

Clinico–Epidemio-Microbiological Exploratory Review Among COVID-19 Patients with Secondary Infection in Central India

T Karuna¹, Rahul Garg², Shweta Kumar², Gyanendra Singh³, Lakshmi Prasad⁴, Kawal Krishen Pandita⁴, Abhijit Pakhare³, Saurabh Saigal⁵, Alkesh Kumar Khurana⁶, Rajnish Joshi², Kamini Walia⁷, Sagar Khadanga²

¹Department of Microbiology, AIIMS, Bhopal, Madhya Pradesh, India; ²Department of General Medicine, AIIMS, Bhopal, Madhya Pradesh, India; ³Department of Community and Family Medicine, AIIMS, Bhopal, Madhya Pradesh, India; ⁴Department of Hospital Administration, AIIMS, Bhopal, Madhya Pradesh, India; ⁵Department of Critical Care, AIIMS, Bhopal, Madhya Pradesh, India; ⁶Department of Pulmonary Medicine & TB, AIIMS, Bhopal, Madhya Pradesh, India; ⁷Indian Council of Medical Research, New Delhi, India

Correspondence: Sagar Khadanga, Department of General Medicine, AIIMS, Bhopal, Madhya Pradesh, India, Email drsagarkhadanga@gmail.com

Purpose: Secondary infections (SI) in COVID-19 have been documented from 3.6% to 72% in various studies with mortality ranging from 8.1% to 57.6%. There is a gap in knowledge for clinico–epidemio-microbiological association among COVID-19 patients with concomitant SI.

Patients and Methods: This is a retrospective chart review, in central India. The study was undertaken for hospitalized adult patients during 1st June 2020 to 30th November 2020, with laboratory proven COVID-19 infection and secondary infection.

Results: Out of the total 2338 number of patients, only 265 (11.3%) patients were investigated for microbiological identification of SI. Male gender was predominant (76.8%) and the mean age was 53.7 ± 17.8 years. Only 3.5% (82/2338) of patients were having microbiologically confirmed (bacterial or fungal) SI. The overall mortality was 50.9% (54/82) with a differential mortality of 88.8% (48/54) in high-priority areas and 21.4% (6/28) in low-priority areas. Blood was the most commonly investigated sample (56%) followed by urine (20.7%) and respiratory secretion (15.8%). *A. baumannii* complex (20/82, 24.3%) was the most common bacteria isolated followed by *K. pneumonia* (12/82, 14.6%) and *E. coli* (11/82, 13.4%). *Candida* spp. (20/82, 24.3%) was the most common fungal pathogen isolated. Sixty percent (12/20) of *Acinetobacter* spp. were carbapenam-resistant and 70.3% of *Enterobacterales* were carbapenam-resistant. Fluconazole resistant *Candida* spp. was isolated only in 10% (2/20) of cases. Diabetes was the most common co-morbidity 54.8% (45/82) followed by hypertension (41.4%) and chronic heart disease (13.4%). The negative predictors of secondary infections are urinary catheterization, placement of central line and mechanical ventilation (invasive and non-invasive).

Conclusion: There is an urgent need of better anti-microbial stewardship practices in India (institutional and extra institutional) for curtailment of secondary infection rates particularly among COVID-19 patients.

Keywords: COVID-19, secondary infection, anti-microbial stewardship practice, mortality, predictor

Introduction

The current coronavirus 2 disease (COVID-19), caused by the β -corona virus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has led to an unprecedented pandemic.¹ This disease has infected more than 259 million people with more than 5 million deaths across the globe till November 2021.² India has reported about 34 million infections and more than 467 thousand deaths so far.³ One of the major complications associated with COVID-19 pneumonia is the secondary infections (SI) of bacterial/fungal origin.^{4–6} Secondary infections may occur as part of COVID-19 illness or as hospital acquired infection.⁷ Secondary infections (SI) in patients with SARS-CoV-2 infection have been associated with negative outcome, especially in intensive care unit (ICU) settings.^{8,9}

The exact cause of SI is unknown. Dys-regulated immune response and lymphopenia has been advocated as the prime factors responsible for associated SI in COVID-19.^{10–15} SI in COVID-19 patients has the propensity for long hospital stay,

vicious huge financial burden and none the less the increased mortality. Though there are some literature about the SI in COVID-19 pneumonia patients from India and across the globe, however there is absolutely scanty data regarding the negative predictors among the COVID-19 infected patients with SI.^{16,17} The present study was undertaken to identify this gap in knowledge.

