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Prevalence of secondary infections, antimicrobial susceptibility and predictors for mortality among critically ill COVID 19 patients admitted to an Intensive Care Unit in India

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ABSTRACT

Background: Critically ill COVID 19 patients requiring intensive care unit admission are at an increased risk of secondary infections owing to the need for invasive or non invasive oxygen therapy, prolonged indwelling catheters and long stay in intensive care unit. Secondary infections can further alter the clinical course and outcomes of these patients

Aims: In this study we aimed to investigate the prevalence, characteristics and factors associated with mortality in critically ill COVID 19 patients with secondary infections.

Methods: This was a single centre retrospective cohort study of adult critically ill COVID 19 patients admitted to the intensive care unit of a tertiary care hospital in India during one year period from May 2020 to April 2021.

Results: Among the 285 patients admitted to the intensive care unit 124 patients were identified with secondary infection. Out of the 250 isolates, 72.3% were gram negative bacilli with highest number of isolates recognised from blood (n=112, 44.8%). The most common organisms identified in our cohort were Klebsiella pneumoniae, Acinetobacter baumannii, Escherichia coli, Candida species and Enterococcus faecalis. Anti-microbial resistance was detected in 58.8% (n=147) of the isolates and majority of the patients received Carbapenem and Polymyxin. Patients with secondary infections were at increased risk of developing septic shock, acute kidney injury and also experienced higher mortality (50%, P-value <0.001). In our study cohort, increasing cumulative dose of steroids [OR 1.002, 95% CI: 1.001-1.004)] and increasing length of intensive care unit stay [OR 1.071, (95% CI: 1.030-1.113)] were found to be predictive of mortality among patients with secondary infection.

Conclusion: Secondary infections were high among the critically ill COVID 19 patients with high antimicrobial resistance and lead to high mortality. This being a single centre retrospective study, prospective evaluation with proper anti-microbial stewardship is needed for more precise results.

Keywords: COVID 19, secondary infections, antimicrobial resistance, risk factors

Introduction

During the pandemic with Corona virus (COVID 19 disease), the infection lead to a wide spectrum of disease. Patients were either asymptomatic, developed a simple upper respiratory infection or a viral pneumonia requiring hospitalisation. Some of them rapidly progressed to acute respiratory distress syndrome (ARDS) requiring intensive care unit (ICU) admission and invasive ventilation for severe hypoxemia.

Co-infections and secondary infections are a common association with severe viral infections of the respiratory tract which can lead to prolonged stay of ICU and hospitalisation and carries a risk of mortality.[1,2]

The prevalence pattern of secondary infections (SIs) in the COVID 19 patients was unknown due to the novelty of the disease. COVID 19 patients admitted to ICU were at a much higher risk of acquiring such infections due to various reasons. Firstly the virus can alter the immune response of the host to the SARS – Co V 2 infection in the form of a cytokine storm, reduced concentration of serum interferon gamma and alterations in the neutrophil and leucocyte characteristics.[3,4,5] Secondly, the ICU admitted patients are at increased need for invasive procedures and organ support. Thirdly, administration of dexamethasone as standard of care as put forth by the RECOVERY trial[6] and drugs like cytokine inhibitors to combat the dysregulated immune system will lead to immunosuppression predisposing them to infections.

Lack of knowledge of the etiology of these infections and their antimicrobial susceptibility in the COVID 19 patients led to inappropriate usage of prophylactic antimicrobials to the hospitalised COVID 19 patients. This poses a threat of developing high rates of antimicrobial resistance (AMR).[7,8,9] Development of AMR is associated with increased cost of hospitalisation and mortality owing to limited choice of antimicrobials and failure to treat even the common infections.[10] Furthermore an unparalleled increase in the need for ICU care as compared to staffing availability and personal protective equipment might magnify the situation by person to person transmission of these resistant pathogens.[11,12] There is a heterogenicity in the reported AMR among the COVID 19 patients across the globe because of the differences in the causative organisms and baseline AMR rate regionally. Furthermore, there are minimal studies highlighting the AMR among the Indian population as compared to other parts of the world. This is a much needed relevant data to substantiate the regional antimicrobial resistance and provide surveillance for the same. [13.14]

In this retrospective cohort study on COVID 19 patients admitted to a dedicated COVID ICU we aimed to investigate the prevalence of SIs, the causative pathogens, their antimicrobial resistance pattern and the prescribed antimicrobial therapy for these infections. We also evaluated the risk factors for developing infection and mortality in these set of patients.

Study methods

This was a single centre retrospective cohort study performed in an ICU dedicated to COVID 19 patients of tertiary care hospital in India. The study was registered under Clinical Trials Registry of India (CTRI) after obtaining ethical clearance from the institutional ethics committee. All adult patients above 18 years of age who were confirmed SARS COV-2 infection with real-time reverse transcription–polymerase chain reaction (RT-PCR) assay or nucleic acid amplification test (NAAT) and admitted to ICU during the one year period from May 2020 to April 2021 were included in the study.

Data extracted from the case records of these patients included demographic details, past medical history, clinical parameters, laboratory data, and APACHE II score at admission to ICU. Treatment details collected included need for mechanical ventilation with duration, vasopressor therapy received, corticosteroids and other immunosuppressive therapy given. Hospital and ICU length of stay (LOS), ICU outcome, development of shock and acute kidney injury (AKI) were recorded.

The primary outcome measured was presence of SIs in these patients. All the patients' case records were screened for SIs based on clinical signs, laboratory analysis and correlated with positive culture reports.

