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Research Article

Multidrug Resistant Fungal Isolates from Blood and Urine Samples in Covid-19 Infected Admitted Patients During the Second Wave of Pandemic in India

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Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic engulfed the whole world with far-reaching consequences on overall health across the globe. In India, second wave of Covid-19 was more devastating; bacterial and fungal co-infections were mostly undiagnosed or under reported due to the constant focus on the virus. Our study was to identify the cases of multidrug resistant fungus in blood and urine in Covid-19 infected patients.

Material and Methods: The retrospective study was carried out during the second wave of Covid-19 pandemic in India in the department of microbiology in a 200 bedded tertiary care hospital in Delhi, over a period of two months- April, and May 2021. Truenat Real Time PCR (Molbio diagnostics Pvt., Ltd., Goa, India) was used for confirming the cases of Covid-19 from nasopharyngeal samples. All blood samples for culture were processed in automated blood culture machine (BACTEC FX40, Becton Dickinson, Heidelberg, Germany). For fungal culture, paired tubes of Sabouraud's Dextrose Agar (SDA) were used. Vitek 2 Compact System 8.01 (bioMérieux, Inc. Durham, North Carolina/USA) was used for the final identification of yeast and yeast like fungus (YYLF) and their antifungal susceptibility pattern (AFSP). Control strains included Candida albicans ATCC (American Type Culture Collection) 14053, Candida parapsilosis ATCC 22019 etc.

Results: During the 2nd wave of pandemic in India, out of total patients undergone testing by Truenat RT-PCR, Confirmed Covid-19 infection (CCI) was found to be 53.09%. Out of this, patients admitted with Severe Covid-19 infection (SCI) was 22.96%. Blood culture positivity rate among admitted cases were 6.72% (54/803); out of this fungemia was seen in 16.67% (9/54). The prevalence of UTI among Covid-19 infected patients was found to be 18.09% (150/829); YYLF relate UTI was seen in 32% (48/150) patients. Fungal urosepsis (FUS) was found in seven cases of Covid-19 infections; causative agents included C. auris 71.43% (5/7), C. albicans 14.28% (1/7) and T. asahii 14.28% (1/7). All the patients with FUS with SCI had history of prolonged intensive care unit (ICU) stay (>10days) with comorbid condition like diabetes mellitus (DM) (57.14%) and hypertension (HTN) (57.14%). All of them (100%) were catheterized and were on central lines. Out of the 7 patients, 5 (71.43%) were on mechanical ventilator. C. auris isolates were 100% resistant to fluconazole (Minimum inhibitory concentration, MIC >32 mg/L) and voriconazole (MIC >1 mg/L); however, 100% sensitive to caspofungin (MIC 0.25) and micafungin (MIC <0.06).

Conclusion: Elderly patients with high risk factors and associated comorbidity were mostly succumbed to MDR YYLF infections along with Covid-19 infection; many leading to urosepsis with high mortality rate. Covid-

virus itself and its management were favourable conditions for IFI. Therefore, looking at the drug resistance, prompt diagnosis and treatment are imperative with respect to secondary infections.

Key Words: coronavirus disease; Covid-19; urinary tract infections

Introduction

The coronavirus disease 2019 (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic engulfed the nations of the world with far-reaching consequences on overall health across the globe. In India, 29.27 million cases had been reported during the pandemic, with a case fatality rate of 1.24% (363,079 deaths) up to June 11, 2021[1, 2]. India was in the grips of devastating second wave of the virus with repeat lock downs in the country. By mid-April, the country was averaging more than 100,000 cases a day. During the second wave, India's healthcare system has been overburdened, causing a dearth of medical oxygen, hospital beds, and other essentialities for the COVID-19 patients [3].

Although COVID-19 was associated with predominantly respiratory symptoms, many literatures suggest multi-organ involvement such as cardiovascular, lower urinary tract etc. [4, 5]. Historically, super-infections have always been associated with poor outcome during viral illnesses [6, 7]. There are various publications suggestive of both bacterial and fungal co-infections and superinfections in Covid-19 infected patients leading to higher mortality rate [8, 9, 10, 11, 12, 13].

Fungal co-infections in COVID-19 patients emerged with higher incidence of acute infections despite anti-fungal treatment. The emergence of multidrug-resistant (MDR) Candida made the situation worse with treatment failure, adverse clinical outcomes, and even disease outbreaks over the pandemic [15,16]. *Candida auris* became the global health threat during Covid-19 pandemic because of its notorious ability for colonization in skin and in the environment leading to severe disease with high mortality rates [17].