Materials and Methods

Setting and Study Design

This was a retrospective chart review conducted at a central government run tertiary care referral health care centre in central India. The study design was approved by the Institutional Human Ethics Committee (IHEC) of All India Institute of Medical Sciences, (AIIMS) Bhopal (Ref: IHEC-LOP/2018/EF0080) in accordance with Declaration of Helsinki. Waiver of consent was approved by the IHEC AIIMS, Bhopal as the research proposal involved only bed side chart review without patient identifier, with no additional intervention or added harm to the patient beyond the routine patient care services.

Patient Enrolment and Clinical Data

Patients were included if they were 18 years or older, admitted to the hospital between 1st June 2020 to 30th November 2020, with laboratory-confirmed SARS-CoV-2 infection and laboratory confirmed bacterial or fungal infection. The clinical and outcome data were obtained from medical records. This included demographic, clinical, laboratory, therapeutic, and outcome data.

Demographic Variables and Admission Details

Patient's age, gender, admission and discharge date and place of admission (categorized as high priority area admission for intensive care unit or high dependency unit and low priority area admission for General wards) were extracted from medical record.

Clinical and Laboratory Data

Information on presence of key co-morbidities like diabetes, hypertension and chronic kidney disease etc. was extracted from medical records. Values of routine laboratory investigations (total leukocyte count, C reactive protein and Lactate Dehydrogenase) on admission were extracted from medical records.

Microbiological Data

Secondary infection (SI) was defined by the presence of a positive culture of a significant clinical sample, associated with clinical signs of infection and/or worsening organ failure. Only bacterial and fungal organisms were considered for SI. For each unique organism, only the first isolate collected at a given body site per patient was included in the analysis. The samples were processed as per standard microbiological methods. The identification of bacteria/fungi was done by conventional culture or VITEK[®] 2. Unspecified organisms (including positive microscopy findings with no culture result recorded), mixed growth or contaminants were excluded from all sample types. CoNS, *Corynebacterium* spp. and *Cutibacterium* spp. were excluded from blood cultures. *Candida* spp. was excluded from respiratory samples. Antimicrobial susceptibility tests (AST) of the clinical isolates were determined by disc diffusion or broth microdilution. The antibacterial drugs tested for gram-negative pathogens included amikacin, amoxicillin/clavulanic acid, ampicillin, cefepime, cefoperazone/sulbactam, ceftazidime, ciprofloxacin, imipenem, levofloxacin, meropenem, nitrofurantoin, piperacillin/tazobactam, tigecycline, and trimethoprim/sulfamethoxazole. The MIC for colistin was determined by the broth microdilution method. The antibiotics for Gram-positive pathogens included vancomycin, teicoplanin, tigecycline, linezolid, and daptomycin. Antifungal drugs included fluconazole, voriconazole, caspofungin, anidulafungin and amphotericin B. Antimicrobial breakpoints were interpreted according to CLSI 2020 and M60 2017 guidelines.^{18,19}

To categorize drug susceptibilities and identify multidrug-resistant (MDR) organisms, we applied the following definitions: *Staphylococcus aureus* was considered methicillin-resistant (MRSA) if the isolate was resistant to oxacillin/cefazolin; *Enterococcus* spp. resistant to vancomycin were categorized as VRE; MDR Enterobacterales were defined by resistance to ceftriaxone (Ceph-R) and carbapenem-resistant Enterobacterales (CRE) isolates were identified by a

meropenem minimum inhibitory concentration (MIC) of 2 µg/mL or greater and carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolates were defined by a meropenem MIC of 4 µg/mL or greater.²⁰

Therapeutic and Outcome Data

Information on treatment and procedures was reviewed and information on urinary catheterization, central line placement, non-invasive ventilation and/or mechanical ventilation was recorded. Outcome of the patient was classified as survived for those who were discharged from hospital and deceased for those who died during the treatment.

Statistical Analysis

All data were collated in Microsoft Excel for analysis. Categorical variables were summarized as frequencies and percentages. Continuous variables are presented as means with standard deviation (SD) or medians with inter-quartile range (IQR). Difference in the distribution of variables between groups created based on presence or absence of multi-drug resistant secondary infection and those who survived or died was done by using Chi-square test for nominal variables and Wilcoxon-rank sum test for numerical variables. SPSS software (IBM SPSS Statistics for Macintosh, Version 26.0., IBM Corp., Armonk, NY) and R software. A p-value of <0.05 was considered to be statistically significant.

Results

Baseline Demographic and Clinical Characteristics

A total of 2338 adult patients confirmed to have COVID-19 infections, were admitted during the study period. From these 2338 patients, only 265 patients were investigated for SI and an appropriate sample was sent for microbiological test to identify a bacterial or fungal origin. Out of these 265 suspected cases of SI, only 82 cases were microbiologically having confirmed SI. So, overall incidence of clinically suspected SI was 11.3% (265/2338), microbiologically confirmed SI was 3.5% (82/2338) and sample positivity rate for SI was 30.9% (82/265).