Blood stream infections (BSI) was identified if known pathogen was isolated from single positive blood culture or commensals were isolated from at least two positive blood cultures.

Secondary infection of the lower respiratory tract (sLRTI) or Ventilator associated pneumonia (VAP) was identified if clinical signs along with a positive culture for a significant pathogen from a mini broncho-alveolar lavage (BAL) sample were detected.

Catheter associated urinary tract infection (CAUTI) was identified if patients had an indwelling catheter for more than 48 hours and a positive urine culture defined as more than 10^5 colony forming units of one or two pathogens per millilitre of urine.

Patients in whom cultures were not sent were considered as not suspected to have a superadded infection. Further details were collected from the records of patients with suspected infection in whom samples from blood, BAL and urine were sent. This included date of first culture(s) and repeat cultures if any sent, site of sample, organism(s) isolated, their antimicrobial susceptibility, antibiotic(s) administered and the duration of therapy.

STATISTICAL ANALYSIS:
Categorical data were expressed as number and percentage while continuous data as mean with standard deviation unless specified. P value was calculated by applying Mann Whitney U test and Chi square test for continuous and categorical values respectively. Binary and multivariable logistic regression analysis was conducted to identify association of risk factors for mortality and adjustment for confounders in patients with Sis

Results

We identified a total of 285 COVID 19 confirmed patients who were admitted to our ICU during the one year period of the pandemic from May 2020 to April

2021, of which 27 patients were excluded as they had an ICU stay of less than 48 hour and the remaining 258 patients were enrolled into the study. Cultures were raised in 146 patients out of whom 22 patients had been considered to have an insignificant growth or commensal. Finally, 124 (48.06%) patients were identified with a clinically significant positive culture report and were considered to have developed secondary infection. The clinical characteristics, outcomes and complications of our study cohort is summarised in the Table 1.

Table 1: Characteristics of patients with COVID-19 disease admitted to ICU:

Parameter	Total (n=258)	With secondary infection (n=124)	Without secondary infection (n=134)	p-value
Demographic Variables				
Age (yr), mean(SD)	61.4 (±14.4)	63.3 (±11.7)	59.7 (±16.4)	0.118
Gender, Male, n (%)	182 (70.5)	84 (67.7)	98 (73.1)	0.342
Comorbidities				
Diabetes mellitus, n (%)	167 (64.7)	90 (72.6)	77 (57.5)	0.011*
Hypertension, n (%)	155 (60.1)	83 (66.9)	72 (53.7)	0.030*
Cardiac disease, n (%)	68 (26.4)	32 (25.8)	36 (26.9)	0.847
Respiratory disease, n (%)	22 (8.5)	13 (10.5)	9 (6.7)	0.279
Renal disease, n (%)	24 (9.3)	11 (8.9)	13 (9.7)	0.819
Neurologic disease, n (%)	18 (7.0)	8 (6.5)	10 (7.5)	0.750
Inflammatory Markers				
Ferritin, median (IQR)	420.3 (199.9-740.3)	410.5 (219.0-756.3)	428.5 (179.3-739.1)	0.866
CRP, median (IQR)	8.6 (3.1-14.3)	9.2 (3.8-14.1)	8.4 (2.6-14.9)	0.359
D dimer, median (IQR)	1.4 (0.6-3.8)	1.5 (0.6-3.9)	1.3 (0.7-3.7)	0.978
LDH, median (IQR)	477.0 (354.5-620.5)	507.0 (404.5-655.5)	440.0 (326.0-586.0)	0.007*
APACHE II, mean(SD)	13.0 (±5.7)	13.5 (±5.2)	12.5 (±6.1)	0.119
Secondary Outcomes				
Mechanical Ventilation, n (%)	94 (36.4)	76 (61.3)	18 (13.4)	<0.001*
Ventilator days, mean(SD)	9.6 (±7.2)	11.3 (±6.9)	2.4 (±1.4)	<0.001*
Vasopressor therapy, n (%)	96 (37.2)	76 (61.3)	20 (14.9)	<0.001*
Acute kidney injury, n (%)	54 (20.9)	36 (29.0)	18 (13.4)	0.002*
Septic shock, n (%)	71 (27.5)	61 (49.2)	10 (7.5)	<0.001*
ICU LOS, mean(SD)	9.7 (±7.0)	14.1 (±6.8)	5.6 (±4.1)	<0.001*
Hospital LOS, mean(SD)	13.0 (±5.7)	21.2 (±10.5)	12.7 (±7.9)	<0.001*
Mortality, n (%)	84 (35.3)	61 (50.0)	23 (19.8)	<0.001*

