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# Study of Secondary Infections in Hospitalized Covid-19 Patients and its Outcome

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***Abstract***

***Background:In this study, it was aimed to describe rates, etiological agents of the secondary infections and its effect on clinical outcomes among hospitalized patients with COVID-19.***

***Materials and Methods: A prospective comparative analysis of the characteristics of patients with and without secondary infection was carried out among 75 hospitalized adult patients with a confirmed diagnosis of COVID- 19 via RT-PCR.***

***Results: A total of 75 hospitalized patients with confirmed COVID-19 were analyzed. Among them 44(58.6%) patients were males and the mean age was 47±16 years. Among included patients, 30 (40.0%) had at least one microbiologically documented secondary infection and 45 (60%) had no secondary infection.***

***Conclusion: Parameters like Higher levels of TC, NLR, APTT, ferritin and procalcitonin can help the clinician to predict that patients are likely to have secondary infection, and cannot be completely ruled out. Duration of stay in hospital and mortality rate was significantly higher in subjects with secondary infection compared to subjects without secondary infection.***

***Keywords: COVID-19, secondary infections, predictor.***

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## INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread throughout the world, and due to the severity of the disease, some patients must be hospitalised, and some severe cases may require intensive care with non-invasive or invasive respiratory support.[1,2] Patients with moderate or severe COVID-19 frequently have substantial comorbidities, require longer hospitalizations, and require mechanical breathing, all of which increase the risk of subsequent infections.[3,4] Although the prevalence of these infections in hospitalised COVID-19 patients is normally low (10-15%), many studies have found that the presence of these infections is related with poor outcomes in critically sick ICU patients.[5-7] As a result, microbiological data are useful in directing evidence-based therapy of subsequent bacterial infections in COVID-19 patients. International antimicrobial stewardship guidelines require that clinicians acquire blood cultures as well as lung samples for bacterial cultures to confirm the secondary illness.[8,9] However, it has been observed in certain studies that routine microbiological examinations cannot be performed due to the risk of exposing healthcare personnel to SARS-Cov-2 during sample collection and processing, which may cause major interruptions in secondary infection detection and treatment.[3,5,10] Furthermore, because it is difficult to exclude out

bacterial coinfection at presentation, as well as secondary infection during the course of the illness, empiric antibiotics, particularly broad spectrum drugs, are commonly administered for patients in both regular wards and ICUs.[11] However, according to recent World Health Organization (WHO) guidelines and the majority of researchers, antibiotic prescription should be limited to severe COVID-19 patients in order to avoid the widespread use of empirical antibiotics, which could lead to the development of multidrug-resistant bacteria.[7-9,12]

Although there are studies on the clinical management of COVID-19 in our country, information on secondary infections is limited. We wanted to report frequencies, etiological agents of secondary infections, and their effect on clinical outcomes among hospitalized COVID-19 patients in this study, which included a comparative analysis of the features of patients with and without secondary infection.

## MATERIALS & METHODS

### Ethics Committee Approval:

A prospective observational analysis was carried out on hospitalized adult patients admitted to a tertiary hospital between May 2021 to August 2021 with a confirmed diagnosis of COVID-19 via reverse transcriptase-polymerase chain reaction assay (RT-PCR) performed on nasopharyngeal throat swab specimens. Approvals were received by the Institutional Ethics Committee.

### Study Design, Participants, and Data Collection:

The study included 75 patients who had comprehensive data on their white blood cell (WBC), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), and procalcitonin (PCT) values. Once informed consent was obtained from the patient, all data were collected, including demographics, comorbidities, clinical parameters, laboratory findings, microbiology data (including culture of blood samples, endotracheal aspirate (ETA), urine, and antimicrobial susceptibility), mode of ventilation, and outcome data (length of hospital stay, discharge, and death). The presence of distinctive clinical symptoms, as well as at least one positive blood, sputum/endotracheal aspirate, and urine culture result after 48 hours of admission, were used to determine the existence of secondary infection.