Among these 82 patients with microbiologically confirmed SI, 54 patients (65.8%) had severe illness and were admitted in high priority area (HPA) like intensive care unit (ICU)/high dependence unit (HDU) and rest of the patients (34.1%) were managed in less priority area (LPA) like general ward. The mean age of admitted patients was 53.7 ± 17.8 (SD) years (range 18–95 years) with male gender predominance 76.8% (63/82). Diabetes (54.8%) and hypertension (41.4%) were the most frequent underlying diseases. As respiratory support, 15 patients (15/82=18.2%) received non-invasive ventilation, and 35 patients (35/82=42.6%) received invasive mechanical ventilation. Urinary catheterization was done in 73.1% (60/82) cases while at least one central line was inserted in 45.1% (37/82=45.1%) cases. The details of these baseline demographic and clinical parameters are provided in [Table 1](#).

Etiology of the Secondary Infections

As previously mentioned, after exclusion of negative and non-significant results, we observed 82 clinically and microbiologically proven SI. Out of these 82 samples tested positive for pathogenic organisms, 56% were from blood, 20.7% from urine, 15.8% from respiratory specimens [broncho-alveolar lavage (BAL), endo-tracheal aspirate (ETA), pleural fluid (PF) and sputum] and 7.3% from pus. Of the pathogens isolated, Gram-negative bacteria were the predominant pathogen (52/82, 63.4%) followed by fungi (20/82, 24.3%). The most common bacterial organisms identified were *A. baumannii* complex (20/82, 24.3%) *K. pneumonia* (12/82, 14.6%) and *E. coli* (11/82, 13.4%). *Candida* spp. (20/82, 24.3%) was the most common fungal pathogen isolated. The detailed frequency of organism's isolation is described in [Figure 1](#) and [Table 2](#).

Among the blood culture isolates (n= 46), *Candida* spp. (14/46, 30.4%) was the most commonly isolated organism followed by *A. baumannii* complex (12/46, 26%). Out of these *A. baumannii* complex isolated from blood 41.6% (5/12) were carbapenem-resistant. Isolations of Enterobacterales from blood was 21.7% (10/46, 21.7%) out of which carbapenem resistance isolates were 60%. Among the total 17 isolates from urine Enterobacterales were the most common (9/17, 52.9%), followed by *Candida* spp. isolates (6/17, 35.2%). Among respiratory isolates (n=13), *A. baumannii* complex (6/

Table 1 Baseline Demographic and Clinical Parameters of COVID-19 Patients with Secondary Infections

Variables	n (%)
Age (years), Mean±SD	53.7 ± 17.8
Male sex	63 (76.8%)
Co-morbidities	
Diabetes Mellitus	45 (54.8%)
Hypertension	34 (41.4%)
Chronic Heart Disease	11 (13.4%)
Chronic Kidney Disease	8 (9.7%)
Type of Ward	
High-priority admission	54 (65.8%)
Low-priority admission	28 (34.1%)
Presence of invasive device	
Urinary catheter	60 (73.1%)
Central line	37 (45.1%)
Endotracheal tube	35 (42.6%)
Mechanical ventilation	35 (42.6%)
Non-invasive ventilation	15 (18.2%)
Laboratory investigations	
Median TLC (IQR)	10.0 ×10 ³ (1.6–21.0 ×10 ³)
Neutrophil count (IQR)	88 (33–96)
MedianC- reactive protein mg/L (IQR)	67 (5–705)
Length of stay, days	
Hospitalized, Median (IQR)	14 (2–52)
ICU stay, Median (IQR)	12 (1–40)
Overall mortality	54%
ICU mortality	48%

Abbreviations: SD, standard deviation; IQR, Inter quartile range; TLC, total leukocyte count; ICU, intensive care unit.

13, 46.1%) and Enterobacterales (6/13, 46.1%) were the commonest. All the *Acinetobacter* spp. isolated from urine were carbapenem-resistant. Carbapenem-resistant Enterobacterales isolated from urine was 83.3% (5/6).

Characteristics of Patients with Multi-Drug Resistant Secondary Infection

Table 3 describes the co-morbidities and risk factors potentially associated with the development of MDR SI among COVID-19 patients. Co-morbidities like diabetes, hypertension, chronic heart disease and chronic kidney disease were not significantly associated with MDR SI. Other laboratory, therapeutic and hospital admission parameters were similarly distributed among those with and without multi-drug resistant infection.