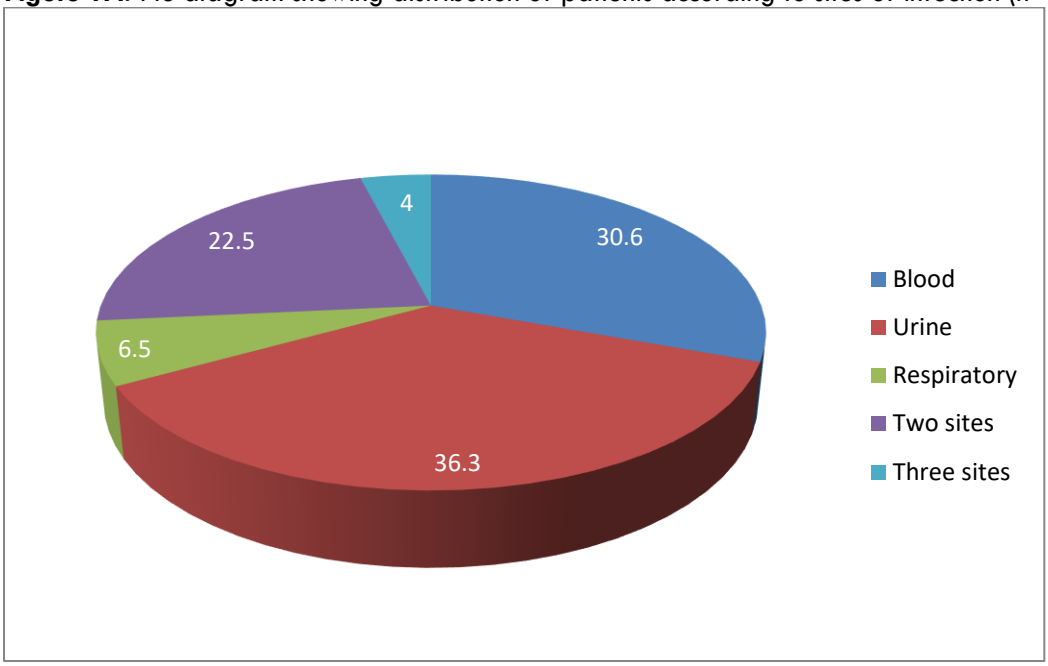
Our study cohort showed a male predominance with a mean age of 61.4(±14.4) years with no significant difference in age between patients with or without SIs. Diabetes mellitus followed by hypertension were the most common comorbid conditions present in these patients and were found to be risk factors for development of SIs.

Other than a raised lactate dehydrogenase (LDH), neither elevated serum ferritin, d-Dimer, C-reactive protein (CRP) nor APACHE II score were found to be significantly associated with development of SIs.

PRIMARY OUTCOME:

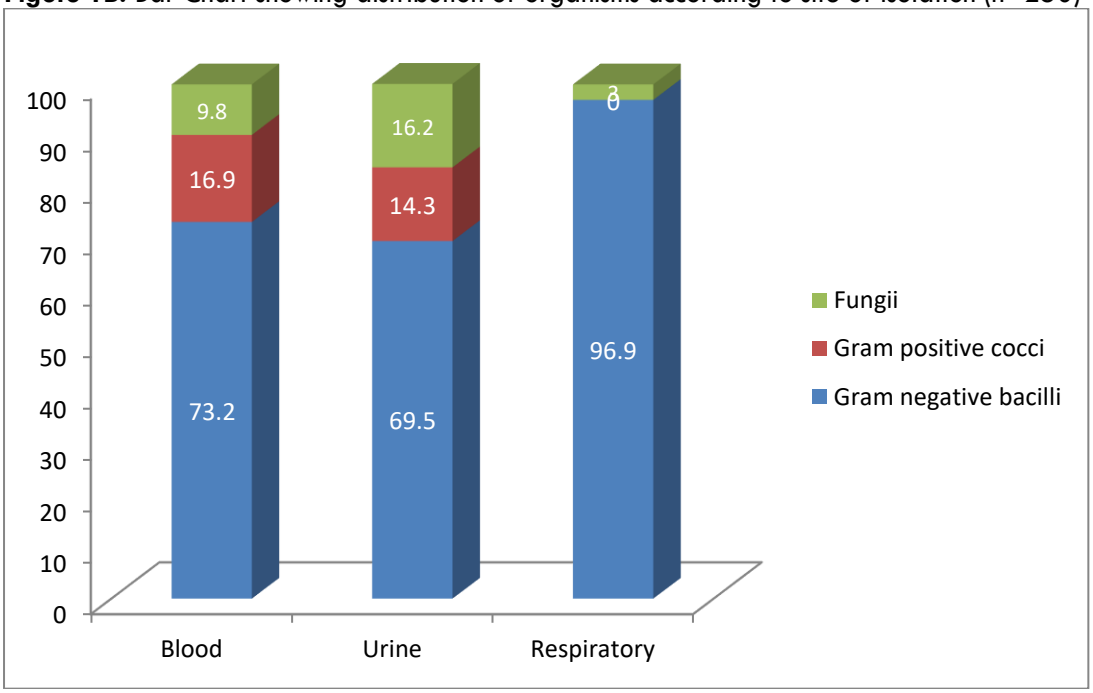
Clinically significant pathogens were isolated from 250 samples including blood, BAL and urine from 124 patients. We observed that the median day of first positive culture was day 5 of ICU stay (IQR 4 - 8). Thirty three patients developed an infection from multiple sites and few patients grew more than one organism. (Figure 1A)

Figure 1A: Pie diagram showing distribution of patients according to sites of infection (n =124)



Recurrent infections in the form of a new pathogen or same pathogen with a different antimicrobial resistance were noted in 50 patients. The most frequently isolated pathogens were gram negative bacilli (GNB) from all three sites with blood (n=112) being the predominant site followed by urine (n=105). (Figure 1B)

Figure 1B: Bar Chart showing distribution of organisms according to site of isolation (n=250)



The distribution of all identified pathogens from the study cohort was given in Table 2.Among the GNB, Klebsiella pneumoniae, Acinetobacter baumannii, Escherichia coli, Pseudomonas aeruginosa and Serratia marcescens were the predominant organisms. Acinetobacter baumannii and Klebsiella pneumoniae caused most BSI (41%). Serratia marcescens caused only bacteremia (n=18, 16%) whereas Escherichia coli bacteremia was noted in only 2 patients. Klebsiella pneumoniae, Acinetobacter baumanii, and Pseudomonas aeruginosa accounted for 97% of secondary pneumonia (sLRTI). Escherichia coli and Klebsiella pneumoniae were associated with almost 45% of CAUTI.