The objective of our study is to evaluate superadded blood stream infection (BSI) and urinary tract infections (UTI) amongst the admitted patients of Covid-19 infection with special reference to MDR fungal infections.

Materials and methods:

Study Design

The retrospective study was carried out during the second wave of Covid-19 pandemic in India in the department of microbiology in a 200 bedded tertiary care hospital in Delhi, over a period of two months- April, and May 2021. The overall patients' data were collected from Laboratory Information System (LIS), requisition forms, WHONET 5.6 software and files from the department of Medical Records Department (MRD). Data analysis included patient profile, medical history, laboratory parameters, microbiological findings, concomitant antimicrobial drug use, and treatments.

Inclusion criteria for the study:

Microbiological testing:

A. Covid-19 True Nat Real Time Polymerase Chain Reaction (RT-PCR):

Patients admitted with acute respiratory illness (ARI) were included in the study. Nasopharyngeal samples were taken from admitted patients and confirmed for Covid-19 by Truenat real time PCR method.). Samples taken using nylon swab were inserted into the Viral Transport Medium (VTM) provided from the same company (Molbio diagnostics Pvt., Ltd., Goa, India). Samples were transported immediately and processed in in-house molecular laboratory as per manufacturer's guideline. (Truenat Beta CoV Chip-based RT-PCR test for Beta Coronavirus, Molbio diagnostics Pvt., Ltd., Goa, India). The target sequence for this assay is E gene of Sarbecovirus and human RNaseP (serves as internal positive control). Confirmatory gene used was RdRP gene or ORF1a gene.

Definition:

A person with a positive Nucleic Acid Amplification Test (NAAT) were labelled as Confirmed Covid-19 infection (CCI) [18].

Severe Covid-19 illness (SCI) is defined by an SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, respiratory frequency >30 breaths/min, or lung infiltrates >50% [19].

A. Blood culture of confirmed Covid-19 positive patients:

Blood for cultures were processed by automated blood culture machine (BACTEC FX40, Becton Dickinson, Heidelberg, Germany). Once the machine flagged positive, we performed Gram stain from the positive blood culture bottle. Based on Gram staining, sub-culture was done in Blood agar (BA), MacConkey agar (MA) and/or Sabouraud's Dextrose Agar (SDA). BA and MA plates were incubated at 37^0C for 24 hours for growth. Growth is analyzed for colony morphology and further processed for automated identification and antimicrobial susceptibility (AST) pattern. All plates with no growth were further re-incubated at 37^0 C for 24 hours. SDA tubes were incubated at both 37^0 C and 25^0 C for 24-72hours.

(i) Inclusion criteria:[20]

(a)Positive Paired blood culture
(b)Same species in paired samples,
(c)Single blood culture with significant pathogen.

(ii) Exclusion criteria:

(a) Possible contaminants as growth (Most likely skin commensals, e.g., *Staphylococcus epidermidis*)
(b) No clinical correlation with the growth
(c) Separate growth in two bottles in paired set of blood culture

B. Urine culture of confirmed Covid-19 positive patients:

All the urine samples were inoculated on Cystine Lactose Electrolyte Deficient (CLED) agar. For YYLF, based on significant colony count, Gram stain and cultural morphology, colonies were inoculated on two Sabouraud's Dextrose Agar (SDA) slants, one was incubated at room temperature whereas, other was kept at 37°C for 24 - 72 hrs.

Inclusion criteria:

(a) Non-duplicate urine sample,
(b) Wet mount showing ≥ 10 White blood cells (WBC)/cubic mm,
(c) Significant growth with colony count ≥ 100,000 Colony Forming Unit (CFU)/ml [20]
(d) Colony count with < 100,000 Colony Forming Unit (CFU)/ml with co-morbidity [eg Type 2 diabetes mellitus (DM) or previous history of urinary tract infection (UTI)] [21]

Exclusion criteria:

(a) Duplicate samples for culture

The growth on the slope was processed for identification of the fungus. To differentiate between *Candida albicans* and Non-albicans Candida (NAC), germ tube test was done.