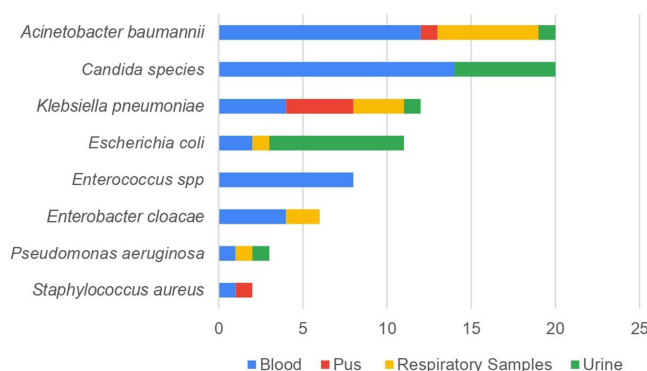


Figure 1 Organisms isolated in different clinical samples among COVID-19 patients with secondary infection.

Table 2 Distribution of Isolates from Various Samples of COVID-19 Patients with Secondary Infection

Source/Organism Group	Total	High-Priority Area, n (%)	Low-Priority Area, n (%)
Blood Isolates, No. (%)			
Total Number	46	34	12
Enterobacterales	10	8 (80)	2 (20)
Ceftriaxone-resistant	7 (70)	7 (70)	0 (0)
Carbapenem-resistant	6 (60)	6 (60)	0 (0)
Candida spp.	14	12	2
Fluconazole-resistant	2 (14.2)	1 (7.1)	1 (7.1)
Enterococcus spp.	8	7 (87.5)	1 (12.5)
VRE	3 (37.5)	3 (100)	0 (0)
Acinetobacter spp.	12	6 (50)	6 (50)
CRAB	5 (41.6)	4 (33.3)	1 (8.3)
<i>Pseudomonas aeruginosa</i>	1	1 (100)	0 (0)
MRSA	1	0 (0)	1 (100)
Urine Isolates, No. (%)			
Total Number	17	7 (41.1)	10 (58.8)
Enterobacterales	9 (52.9)	2 (11.7)	7 (41.1)
Ceftriaxone -resistant	8 (88.8)	2 (22.2)	6 (66.6)
Carbapenem-resistant	4 (44.4)	1 (11.1)	3 (33.3)
Candida spp.	6 (35.2)	4 (66.6)	2 (33.3)
Fluconazole-resistant	0 (0)	0 (0)	0 (0)
<i>Pseudomonas aeruginosa</i>	2 (11.7)	1 (50)	1 (50)
Respiratory Isolates, No. (%)			
Total Number	13	10 (76.9)	3 (23)
Enterobacterales	6 (46.1)	3 (23)	3 (23)
Ceftriaxone-resistant	5 (83.3)	3 (50)	2 (33.3)
Carbapenem-resistant	5 (83.3)	3 (50)	2 (33.3)
Acinetobacter species	6	6 (100)	0 (0)
CRAB	6 (100)	6 (100)	0 (0)
<i>Pseudomonas aeruginosa</i>	1	1 (100)	0 (0)
Pus Isolates, No. (%)			
Total Number	6	3 (50)	3 (50)
Enterobacterales	4 (66.6)	3 (50)	1 (16.6)
Ceftriaxone-resistant	4 (66.6)	3 (50)	1 (16.6)
Carbapenem-resistant	4 (66.6)	3 (50)	1 (16.6)

(Continued)

Table 2 (Continued).

Source/Organism Group	Total	High-Priority Area, n (%)	Low-Priority Area, n (%)
Acinetobacter spp.	1 (16.6)	0 (0)	1 (100)
CRAB	1 (16.6)	0 (0)	1 (100)
MSSA	1 (16.6)	0 (0)	1 (100)

Abbreviations: VRE, Vancomycin resistant *Enterococci*; CRAB, Carbapenem resistant *Acinetobacter baumannii*; MRSA, Methicillin resistant *Staphylococcus aureus*; MSSA, Methicillin susceptible *Staphylococcus aureus*.