### Statistical Analysis:

Descriptive statistics of the obtained data were given in tables as mean, standard deviation (SD), median, number and % frequencies. The compliance of numerical data to the normal distribution was examined using the Shapiro-Wilks test. While the relationship of secondary infection status with numerical type features was examined with the Mann-Whitney U test, its relationship with the categorical features was evaluated with the Pearson chi-square test. $p < 0.05$ was accepted as the statistical significance level and Statistical Package for the Social Sciences (SPSS ver. 23) program was used in calculations.

## RESULTS

A total of 75 hospitalized patients with confirmed COVID-19 were analyzed. Among them 44(58.6%) patients were males and the mean age was 47±16 years. Among included patients, 30 (40.0%) had at least one microbiologically documented secondary infection and 45 (60%) had no secondary infection. The study population was divided into two subgroups as patients with and without secondary infection. The mean age in patients with secondary infection (50±16 vs 44±17 years) was not significantly different than those without ($p>0.05$).

When laboratory values examined, mean DBP (77.2±11.4 vs 69.5±13.4), TC (13582.4±6305.7 vs 18550.0±8700.8), NLR (15.8±14.3versus 19.1±13.51), APTT (23.1±3.6

vs 27.7±9.5), FERRITIN (607.1±504.0vs 1100.6±645.4), PROCALCITONIN (6.3±16.5 vs 9.3 ±6.9) levels were significantly higher among patients with secondary infection compared to those without ($p<0.05$). Albumin (3.2±0.5 vs 2.8± 0.6) was significantly lower among patients with secondary infection compared to those without ($p>0.05$).
Duration of stay in hospital was significantly higher in subjects with secondary infection compared to subjects without secondary infection 17±8 days versus 25±11 days, $p<0.05$.

**Table 1: Comparison of numerical properties between patients with and without secondary infection.**

| | NEGATIVE | | POSITIVE | | p value |
|---|---|---|---|---|---|
| | **Mean** | **SD** | **Mean** | **SD** | |
| AGE (years) | 44 | 17 | 50 | 16 | 0.085 |
| DURATION OF STAY IN HOSPITAL (days) | 17 | 8 | 25 | 11 | 0.032 |
| PR (bpm) | 94 | 14 | 92 | 14 | 0.575 |
| SPO2 (%) | 95 | 3 | 95 | 5 | 0.799 |
| SBP (Systolic blood pressure) (mm Hg) | 116.2 | 23.4 | 114.4 | 21.7 | 0.736 |
| DBP (Diastolic blood pressure) (mm Hg) | 77.2 | 11.4 | 69.5 | 13.4 | 0.010 |
| RR (respiratory Rate) (cpm) | 22.3 | 4.2 | 23.5 | 4.5 | 0.240 |
| HB (g/dl) | 11.7 | 2.6 | 12.1 | 2.4 | 0.418 |
| TC (cumm) | 13582.4 | 6305.7 | 18550.0 | 8700.8 | 0.005 |
| N (%) | 86.6 | 7.1 | 88.5 | 6.3 | 0.244 |
| L (%) | 9.6 | 6.1 | 6.5 | 4.0 | 0.017 |
| N/L | 15.8 | 14.3 | 19.1 | 13.5 | 0.021 |
| PLT (lakhs/cumm) | 2.6 | 1.5 | 2.5 | 1.3 | 0.729 |
| RBS (mg/dl) | 204.0 | 103.6 | 172.9 | 97.9 | 0.197 |
| UREA (mg/dl) | 56.4 | 55.8 | 70.6 | 69.7 | 0.333 |
| CREAT (mg/dl) | 2.0 | 2.9 | 1.7 | 2.1 | 0.648 |
| TB (mg/dl) | 0.6 | 0.3 | 0.7 | 0.4 | 0.351 |
| DB (mg/dl) | 0.3 | 0.2 | 0.4 | 0.2 | 0.391 |
| TP (g/dl) | 6.1 | 0.9 | 5.7 | 1.0 | 0.080 |
| ALB (g/dl) | 3.2 | 0.5 | 2.8 | 0.6 | 0.020 |
| AST (U/L) | 45.1 | 34.1 | 38.0 | 23.9 | 0.323 |
| ALT (U/L) | 32.4 | 26.2 | 36.6 | 40.3 | 0.586 |
| ALP (U/L) | 113.9 | 48.3 | 123.6 | 48.3 | 0.396 |
| Na (mmol/L) | 137.1 | 4.8 | 137.9 | 4.9 | 0.489 |
| K (mmol/L) | 4.3 | 0.9 | 4.2 | 0.9 | 0.729 |
| Cl (mmol/L) | 100.3 | 9.2 | 99.5 | 4.5 | 0.640 |
| CRP (mg/L) | 52.0 | 66.4 | 86.6 | 97.2 | 0.071 |
| D DIMER (µ/mL) | 1.5 | 1.6 | 1.5 | 1.0 | 0.985 |
| FIBRINOGEN (mg/dl) | 415.8 | 87.1 | 420.2 | 84.7 | 0.827 |
| LDH (U/L) | 507.6 | 290.2 | 607.4 | 276.1 | 0.141 |
| PT (sec) | 11.4 | 1.0 | 15.7 | 17.6 | 0.105 |
| INR | 1.3 | 1.4 | 1.2 | 0.2 | 0.700 |
| APTT (sec) | 23.1 | 3.6 | 27.7 | 9.5 | 0.004 |
| FERRITIN (ng/ml) | 607.1 | 504.0 | 1100.6 | 645.4 | 0.000 |
| PROCALCITONIN (ng/ml) | 6.3 | 16.5 | 9.3 | 6.9 | 0.003 |