Table 2: Distribution of organisms by sites of infection

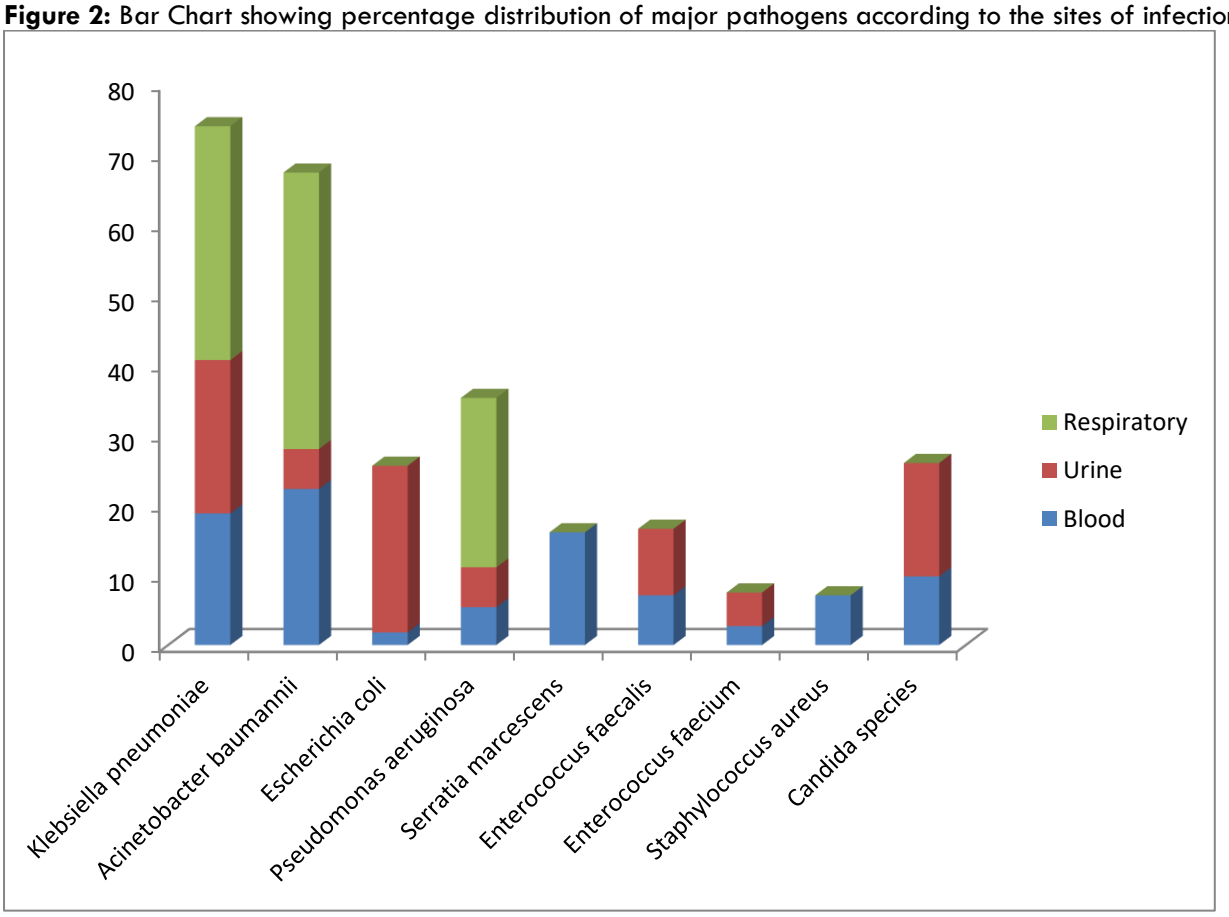
Organisms	**Blood culture**		**Urine culture**		**MiniBAL culture**	
	n=112	%	n=105	%	n=33	%
Gram Negative Bacilli						
Klebsiella pneumoniae	21	18.8	23	21.9	11	33.3
Acinetobacter baumannii	25	22.3	6	5.7	13	39.4
Escherichia coli	2	1.8	25	23.8	0	0

Organisms	Blood culture		Urine culture		MiniBAL culture	
Pseudomonas aeruginosa	6	5.4	6	5.7	8	24.2
Serratia marcescens	18	16.1	0	0	0	0
Enterobacter species	3	2.7	4	3.8	0	0
Morganella morgagnii	0	0	5	4.8	0	0
Proteus. vulgaris	0	0	3	2.9	0	0
Burkholderia species	2	1.8	0	0	0	0
Ralstonia species	2	1.8	0	0	0	0
Providencia species	1	0.9	1	1	0	0
Citrobacter species	1	0.9	0	0	0	0
Stenotrophomonas maltophilia	1	0.9	0	0	0	0
Gram Positive Cocci						
Enterococcus faecalis	8	7.1	10	9.5	0	0
Enterococcus faecium	3	2.7	5	4.8	0	0
Staphylococcus aureus	8	7.1	0	0	0	0
Fungi						
Candida species	11	9.8	17	16.2	0	0
Aspergillus species	0	0	0	0	1	3

Common gram positive cocci (GPC) isolated in our study were Enterococcus faecalis and Enterococcus faecium accounting for nearly 10% and 14% of BSI and CAUTI respectively followed by Staphylococcus aureus causing 7% bacteremia.