Table 3 Clinical and Laboratory Parameters of COVID-19 Patients Admitted in Different Areas

Variables	Low-Priority Area (N=28)	High-Priority Area (N=54)	p-value
Age	44.0 (33.8, 64.5)	59.5 (40.0, 65.0)	0.116
Male sex (%)	21 (75.0%)	42 (77.8%)	0.77
Co-morbidities			
Diabetes Mellitus	15 (53.6%)	30 (55.6%)	0.864
Hypertension	9 (32.1%)	25 (46.3%)	0.217
Chronic Heart Disease	1 (3.6%)	10 (18.5%)	0.088
Chronic Kidney Disease	2 (7.1%)	6 (11.1%)	0.709
Presence of invasive devices			
Urinary catheter	8 (28.6%)	52 (96.3%)	<0.001
Central line	5 (17.9%)	32 (59.3%)	<0.001
Mechanical ventilation	3 (10.7%)	32 (59.3%)	<0.001
Non-invasive ventilation	0 (0.0%)	15 (27.8%)	0.002
Isolation of MDRO	12 (42.9%)	33 (61.1%)	0.115
Clinical outcome			
Discharged	22 (78.6%)	6 (11.1%)	<0.001
Expired	6 (21.4%)	48 (88.9%)	<0.001
Laboratory investigations			
WBC ($\times 10^3$), Median (IQR)	9.4 (5.3–14.8)	10 (6.5–15.9)	0.56
CRP, Median (IQR)	25.0 (10.5, 57.0)	73.0 (32.0, 185.0)	0.023
LDH, Median (IQR)	572.0 (269, 695)	188.5 (51.8, 510)	0.099
Length of stay			
Hospital stays (in days), Median (IQR)	11.0 (7–22)	16.0 (8–23)	0.466
ICU stay (in days)	1.0 (1.0, 1.0)	13.0 (7.0, 18.0)	0.095

Abbreviations: SD, standard deviation; IQR, Inter quartile range; MDRO, multi drug resistant organism; ICU, intensive care unit.

Characteristics of Survivors and Non-Survivors

Table 4 describes the distribution of characteristics with mortality among COVID-19 patients with SI. The in-hospital mortality was more with increased age and when admitted to high-priority area, which may be proxy for severe disease with an associated component of hospital acquired infection. As expected, higher proportion of those who died required invasive devices viz. urinary catheter, central line, mechanical ventilation and noninvasive high flow ventilation. All patients who were discharged alive from the HPA (6/54) ultimately survived and discharged to home. Isolation of MDR organisms and associated diseases like diabetes, hypertension, chronic heart disease and chronic kidney disease were similarly distributed among survivors and non-survivors.

Discussion

We report an important facet of secondary infections among COVID-19 patients involving the clinical and epidemiological characteristics from a large Indian academic centre, during the first wave which hit Central India around March

Table 4 Outcome Analysis of Survivors and Non-Survivors in COVID-19 Patients with Secondary Infections

Variables	Survivors (N = 28)	Non Survivors (N=54)	p-value
Age, Median (IQR)	43.0 (34.25–63.75)	60.0 (40.0–67.0)	0.07
Age, Median±SD	48.79 ±17.51	56.26 ±17.6	0.07
Type of admission			
Low-priority area	22	6	<0.001
High-priority area	6	48	<0.001
Co-morbidities			
Diabetes Mellitus	15	30	0.86
Hypertension	10	24	0.44
Chronic Heart Disease	1	10	0.08
Chronic Kidney Disease	1	7	0.25
Presence of invasive devices			
Urinary catheter	7	58	<0.001
Central line	2	35	<0.001
Mechanical ventilation	3	32	<0.001
Non-invasive ventilation	1	14	0.013
MDRO	15	30	0.86

Abbreviations: IQR, inter quartile range; SD, standard deviation; MDRO, multi drug resistant organism.

2020. The current evidence across the globe, suggests that secondary infections are common, particularly in patients with severe COVID-19.^{7–9} We recorded an overall low incidence of secondary infections (82/2338, 3.5%), but with a high incidence of overall mortality of (54/82, 60.9%) among the microbiologically proven COVID-19 patients with SI. On subgroup analysis, mortality among COVID-19 patients with SI patients admitted to high priority areas was 88.8% (48/54) and admitted to less priority areas are 21.4% (6/28). The overall incidence of SI of 3.5%, is in concordance with a recently published multi-centric retrospective study from India, which reported a SI rate of 3.6% from 10 different centres.^{17,21} However, as mentioned in Table 5, the incidence of SI varied significantly across various countries. SI has been reported as <10% from Italy (4.4% by Ripa et al, 2020), Spain (4.7% by Garcia-Vidal et al, 2021), China (6.8% by Li et al, 2020) and Switzerland (8.3% by Sogaard et al, 2021). SI has been reported from 10% to 30% from China (10.1% by Cai et al, 2020), in meta-analysis (14.3% by Langford et al, 2020), Egypt (19.4% by Nassar et al, 2021) and USA

Table 5 Incidence of Secondary Infections Rate (%) Among COVID-19 Patients in Various Countries