C. Yeast and Yeast like fungus Identification and antifungal susceptibility pattern (AFSP):

Usually Yeast and yeast like fungus (YYLF) grows within 24-72hours; which were analyzed for colony morphology. Gram stain and/ Lactophenol cotton blue (LPCB) were carried out to see the structure and arrangement under microscope. Vitek 2 Compact System 8.01 (bioMérieux, Inc. Durham, North Carolina/USA) was used for the final identification and AFST. Control strains for YYLF included *Candida albicans* ATCC (American Type Culture Collection) 14053, *Candida parapsilosis* ATCC 22019 and *Candida krusei* ATCC 14243. MIC of Fluconazole, Voriconazole, 5-flucytosine, Amphotericin B, Micafungin, Caspofungin were standardized as per CLSI guidelines (2017) [22].

Results:

Covid-19 positivity rate during peak of 2nd wave in India (April and May 2021):

Total non-duplicate samples received for molecular confirmation of Covid-19 during the peak of 2nd wave of Covid-19 pandemic were 2679 and 1316 in April and May 2021 respectively. CCI in April and May were 62.71% (1680/ 2679) and 33.5% (441/1316) respectively; overall CCI being 53.09 %.

Patients with SCI were admitted during the 2nd wave of Covid-19 pandemic in India. Patients admitted with CCI with SCI were 350 (20.8%) and 137 (31%) in April and May 2021 respectively; overall admitted cases being 22.96%.

Results of blood cultures in patients with CCI:

Total number of non-duplicate blood samples received were 1147. Out of these samples, 344 were paired blood culture sets, from 344 patients; 459 were single blood cultures with significant growth with corresponding clinical history. The total number of patients undergone blood culture were 803.

Overall, blood culture positivity rate was 12.45% (100/803). Out of these, Coagulase negative Staphylococcus (CONS) comprised of 7% (56/803). On clinical correlation, CONS were found to be contaminants in 46 cases (5.73%). So, excluding contaminants, the positivity rate of blood culture was 6.72% (54/803).

Out of all pathogenic bacterial and fungal isolates in blood culture comprised of 83.33% (45/54) and 16.67% (9/54) respectively. The causative agent of fungemia was -*C. auris* 77.77% (7/9); rest were *C. albicans* 11.11% (1/9) and *T. asahii* 11.11% (1/9)

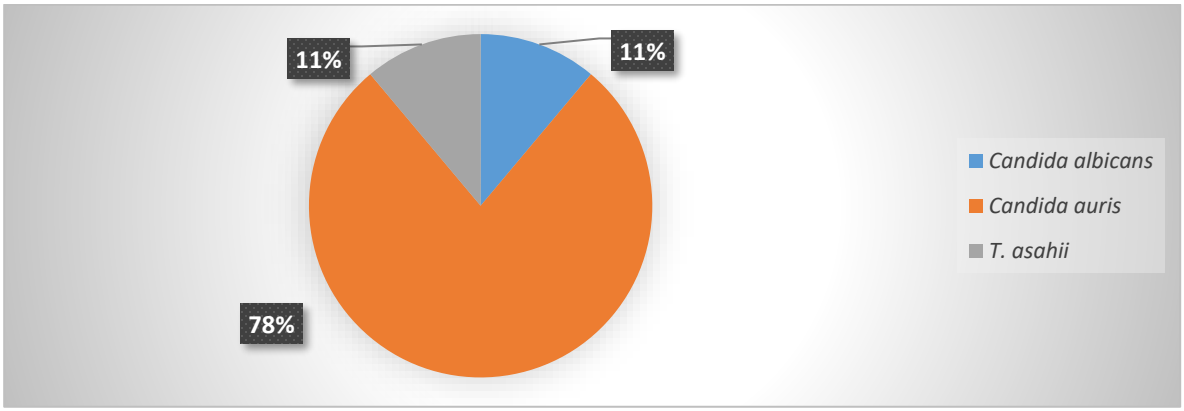

Figure 1: Causative agents of Fungemia in patients with CCI

Results of urine cultures in patients with CCI:

Total number of non-duplicate urine samples received during the peak of 2nd wave were 829. The prevalence of UTI among Covid-19 infected patients was found to be 18.09% (150/829). Prevalence of UTI by YYLF was found to be 32% (48/150). Growth with double isolates were 11 (7.33%), while the rest 139 (92.66%) had single isolate. Out of all fungal isolates, the predominating one was *C. auris*, 35.42% *(*17/48) followed by *Trichosporon asahii*, 25% (12/48).