Candida species were responsible for 16.2% of CAUTI and 9.8% of BSI in our study cohort. Figure 2 highlights the major pathogens identified from all three sites.

Figure 2: Bar Chart showing percentage distribution of major pathogens according to the sites of infection



Almost 58.8% (n=147) of pathogens isolated from our study cohort exhibited antimicrobial resistance in the form of multi drug resistance (MDR) and extensively drug rsistance (XDR). Acinetobacter baumannii showed the highest resistance with 59 % (n=26) Carbapenem resistant strains followed by Klebsiella pneumoniae with 54.5% (n=30) Carbapenem resistant strains. Majority of the Escherichia coli isolates (33.3%) of our study cohort were resistant to third generation Cephalosporins [extended spectrum beta lactamases (ESBL)]. One Vancomycin Resistant Enterococcus faecium (VRE) and three Methicillin resistant Staphylococcus aureus (MRSA) were recognised. About 27.6% (n=8) Candida isolates were fluconazole resistant. The antimicrobial susceptibility of commonly isolated pathogens of our study was shown in Table 3.

Table 3: Distribution of the major organisms by their antimicrobial susceptibility pattern

Organism	**No of pathogens**	**Antibiotic susceptibility (n %)**			
Gram negative organisms		**BL-BLI**	**ESBL**	**MDR**	**XDR**
Acinetobacter baumannii	44	13(29.5)	5 (11.4)	13(29.5)	13(29.5)
Klebsiella pneumoniae	55	17(30.9)	8(14.5)	6 (10.9)	24(43.6)
Pseudomonas aeruginosa	20	1(5.0)	16 (80.0)	1 (5.0)	2 (10.0)
Serratia marcescens	18	18(100.0)	0	0	0
Escherichia coli	27	11 (40.7)	9 (33.3)	4 (14.8)	3 (11.1)
Gram positive organisms		**Ampicillin Sensitive**	**MDR**	**MRSA**	**VRE**
Enterococcus faecalis	18	8 (44.4)	10 (55.6)	0	0
Enterococcus faecium	8	2 (25.0)	5 (62.5)	0	1 (12.5)
Staphylococcus aureus	8	5 (62.5)	0	3 (37.5)	0
Fungi		**Fluconazole Sensitive**	**Fluconazole Resistant**		
Candida species	29	21 (72.4)	8 (27.6)		

The most commonly prescribed antibiotics for gram negative infections in our study cohort were Meropenem (39.9%) followed by Polymyxins (Polymyxin B and Colistin) in 29.5% of infections Fifty percent of gram positive pathogens required Vancomycin. About 34.5% of Candida infections were treated with Caspofungin and 20.7% of fungal isolates were untreated as the patients died before cultures were available.

Secondary outcomes:

Patients with SIs had a significant and prolonged requirement for mechanical ventilation, longer length of stay in ICU and hospital. These patients also had a significant risk of developing shock which was requiring vasopressor therapy probably secondary to sepsis and increased risk of acute kidney injury. The overall mortality of our study population was 35.3% (84/ 238) with a significantly higher mortality in patients who developed SIs compared to patients with no SIs (50% vs. 19.8%, p value <0.001).

When we assessed the risk factors for mortality in patients with SIs by conducting binary logistic regression, increasing age [OR -1.054, (95% CI:1.031-1.078)], development of AKI [OR 4.156, (95% CI: 2.162-7.989)], development of septic shock (OR 9.474,(95% CI: 4.965-18.076)], increasing cumulative dose of steroids [OR 1.002, 95% CI: 1.001-1.004)] and increasing length of ICU stay [OR 1.071, (95% CI: 1.030-1.113)] were found to be significantly associated with mortality among patients with secondary infection in COVID-19.

However, only increasing age [AOR 1.074, (95% CI-1.030-1.121)], development of septic shock (AOR 10.647, (95% CI: 3.838-29.538)] and incremental cumulative dose of steroids [AOR 1.003, (95% CI: 1.001-1.005)] were predictors of mortality in these patients after adjustment with other confounding parameters. (Table 4)

Table 4: Binary and multivariable logistic regression analysis to identify factors associated with mortality among patients with secondary infection in COVID-19

Risk factor	**OR (95% CI)**	**p-value**	**AOR (95% CI)**	**p-value**
Age	1.054 (1.031-1.078)	**<0.001***	1.074 (1.030-1.121)	**0.001***
Diabetes	1.311 (0.744-2.310)	0.349	0.652 (0.238-1.784)	0.405
Acute kidney injury	4.156 (2.162-7.989)	**<0.001***	1.752 (0.640-4.793)	0.275
Septic shock	9.474 (4.965-18.076)	**<0.001***	10.647 (3.838-29.538)	**<0.001***
Cumulative dose of steroids	1.002 (1.001-1.004)	**0.002***	1.003 (1.001-1.005)	**0.004***
ICU LOS	1.071 (1.030-1.113)	**<0.001***	0.991 (0.919-1.069)	0.811

Discussion:

In this retrospective study we investigated the prevalence of secondary infections in COVID 19 positive patients admitted to ICU as they are at high risk of developing SIs and mortality similar to other respiratory viral pandemics like Influenza A (H1N1)[1] and Middle East Respiratory Syndrome (MERS).[2] A meta-analysis by Sands KE et al.[12] showed that hospital acquired infections in ICU was common in COVID 19 patients compared to non covid patients. Out of the 124 patients with an identified

infection 250 pathogens were isolated from blood, urine and respiratory samples of our study cohort.