Author	Country	Incidence of Secondary Infections (%)	Mortality (%)
Current study	India	3.50%	60.90%
Garcia-Vidal et al, 2021 ¹⁶	Spain	4.70%	18.60%
Vijay et al, 2021 ¹⁷	India	3.60%	56.70%
Russell et al, 2021 ²²	UK	70.60%	NA
Nasir et al, 2021 ²⁷	Pakistan	72%	42%
Sogaard et al, 2021 ²⁸	Switzerland	8.30%	NA
Nassar et al, 2021 ²⁹	Egypt	19.40%	24.40%
Langford et al, 2020 ⁷	Meta-analysis	14.30%	NA
Ripa et al, 2020 ⁸	Italy	4.40%	NA
Bardi et al, 2020 ²³	Spain	40.70%	36% (ICU)
Li et al, 2020 ²⁵	China	6.80%	49.00%
Mehta et al, 2020 ³⁰	USA	30%	27%
Cai et al, 2020 ³¹	China	10.10%	NA
Sharov et al, 2020 ³²	Russia	41.50%	8.16%

(30% by Mehta et al, 2020). SI has been reported >30% from Spain (40.7% by Bardi et al, 2020), Russia (41.5% by Sharov et al, 2020), UK (70.6% by Russell et al, 2021) and Pakistan (72% by Nasir et al, 2021). The details of incidence of SI in COVID-19 patients have been provided in Table 5. The increased mortality (60.9%) in our study is almost similar to the multicentric study conducted by Vijay et al, 2021 (56.7%) from India.¹⁷ Similar high mortality is also reported from China (49% by Li et al, 2020), Pakistan (42% by Nasir et al, 2021) and Spain (36%, Bardi et al, 2020). However, a lower mortality of <30% has been documented in Russia (8.16% by Sharov et al, 2020), Spain (18.6% by Garcia-Vidal et al, 2021), Egypt (24.4% by Nassar et al, 2021) and USA (27% by Mehta et al, 2020). The details of incidence of mortality in COVID-19 patients with SI have been provided in Table 5. The increased mortality in our study may be due to the many factors viz. admitting severe cases being a referral COVID-19 centre, the fear and chaos during the early days of pandemic, lack of uniform guideline of management, poor infection control practices and lack of antimicrobial stewardship practices.

Among the co-morbidities associated with COVID-19 patients with SI, we found diabetes mellitus (54.8%) and hypertension (41.4%) being the commonest in comparison to ISARIC WHO CCP-UK multi-centric study (involving 260 hospitals from the UK) where in hypertension (48.4%) and chronic cardiac diseases (32.3%) were the most common accompaniments.²² India being the diabetic capital of the globe, it is not surprising that diabetes was the most common co-morbidity among COVID-19 patients with SI.

Microbiological cultures were sent only in 11.3% (265/2338) of hospitalised cases. Microbiological diagnosis of bacterial or fungal infection is challenging, especially in the context of COVID-19. Fewer diagnostic procedures might have been done during the pandemic because of extremely high patient turnover and concerns regarding healthcare worker safety. Blood was the most common site of infection, and this is in concordance with studies from India.^{17,21} Similar finding was also observed for Italy and Spain.^{8,23} However, respiratory samples were most common in USA, UK and China.^{22,24,25} While microbiological aetiology with significant pathogens were established only in 3.5% (82 patients out of 2338) of cases, true SI rate might be much higher in view of almost universal receipt of antibiotics in COVID-19 patients prior to sending samples and sending less number of samples for microbiological confirmation due to various of reasons. We also excluded serological investigations for fungi or atypical bacteria, as these were inconsistently and rarely recorded, and the serum galactomannan assay cross-reacts with β -lactams.

Gram-negative infections have dominated as far as the type of organisms is concerned and are similarly seen in studies reported from other parts of the world describing secondary bacterial infections and super-infections.^{16,17,26} WHO priority pathogens were the commonest isolations mainly from high-priority areas. *Acinetobacter* and *Klebsiella* were the major bacterial pathogens isolated from blood culture. Sixty percent of the Enterobacterales isolated from blood were carbapenem-resistant and 41.6% of *Acinetobacter* spp. Isolated from blood were carbapenem-resistant. *Candida* spp. (14/46, 30.4%) was the commonest fungal isolates identified from blood culture and 14.2% (2/14) were fluconazole resistant.¹⁷ Similar incidence of high multi drug resistant organisms has been documented by Vijay et al, 2021 from India. Increased use of antibiotics out of proportion to the number of microbiologically confirmed bacterial infections may have contributed to colonization and infection caused by *Candida* spp. in this population and deserves further exploration.