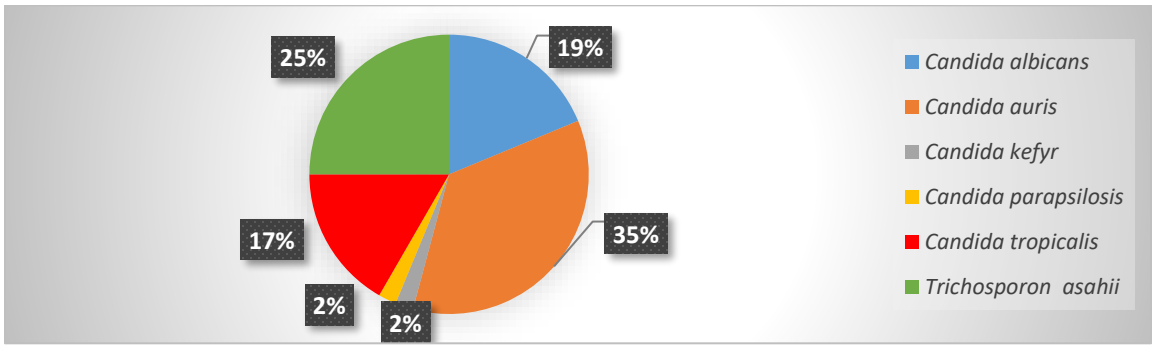

Figure 2: Causative agents of Yeast and Yeast like fungus in patients with CCI

Common isolates in Blood and Urine in patients with CCI:

Out of total 487 admitted cases, 16 (3.28%) patients had common isolates in both blood and urine samples.

Out of these, samples with common fungal and bacterial isolates were 56% (9/16) and 44% (7/16) respectively. The predominant fungus causing common infections include *C. auris* 78% (7/9).

Out of total nine cases with common causative organisms for BSI and UTI, seven had line related UTI prior to BSI which can be labelled as fungal urosepsis (FUS). Causative agents of FUS include *C. auris* 71.43% (5/7), *C. albicans* 14.28% (1/7) and *T. asahii* 14.28% (1/7).

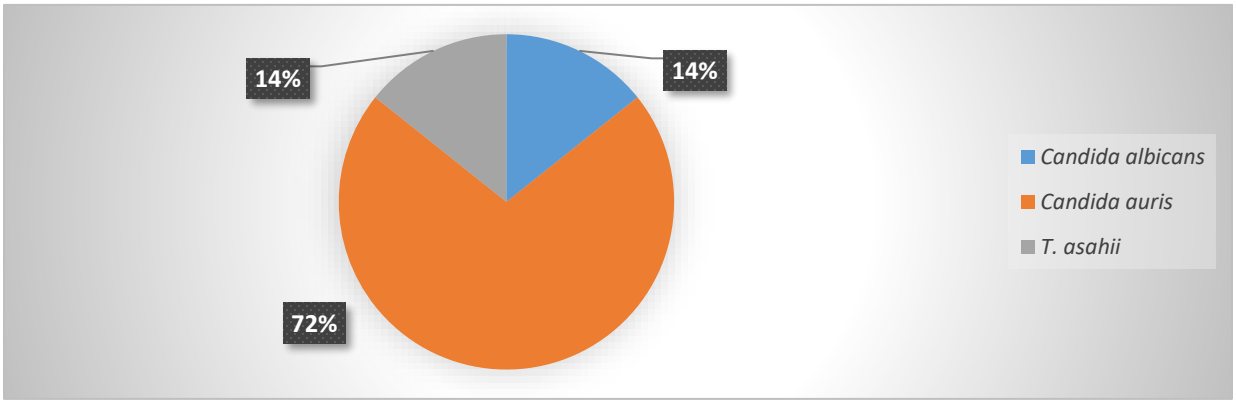

Figure 3: Causative agents of fungal urosepsis in patients with SIC

Demographic profile of CCI with urosepsis:

Out of seven cases, six (85.71%) belonged to elderly age group >=60 years with male to female ratio 5:2. All the patients with FUS with SCI with history of prolonged intensive care unit (ICU) stay (>10 days) with comorbid condition like diabetes mellitus (DM) (57.14%) and hypertension (HTN) (57.14%). All of them (100%) were catheterized and were on central lines. Out of the 7 patients, 5 (71.43%) were on mechanical ventilator. All the seven patients were given prolonged broad-spectrum antibiotics, steroids and immunomodulators. The mortality rate, 71.43% (5/7) was high among these patients.