In a systematic review and meta-analysis of 138 studies on the prevalence of co-infections and secondary infections, Bradley J. Langfold et al[13] identified that admission to ICU was by itself associated with the development of infection (Odds ratio of 7.52) as compared to patients admitted to ward.(4.9% and 8.4% vs. 8.4% and 39.9% of co-infections and secondary infections respectively). In our study the incidence of SIs was as high as 48%. However, reports from similar studies in the past were highly variable both globally [15-20] and in India.[21, 22, 23]

The most common comorbid conditions associated with our study population were diabetes and hypertension and were similar to that observed by Karuna et al[23] and Yadav et al.[24] This was in contrast to the observation from the multicentre study of 269 UK hospitals, the ISARIC WHO CCP UK study where hypertension and cardiac diseases predominated their population.[17]

De Bruyn et al[20] and Haque et al[22] observed that diabetes was one of the risk factors for SIs in their patients which were similar to our study as well. Corticosteroid therapy as a primary variable associated with SIs was noted in the study cohort of Afnan et al,[18] de Bruyn et al[20] and Haque et al.[21] But we could not establish the same because all our patients were treated with steroids as a standard protocol in our ICU.

Highest number of organisms isolated from blood stream infections in our study was in concordance with the study by Vijay et al[25] and Khurana et al[22] from India and Ripa et al[26] from Italy. This was in contrast to that reported from China,[16,1 9] UK,[17] Belgium,[20] Italy[27] and India[22, 24] where secondary pneumonia was the commonest. A multicentre study from 6 ICUs (OUTCOMEREA) by N. Buetii[15] showed that ICU admitted COVID 19 patients were at higher risk for BSIs than non covid patients as ICU stay prolonged more than 7 days. In our study the prolonged ICU stay (9.7 ±7.0 days) could be a reason for the higher occurrence of BSIs.

There was a high incidence of CAUTIs in our study population. Multiple reasons could be cited, firstly, prolonged mechanical ventilation including prone position leading to prolonged need for indwelling catheter. Secondly, due to the impact of the pandemic an unparalleled increase in ICU beds compared to facilities and trained staff availability might be another burden. Thirdly poor hand hygiene practices because of the isolation policies like wearing gloves giving a false assurance of sterility might have increased our CAUTI rates.[12]

In contrast to this, we observed a low rate of secondary pneumonia. Though 76 patients identified with SIs were on invasive mechanical ventilation, only 20 patients developed a secondary pneumonia with 33 isolates (13.2%) identified. In contrast to our finding, studies by Li et al,[16] Russell et al,[17] Haque et al [22] and Liana et al[27] showed a high incidence of secondary pneumonia. The possible explanation for this low incidence of secondary pneumonia in our study could be the usage of closed suction devices for all our patients on invasive ventilation. This might have reduced the number of ventilator disconnections and hence the contamination with pathogens and colonisation of breathing circuits. A systematic review and meta-analysis by Sanaie et al[28] supported our study in that closed tracheal suction device usage was associated with reduced VAP rates.

The top list of pathogens in our study cohort correlated with the World Health Organisation (WHO) priority pathogens[29] and was comparable with previously reported observations. GNB were responsible for majority of BSI in our study population similar to reports from other studies. [16, 18, 19,21, 22, 25] In contrast to our findings, European studies from France[15] UK,[17] Belgium[20] and Italy[26, 27] showed a higher prevalence of gram positive bacteremia. The predominance of GNB in causing secondary pneumonia in our study was in concordance with findings from across the world.[16 -27, 30] Marco ripa et al[26] compared the antimicrobial resistance pattern during pre-pandemic and pandemic era and found increased resistance among Acinetobacter and Enterococcus faecium post Covid pandemic. In their study by Anahita et al,[30] they observed decreased multi drug resistance among organisms causing VAP in COVID 19 patients compared to non covid patients. In the study by Ll et al[16] from China, Carbapenem resistance was detected in 91.7% and 76.6% of Acinetobacter baumannii and Klebsiella pneumoniae. Also 75% of extended spectrum beta lactamase producing E.coli were isolated from urine in their study.

We also observed a high rate of antimicrobial resistance among our study pathogens. Nearly 66% of our GNB were resistant to third generation Cephalosporins and Carbapenems and sensitive only to Polymyxins. Similarly among the GPC, 55% of Enterococccus faecalis and 62.5% Enterococccus faecium were resistant to Ampicillin. Among the fungal pathogens, 28% of Candida species showed Fluconazole resistance. In the study by Vijay et al,[25] 47% of the pathogens were multidrug resistant with 92.6% Acenatobacter baumanii and 72.8% Klebsiella pneumoniae resistant to carbapenems and 32% Vancomycin resistant Enterococci. Overall, 64-69% of GNB with third generation Cefalosporins and Carbapenem resistance were detected in the study by Khurana et al.[21]

Despite the detection of high MDR, Vijay et al[25] observed that a greater percentage of their study population received Beta lactum-Beta Lactamase Inhibitors (BL-BLI) compared to carbapenems, however Polymyxin and Meropenem were the most commonly prescribed antibiotic in our study cohort.

