Occupied	Occupied	Occupied	Occupied	Occupied	Occupied
Timing of air culture from admission				15	22	16	29	9	10	24	8
Mechanical ventilation at air culture				No	No	Yes	Yes	No	No	Yes	Yes
Duration of ventilator care at air culture						16	28			23	10
CAPA Diagnosis				No	No	Yes	Yes	No	No	Yes	Yes
Timing of CAPA diagnosis from admission						7	12			4	13

IR : Isolation room, Asp spp. : Aspergillus species, CAPA : COVID-19 associated pulmonary aspergillosis

Table 2.Comparative data on the clinical characteristics and outcomes between severe COVID-19 patients with and without CAPA

	Patients with CAPA (N=51)	Patients without CAPA (N=51)	p-value
Clinical characteristics			
Age(years), Median [IQR]	71 []64-78]	64 [56-73]	**0.006**
Age > 65, n (%)	38 (74.5%)	25 (49.0)	**0.008**
Male gender, n (%)	30 (58.8)	32 (62.7)	0.685
BMI(kg/m2), Median [IQR]	23.49 [20.94-28.63]	24.34 [20.39-26.44]	0.534
Comorbiditis			
Hypertension, n (%)	30 (58.8)	31 (60.8)	0.84
Diabetes, n (%)	25 (49.0)	21 (41.2)	0.426
CAOD, n (%)	14 (27.5)	6 (11.8)	**0.046**
Heart failure, n (%)	5 (9.8)	1 (2.0)	0.205
Cerebrovascular disease, n (%)	5 (9.8)	6 (11.8)	0.75
Chronic kidney disease, n (%)	15 (29.4)	8 (15.7)	0.97
Chronic lung disease, n (%)	5 (9.8)	7 (13.7)	0.539
Chronic liver disease, n (%)	3 (5.9)	5 (9.8)	0.715
Autoimmune disease, n (%)	2 (3.9)	1 (2.0)	1.000
Cancer, n (%)	13 (25.5)	11 (21.6)	0.641
Any immunocompromised status, n (%)	8 (15.7)	6 (11.8)	0.565
Hematologic malignancy, n (%)	1 (2.0)	0 (0)	1.000
Solid organ transplant, n (%)	5 (9.8)	4 (7.8)	1.000
HIV/AIDS, n (%)	1 (2.0)	0 (0)	1.000
Severity of COVID-19 at Admission			1.000
Oxygen not needed, n (%)	3 (5.9)	3 (5.9)	
Oxygen needed, but no HFNC, n (%)	9 (17.6)	9 (17.6)	
High flow nasal cannula, n (%)	23 (45.1)	23 (45.1)	
Intubation/Ventilator, n (%)	16 (31.4)	16 (31.4)	
Worst severity after admission§			
Mechanical ventilator, n (%)	32 (62.7)	21 (41.2)	**0.029**
CRRT, n (%)	2 (3.9)	4 (7.8)	0.678
ECMO, n (%)	2 (3.9)	1 (2.0)	1.000
Inotropics, n (%)	29 (56.9)	22 (43.1)	0.166
Laboratory findings§			
Neutropenia (Neutrophil<1000), n (%)	0 (0)	2 (3.9)	0.495
Lymphopenia (Lymphocyte<1000), n (%)	50 (98.0)	39 (76.5)	**0.001**
Severe Lymphopenia (Lymphocyte<500), n (%)	37 (72.5)	17 (33.3)	**0.000**
Hyperglycemia, n (%)	20 (39.2)	14 (27.5)	0.208
Ferritin, maximum, Median [IQR]	1183 [535-1613]	1185 [476-1668]	0.961
LDH, maximum, Median [IQR]	641 [558-819]	571 [429-699]	**0.017**
IL-6, maximum, Median [IQR]	396 [61-944]	215 [44-713]	0.222
CRP, maximum, Median [IQR]	180 [85-232]	123 [37-215]	0.057
COVID-19 treatments§			
Remdesivir, n (%)	51 (100)	42 (82.4)	**0.003**
Tocilizumab, n (%)	31 (60.8)	26 (51.0)	0.16
Baricitinib, n (%)	3 (5.9)	3 (5.9)	1.000
Antibiotics, n (%)	46 (90.2)	37 (72.5)	**0.022**
Corticosteroids, n (%)	51	47	0.118
Cumulative dose during admission, Median [IQR]	1436 [1031-2829]	815 [402-1462]	0.000
Cumulative dose, Median [IQR]	631 [358-1239]†	608 [402-768]‡	0.252
Mean dose, Median [IQR]	64 [40-80]*	61 [40-78]**	0.668
Mean dose > 1.0mg/kg/day, n (%)	23 (45.1)	22 (43.1)	0.842
Mean dose > 0.5mg/kg/day, n (%)	50 (98.0)	43 (84.3)	**0.031**
Outcomes			
Hospital length of stay, Median [IQR]	32 ([8-87]	15 [9-31]	**<0.001**
14-Day mortality, n (%)	7 (13.7)	5 (9.8)	0.539
28-Day mortality, n (%)	23 (45.1)	8 (15.7)	**0.001**
In-hospital mortality, n (%)	37 (72.6)	11 (21.6)	**<0.001**
Successful Extubation, n (%)	9 (57.5)	13 (61.9)	**0.005**

CAPA : COVID-19 associated pulmonary aspergllosis, COVID-19 : Coronavirus Disease-19, IQR : Interquartile range, CAOD : Coronary artery occlusive disease, HIV : human immunodeficiency virus, AIDS : Acquired immunodeficiency syndrome, CRRT : Continuous renal replacement therapy, ECMO : Extracorporeal membrane oxygenation, LDH : Lactate dehydrogenase, IL-6 : Interleukin 6, CRP : C-reactive protein, § In CAPA group, the status before CAPA diagnosis was used. †Cumulative steroid dose before CAPA diagnosis in CAPAP group, ‡ Cumulative steroid dose over ther first ten days after steroid use in non-CAPA group * Average of daily steroid dose before CAPA diagnosis in CAPA group, ** Average of daily steroid dose over the first ten days after steroid use in non-CAPA group