Patient No.	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age(yr)/Sex	68/M	61/M	73/M	87/M	70/F	46/M	64/F
Days of Hospitalization	11days	33days	43days	25 days	15 days	16days	11days
Fungus	*C. auris*	*C. auris*	*C. auris*	*C. auris*	*C. auris*	*T. asahii*	*C.albicans*
Co- morbidity	DM	DM, HTN	nil	DM, HTN	nil	DM, HTN	HTN
Antibiotics	IMP	IMP and MNO	CZA	DO and CTR	IMP and AK	IMP and TG	IMP
Steroid	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Immunomodulator	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Urinary Catheter	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Central line	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mechanical ventilation	Yes	No	Yes	No	Yes	Yes	Yes
Outcome	Expired	Not expired	Not expired	Expired	Expired	Expired	Expired

Note: DM: Diabetes mellitus, HTN: Hypertension, IMP: Imipenem, MNO: minocycline, CZA: Ceftazidime-avibactum, DO- Doxycycline, CTR: ceftriaxone, AK: amikacin, TG: tigecycline

Table 1: Demographic profile of patients with SIC with FUS

Patient No.	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Lymphocytes (20-40%)	4.7	30.9	21.6	13.9	7.2	3.9	6.3
TLC (4.2-11.0 10x3/mm3)	18.6	6.7	3.6	11.9	3.8	15.4	18.6
Hb (13-17 g/dl)	14	9.6	8.9	11	8.8	13	10
D. Dimer (< 500ng/ml)	1449	502.30	4295.61	3108	1617.45	4246	3019
LDH (120-246 U/L)	955.6	980	736.1	888	671		699.6
Ferritin (6.24-246 U/L)	3110	537	429	699	734	2240	293
PCT (<0.077 ng/ml)	0.49	0.18	0.41	0.21	13.5	0.07	0.91
CRP (<10 mg/l)	44.7	40.88	249	59.7	323.9	22.97	3.12

Urea (15-36 mg/dl)	103.4	57.4	44.8	35.8	37.7	105	138
Creatinine (0.5-1.04 mg/dl)	0.88	0.54	0.21	0.7	0.68	1.59	0.95
Alk phosphatase (38-126 U/L)	69.7	84.9	90.5	111.5	215.5	159.5	60.8
Ct- value of ORF-1a gene in PCR for Covid-19 test	17	21	29	24	22	24	23

Note: Covid markers (serum ferritin, CRP, D. Dimer, LDH, Alkaline phosphatase) were elevated in all the patients.

Table 2: Laboratory parameters of patients with SIC with FUS

Antifungal susceptibility pattern (AFSP) of Fungal isolates:

C. auris isolates were 100% resistant to fluconazole (Minimum inhibitory concentration, MIC >32 mg/L) and voriconazole (MIC >1 mg/L); however, 100% sensitive to caspofungin (MIC 0.25) and micafungin (MIC <0.06). *T. asahii* was susceptible Amp B and *C.albicans* was sensitive to all antifungals.

Patient No.	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Fluconazole	32	32	32	32	32	32	<=0.5
Voriconazole	1	1	1	1	1	0.25	<=0.12
Amphotericin- B	8	8	8	8	1	0.5	0.5
5-Flucytosine	>=64	>=64	>=64	>=64	<=1	8	<=1
Caspofungin	0.25	0.25	0.25	0.25	0.25	>=8	<=0.12
Micafungin	<=0.06	<=0.06	<=0.06	<=0.06	<=0.06	>=8	<=0.06

Table 3: MICs Antifungals for YYLF causing urosepsis in patients with SIC

Discussion:

SARS- CoV positive patients had 20% bacterial and fungal coinfection in 2003; coinfection was quite high, 70.6% in cases who underwent invasive operations [23]. SARS-Cov-2 is also not exceptional viral infection in relation to superinfections and co-infections; depending on the wave, country, availability of manpower in health care, severity of Covid-19 infection literature reveals various rates of superinfections and co-infections {3.2-6.1% [8], 8% [9], 7%-14% [10], 12.6% [11], 13.5-44% [12] and 59% [13]}.

In our study, BSI in Covid-19 positive patients were found to be 6.72%, which contrasts with some studies, 0.72% [8] and 12.5% [14]. Another study revealed blood culture positivity rate as 3.8% which is in correlation with our finding [11].