The RECOVERY trial[6] showed reduced 28 day mortality in patients requiring mechanical ventilation and oxygen support, but did not evaluate the association between steroid therapy and secondary infections. Ritter et al,[31] addressed the impact of steroids on secondary infections and all-cause mortality without studying the association of steroids with mortality among patients with secondary infections alone. In the study by Liana et al,[27] however the unadjusted mortality was high in patients on longer duration of steroid. In contrast with their findings, we observed an association of steroids with high mortality in our patients who developed secondary infections.

This study had several limitations. Firstly, it was a single centre retrospective study with a small sample size. Secondly, due to the retrospective correlation of clinical signs of infection with microbiological culture reports differentiation between true infection and colonisation may not be accurate.

Conclusion

High incidence of secondary infections was observed in critically ill COVID 19 patients and carried a significant mortality risk. Majority of these infections were caused by the organisms recognised by WHO as 'critical' and 'high priority' pathogens exhibiting resistance which translated to treatment failure. This will add on to the threat of increasing antimicrobial resistance in the community at large. Therefore appropriate selection and timing of antimicrobials is the cornerstone to treat such infections when suspected.

Conflicts of Interest Statement: Nil

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References:

1. MacIntyre, C.R., Chughtai, A.A., Barnes, M. *et al.* The role of pneumonia and secondary bacterial infection in fatal and serious outcomes of pandemic influenza a(H1N1)pdm09. *BMC Infect Dis* **18**, 637 (2018). https://doi.org/10.1186/s12879-018-3548-0
2. Saad M, Omrani AS, Baig K, Bahloul A, Elzein F, Matin MA, Selim MA, Al Mutairi M, Al Nakhli D, Al Aidaroos AY, Al Sherbeeni N. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. International journal of infectious diseases. 2014 Dec 1;29:301-6. https://doi.org/10.1016/j.ijid.2014.09.003
3. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W, Tian DS. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clinical infectious diseases. 2020 Jul 28;71(15):762-8. https://doi.org/10.1093/cid/ciaa248
4. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, Zhang M, Tan J, Xu Y, Song R, Song M. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. Journal of translational medicine. 2020 Dec;18:1-2. https://doi.org/10.1186/s12967-020-02374-0
5. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The lancet. 2020 Mar 28;395(10229):1033-4. https://doi.org/10.1016/S0140-6736(20)30628-0
6. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. New England Journal of Medicine. 2021 Feb 25;384(8):693-704. DOI: 10.1056/NEJMoa2021436
7. Langford BJ, So M, Raybardhan S, Leung V, Soucy JP, Westwood D, Daneman N, MacFadden DR. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. Clinical microbiology and infection. 2021 Apr 1;27(4):520-31. https://doi.org/10.1016/j.cmi.2020.12.018
8. Langford BJ, Soucy JP, Leung V, So M, Kwan AT, Portnoff JS, Bertagnolio S, Raybardhan S, MacFadden DR, Daneman N. Antibiotic resistance associated with the COVID-19 pandemic: a systematic review and meta-analysis. Clinical Microbiology and Infection. 2023 Mar 1;29(3):302-9. https://doi.org/10.1016/j.cmi.2022.12.006
9. Rehman S. A parallel and silent emerging pandemic: Antimicrobial resistance (AMR) amid COVID-19 pandemic. Journal of Infection and Public Health. 2023 Apr 1;16(4):611-7. https://doi.org/10.1016/j.jiph.2023.02.021
10. Petrakis V, Panopoulou M, Rafailidis P, Lemonakis N, Lazaridis G, Terzi I, Papazoglou D, Panagopoulos P. The impact of the COVID-19 pandemic on antimicrobial resistance and management of bloodstream infections. Pathogens. 2023 May 30;12(6):780. https://doi.org/10.3390/pathogens12060780
11. Sands KE, Blanchard EJ, Fraker S, Korwek K, Cuffe M. Health Care–Associated Infections Among Hospitalized Patients With COVID-19, March 2020-March 2022. *JAMA Netw Open* 2023;6(4):e238059. doi:10.1001/jamanetworkopen.2023.8059
12. Saini V, Jain C, Singh NP, Alsulimani A, Gupta C, Dar SA, Haque S, Das S. Paradigm shift in antimicrobial resistance pattern of bacterial isolates during the COVID-19 pandemic. Antibiotics. 2021 Aug 7;10(8):954. https://doi.org/10.3390/antibiotics10080954
13. Langford BJ, So M, Simeonova M, Leung V, Lo J, Kan T, Raybardhan S, Sapin ME, Mponponsuo K, Farrell A, Leung E. Antimicrobial resistance in patients with COVID-19: a systematic review and meta-analysis. The Lancet Microbe. 2023 Mar 1;4(3):e179-91. https://doi.org/10.1016/S2666-5247(22)00355-X
14. Yang X, Li X, Qiu S, Liu C, Chen S, Xia H, Zeng Y, Shi L, Chen J, Zheng J, Yang S. Global antimicrobial resistance and antibiotic use in COVID-19 patients within health facilities: a systematic review and meta-analysis of aggregated participant data. Journal of Infection. 2024 May 14:106183. https://doi.org/10.1016/j.jinf.2024.106183
15. Buetti, N., Ruckly, S., de Montmollin, E. *et al.* COVID-19 increased the risk of ICU-acquired bloodstream infections: a case–cohort study from the multicentric OUTCOMEREA network. *Intensive Care Med* **47**, 180–187 (2021). https://doi.org/10.1007/s00134-021-06346-w
16. 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* **9**, 153 (2020). https://doi.org/10.1186/s13756-020-00819-1
17. Russell CD, Fairfield CJ, Drake TM, Turtle L, Seaton RA, Wootton DG, Sigfrid L, Harrison EM, Docherty AB, de Silva TI, Egan C. 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. The Lancet Microbe. 2021 Aug 1;2(8):e354-65. https://doi.org/10.1016/S2666-5247(21)00090-2
18. Alshrefy AJ, Alwohaibi RN, Alhazzaa SA, et al. Incidence of Bacterial and Fungal Secondary Infections in COVID-19 Patients Admitted to the ICU. Int J Gen Med. 2022;15:7475-7485. Published 2022 Sep 24. doi:10.2147/IJGM.S382687
19. Zhang H, Zhang Y, Wu J, Li Y, Zhou X, Li X, Chen H, Guo M, Chen S, Sun F, Mao R. Risks and features of secondary infections in severe and critical ill COVID-19 patients. Emerging microbes & infections. 2020 Jan 1;9(1):1958-64. https://doi.org/10.1080/22221751.2020.1812437
20. De Bruyn, A., Verellen, S., Bruckers, L. *et al.* Secondary infection in COVID-19 critically ill patients: a retrospective single-center evaluation. *BMC Infect Dis* **22**, 207 (2022). https://doi.org/10.1186/s12879-022-07192-x
21. Khurana S, Singh P, Sharad N, Kiro VV, Rastogi N, Lathwal A, Malhotra R, Trikha A, Mathur P. 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 journal of medical microbiology. 2021 Apr 1;39(2):147-53. https://doi.org/10.1016/j.ijmmb.2020.10.014