Among the Enterobacterales isolated from urine, 88% were ceftriaxone-resistant and 44% were carbapenem-resistant. Among the total number of urinary isolates, 35% (6/17) were *Candida* spp. and all of them were fluconazole sensitive. This emphasizes that fluconazole resistant *Candida* spp. are uncommon in central part of India. Eighty eight percent of the Enterobacterales isolated from respiratory samples were carbapenem-resistant. It is noteworthy that 100% *Acinetobacter* spp. isolated from respiratory samples were carbapenem-resistant. Similar incidence of high multi drug resistant organisms has been documented by Vijay et al, 2021 from India.

High isolation of WHO critical pathogens from high-priority areas highlights poor infection control practices and irrational antibiotic prescription practices during the 1st wave of COVID 19 waves. This is not surprising, because of several reasons: difficulties for health-care workers to adhere to standard precautions (long shifts wearing the same equipment and possible shortages of certain equipment); focus on self-protection rather than on cross-transmission of bacteria across patients; overcrowded wards; shortages of professionals with appropriate training in infection control procedures.

Our study has several limitations. Retrospectively assigning clinical significance to culture results can be challenging. Secondly, panic and confusion during the 1st phase of pandemic may have resulted in a lower rate of collection of samples. Thirdly, the distinction between infection and contamination/colonization could not be possible retrospectively. Lastly considering the limited sample size we have not performed multivariate analysis or modeling to identify independent predictors of mortality among COVID-19 patients with SI.

Conclusion

Secondary infections (SI) among COVID-19 patients are common in India and across the globe. Co-morbidities like diabetes, hypertension, chronic heart disease or chronic kidney disease are not associated with significant difference in occurrence of SI among COVID-19 patients. However, presence of any invasive device like urinary catheter, central line and mechanical or non invasive ventilation are associated with significant SI in high priority areas. Increased level of CRP and LDH are also associated with significant SI in high priority areas. The study has limitations of non performance of multivariate analysis or modeling to identify independent predictors of mortality among COVID-19 patients with SI.

Acknowledgments

Indian Council of Medical Research (ICMR) funded the project and provided technical assistance.

Disclosure

The authors report no conflicts of interest in this work.

References

- Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. *Int J Antimicrob Agents*. 2020;55(3):105924. doi:10.1016/j.ijantimicag.2020.105924
- WHO Coronavirus (COVID-19) dashboard. Available from: <https://covid19.who.int>. Accessed November 27, 2021.
- India: WHO Coronavirus Disease (COVID-19) dashboard with vaccination data. Available from: <https://covid19.who.int>. Accessed November 27, 2021.
- Zhou P, Liu Z, Chen Y, Xiao Y, Huang X, Fan XG. Bacterial and fungal infections in COVID-19 patients: a matter of concern. *Infect Control Hosp Epidemiol*. 2020;41(9):1124–1125. doi:10.1017/ice.2020.156
- Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. *J Infect Dis*. 2008;198(7):962–970. doi:10.1086/591708
- Morris DE, Cleary DW, Clarke SC. Secondary bacterial infections associated with influenza pandemics. *Front Microbiol*. 2017;8:1041. doi:10.3389/fmicb.2017.01041
- Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. *Clin Microbiol Infect*. 2020;26(12):1622–1629. doi:10.1016/j.cmi.2020.07.016
- Ripa M, Galli L, Poli A, et al. Secondary infections in patients hospitalized with COVID-19: incidence and predictive factors. *Clin Microbiol Infect*. 2021;27(3):451–457. doi:10.1016/j.cmi.2020.10.021
- Helle KB, Sadiku A, Zelleke GM, et al. Is increased mortality by multiple exposures to COVID-19 an overseen factor when aiming for herd immunity? *PLoS One*. 2021;16(7):e0253758. doi:10.1371/journal.pone.0253758
- Melenotte C, Silvini A, Goubet AG, et al. Immune responses during COVID-19 infection. *Oncol Immunology*. 2020;9(1):1807836. doi:10.1080/2162402X.2020.1807836
- Torres T, Puig L. Managing cutaneous immune-mediated diseases during the COVID-19 pandemic. *Am J Clin Dermatol*. 2020;21(3):307–311. doi:10.1007/s40257-020-00514-2
- Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Sig Transduct Target Ther*. 2020;5(1):33. doi:10.1038/s41392-020-0148-4
- Zhao Q, Meng M, Kumar R, et al. Lymphopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a systemic review and meta-analysis. *Int J Infect Dis*. 2020;96:131–135. doi:10.1016/j.ijid.2020.04.086
- Yang L, Liu S, Liu J, et al. COVID-19: immunopathogenesis and immunotherapeutics. *Sig Transduct Target Ther*. 2020;5(1):128. doi:10.1038/s41392-020-00243-2
- Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. *J Intensive Care*. 2020;8(1):36. doi:10.1186/s40560-020-00453-4
- Garcia-Vidal C, Sanjuan G, Moreno-García E, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. *Clin Microbiol Infect*. 2021;27(1):83–88. doi:10.1016/j.cmi.2020.07.041
- Vijay S, Bansal N, Rao BK, et al. Secondary infections in hospitalized COVID-19 patients: Indian experience. *Infect Drug Resist*. 2021;14:1893–1903. doi:10.2147/IDR.S299774
- Weinstein MP; Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing*; 2019.
- Alexander BD, Procop GW, Dubresne P, editors; Clinical and Laboratory Standards Institute. *Performance Standards for Antifungal Susceptibility Testing of Yeasts*. CLSI; 2017.

20. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect.* 2012;18(3):268–281. doi:10.1111/j.1469-0691.2011.03570.x
21. Khurana S, Singh P, Sharad N, et al. Profile of co-infections & secondary infections in COVID-19 patients at a dedicated COVID-19 facility of a tertiary care Indian hospital: implication on antimicrobial resistance. *Indian J Med Microbiol.* 2021;39(2):147–153. doi:10.1016/j.ijmb.2020.10.014
22. Russell CD, Fairfield CJ, Drake TM, et al. Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study. *Lancet Microbe.* 2021;2(8):e354–e365. doi:10.1016/S2666-5247(21)00090-2
23. Bardi T, Pintado V, Gomez-Rojo M, et al. Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome. *Eur J Clin Microbiol Infect Dis.* 2021;40(3):495–502. doi:10.1007/s10096-020-04142-w
24. Gomez-Simmonds A, Annavaiah MK, McConville TH, et al. Carbapenemase-producing Enterobacterales causing secondary infections during the COVID-19 crisis at a New York City hospital. *J Antimicrob Chemother.* 2021;76(2):380–384. doi:10.1093/jac/dkaa466
25. Li J, Wang J, Yang Y, et al. Etiology and antimicrobial resistance of secondary bacterial infections in patients hospitalized with COVID-19 in Wuhan, China: a retrospective analysis. *Antimicrob Resist Infect Control.* 2020;9(1):153. doi:10.1186/s13756-020-00819-1
26. He S, Liu W, Jiang M, et al. Clinical characteristics of COVID-19 patients with clinically diagnosed bacterial co-infection: a multi-center study. *PLoS One.* 2021;16(4):e0249668. doi:10.1371/journal.pone.0249668
27. Nasir N, Rehman F, Omair SF. Risk factors for bacterial infections in patients with moderate to severe COVID-19: a case-control study. *J Med Virol.* 2021;93(7):4564–4569. doi:10.1002/jmv.27000
28. Søgaard KK, Baettig V, Osthoff M, et al. Community-acquired and hospital-acquired respiratory tract infection and bloodstream infection in patients hospitalized with COVID-19 pneumonia. *J Intensive Care.* 2021;9(1):10. doi:10.1186/s40560-021-00526-y
29. Nassar Y, Mokhtar A, Elhadidy A, et al. Outcomes and risk factors for death in patients with coronavirus disease-2019 (COVID-19) pneumonia admitted to the intensive care units of an Egyptian University Hospital. A retrospective cohort study. *J Infect Public Health.* 2021;14(10):1381–1388. doi:10.1016/j.jiph.2021.06.012
30. Mehta M, Purpura LJ, McConville TH, et al. What about tocilizumab? A retrospective study from a NYC hospital during the COVID-19 outbreak. *PLoS One.* 2021;16(4):e0249349. doi:10.1371/journal.pone.0249349
31. Cai Q, Huang D, Ou P, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. *Allergy.* 2020;75(7):1742–1752. doi:10.1111/all.14309
32. Sharov KS. SARS-CoV-2-related pneumonia cases in pneumonia picture in Russia in March-May 2020: secondary bacterial pneumonia and viral co-infections. *J Glob Health.* 2020;10(2):020504. doi:10.7189/jogh.10.020504

Infection and Drug Resistance

Dovepress

Publish your work in this journal

Infection and Drug Resistance is an international, peer-reviewed open-access journal that focuses on the optimal treatment of infection (bacterial, fungal and viral) and the development and institution of preventive strategies to minimize the development and spread of resistance. The journal is specifically concerned with the epidemiology of antibiotic resistance and the mechanisms of resistance development and diffusion in both hospitals and the community. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/infection-and-drug-resistance-journal>