Our study showed fungemia in 1.12% (9/803) of Covid-19 positive cases which corresponds with the findings of various literatures 0.36% [9], 2.5% [24], 9.1% [14] and 16.89% [25]. *C. auris* (78%) related fungemia predominated in our study which was in concordance with another finding, 67% [24] but in contrast to other literature, 5% [25]. One case of fungemia by *T. asahii* was detected in our study. Another recent study documented five cases of *T. asahii* fungemia in COVID-19 patients who were overexposed to antimicrobials and corticosteroids [26].

Explicit studies are limited to know the prevalence of UTI in COVID-19 infected patients. However, studies reveal that the predominant infections in Covid-19 patients leading to severe sepsis were pneumonia (45%) followed by urinary tract infections (31%) [27, 28]. Our study showed the UTI prevalence as 18.09%. This was in concordance with the findings of other studies, 12% in 1st wave of pandemic [29] and 8% amongst patients admitted in ICU [30] and non-concordance with the prevalence of 3% [31]. In another study done in early part of Covid-19 pandemic, UTI was found to be the predominating secondary infections [co-infection 2.66% (19/712) and superinfection 6.88% (46/712)] [32].

Studies on fungal UTIs are very limited related to Covid-19 infection. There are literatures on case reports and case series related to candiduria. One study reveals coinfection by *Candida spp.* in 1.47% (1/68) and superinfection in 11.32% (6/53) patients [32]. Cases of UTI in post-Covid stage by *Candida tropicalis*, *Candida glabrata* were mentioned in one article [33]; Candiduria by *T.asahii* [34] and *C. auris* [35] are available in literature.

Covid-19 opened a pandora's box for all opportunistic infections. This is because of altered immune mechanism leading to decreased phagocytic function, steroid related neutrophil dysfunction etc. [33]. Covid-19 induced lymphopenia (both T $CD4^+$ and $CD8^+$) provides a favourable environment for the acquisition of persistent fungal secondary infections. Simultaneous high-risk factors (e.g., mechanical ventilation, central lines, indwelling catheters, steroids, monoclonal antibodies etc.). also play a major role in invasive fungal infections (IFI) [24]. Another important aspect was rampant use of broad-spectrum antibiotics in Covid-19 infected patients that helped in propagating fungal infections. International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) report demonstrated that 62% of patients with COVID-19 had received antimicrobial therapy despite low prevalence of bacterial infections [36].

MDR *Candida auris* is a global thread due to its limited susceptibility to antifungals such as echinocandins [24, 26]. Table 3 explains the MDR status of *C. auris*. During 2nd wave of pandemic in India, many HCWs were also down with Covid-19 infections for which they were kept on isolation and the contacts were on quarantine. This led to limited staff in patient care areas to provide care to the admitted patients. With overloaded burden of work in healthcare, there was probability of breach in infection control practices like hand hygiene, disinfection and erroneous donning and doffing of personnel protective equipment (PPE), which can lead to transmission of MDR pathogens including *C. auris*

Laboratory reports of about 85% of the COVID patients showed lymphopenia making them more vulnerable to opportunistic infections like MDR *C. auris* [37]. The multivariable analysis showed that prolonged length of stay (LOS) and a high quick sequential organ failure assessment (qSOFA) score were the only risk factors independently associated with positive

culture for *C. auris* [38]. Table 2 explains the laboratory parameters of cases of FUS.

Mortality rate in cases of fungal urosepsis was found to be 71.43% (5/7) [Table 1]. Increased LOS, high "Candida score" and septic shock were associated with increased mortality within 30 days of positive culture for *C. auris* [38]. There are studies which suggests that SARS-CoV-2 helps in platelet activation and aggregation, resulting in thrombosis and coagulopathy, leading to risk of pulmonary embolism in patients with urosepsis resulting in high mortality [27].

Conclusion:

Secondary BSIs and UTIs were quite common in SARS-Cov-2 infected patients. Prevalence of coinfections and superinfections were negligible in literatures in the early part of the pandemic. This may be because of the scare associated with the disease, burden on human resource in health care, improper guideline to process secondary infections apart from Covid-19 itself, drawbacks of donning of PPE for prolonged period etc. Elderly patients with high risk factors and associated comorbidity were mostly succumbed to MDR YYLF infections; many leading to urosepsis with high mortality rate. Covid-19 virus itself and its management were favourable conditions for IFI. Therefore, prompt diagnosis and treatment are imperative with respect to secondary infections. Diagnostic stewardship associated with antibiotic stewardship along with proper infection measures are the tools to decolonize the MDR YYLFs in health care.

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