22. Haque, Obaid I.1,; Shameem, Mohammad2; Hashim, Wamin3. Secondary infections in critically ill patients with COVID-19: A retrospective single-center study. Lung India 40(3):p 210-214, May–Jun 2023. DOI: 10.4103/lungindia.lungindia_293_22
23. Karuna T, Garg R, Kumar S, Singh G, Prasad L, Krishen Pandita K, Pakhare A, Saigal S, Khurana AK, Joshi R, Walia K. Clinico–Epidemio-Microbiological Exploratory Review Among COVID-19 Patients with Secondary Infection in Central India. Infection and Drug Resistance. 2022 Jan 1:1667-76. https://doi.org/10.2147/IDR.S355742
24. Boorgula SY, Yelamanchili S, Kottapalli P, Naga MD. An update on secondary bacterial and fungal infections and their antimicrobial resistance pattern (Amr) in COVID-19 confirmed patients. Journal of Laboratory Physicians. 2022 Sep;14(03):260-4. DOI: 10.1055/s-0041-1741438
25. Vijay S, Bansal N, Rao BK, Veeraraghavan B, Rodrigues C, Wattal C, Goyal JP, Tadepalli K, Mathur P, Venkateswaran R, Venkatasubramanian R. Secondary infections in hospitalized COVID-19 patients: Indian experience. Infection and drug resistance. 2021 May 24:1893-903. https://doi.org/10.2147/IDR.S299774
26. Ripa M, Galli L, Poli A, Oltolini C, Spagnuolo V, Mastrangelo A, Muccini C, Monti G, De Luca G, Landoni G, Dagna L. Secondary infections in patients hospitalized with COVID-19: incidence and predictive factors. Clinical Microbiology and Infection. 2021 Mar 1;27(3):451-7. https://doi.org/10.1016/j.cmi.2020.10.021
27. Signorini L, Moioli G, Calza S, Van Hauwermeiren E, Lorenzotti S, Del Fabro G, Renisi G, Lanza P, Saccani B, Zambolin G, Latronico N. Epidemiological and clinical characterization of superinfections in critically ill coronavirus disease 2019 patients. Critical care explorations. 2021 Jun 1;3(6):e0430 *DOI:* 10.1097/CCE.0000000000000430
28. Sanaie S, Rahnemayan S, Javan S, Shadvar K, Saghaleini SH, Mahmoodpoor A. Comparison of Closed vs Open Suction in Prevention of Ventilator-associated Pneumonia: A Systematic Review and Meta-analysis. *Indian J Crit Care Med.* 2022;26(7):839-845. https://doi.org/10.5005%2Fjp-journals-10071-24252
29. WHO Bacterial Priority Pathogens List, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance ISBN 978-92-4-009346-1 (electronic version) ISBN 978-92-4-009347-8 (print version)
30. Rouzé A, Martin-Loeches I, Povoa P, Makris D, Artigas A, Bouchereau M, Lambiotte F, Metzelard M, Cuchet P, Boulle Geronimi C, Labruyere M. Relationship between SARS-CoV-2 infection and the incidence of ventilator-associated lower respiratory tract infections: a European multicenter cohort study. Intensive care medicine. 2021 Feb;47:188-98. https://doi.org/10.1007/s00134-020-06323-9
31. Ritter LA, Britton N, Heil EL, Teeter WA, Murthi SB, Chow JH, Ricotta E, Chertow DS, Grazioli A, Levine AR. The impact of corticosteroids on secondary infection and mortality in critically ill COVID-19 patients. Journal of intensive care medicine. 2021 Oct;36(10):1201-8. https://doi.org/10.1177/08850666211032175