| | | | | | |
|---|---|---|---|---|---|
| CTSS (CT severity score) out of 25 | 10 | 6 | 12 | 6 | 0.309 |

Considering 30 patients with secondary infections, 13(43%) were females and 17(57%) were males. The association between gender and secondary infection was found to be statistically significant. Out of all 75 subjects 7 (16%) without secondary infection died whereas 9 (30%) with secondary infection died.

Patients with Hypertension, Diabetes, CKD, Cardiac Disease, Neurological disease, and Diarrhea have had significantly higher secondary infection rate.

Proportions of symptoms like fever, cough, anosmia, sore throat, hemoptysis, chest pain, vomiting, rhinorrhea, and myalgia could not be used a predictor of secondary infection as they were symptoms of the primary disease condition i.e., COVID-19.

**Table 2: Comparison of categorical properties between patients with and without secondary infection.**

| | | Negative (N=45) | | Positive (N=30) | | p value |
|---|---|---|---|---|---|---|
| | | **Count** | **Column N %** | **Count** | **Column N %** | |
| Sex | Female | 18 | 40% | 38 | 84% | 0.000 |
| | Male | 27 | 60% | 7 | 16% | |
| Outcome | Death | 7 | 16% | 9 | 30% | 0.000 |
| | Discharge | 38 | 84% | 21 | 70% | |
| Hypertension | | 7 | 16% | 8 | 27% | 0.030 |
| Diabetes | | 11 | 24% | 11 | 37% | 0.002 |
| CKD | | 7 | 16% | 38 | 84% | 0.012 |
| Thyroid | | 5 | 11% | 3 | 10% | 0.421 |
| IHD/CARDIAC DISEASE | | 2 | 4% | 4 | 13% | 0.000 |
| Chronic respiratory disease | | 2 | 4% | 1 | 3% | 0.323 |
| Liver disease | | 1 | 2% | 1 | 3% | 0.642 |
| Neurological disease | | 0 | 0% | 2 | 7% | 0.000 |
| DVT | | 5 | 11% | 2 | 7% | 0.273 |
| Fever | | 29 | 64% | 16 | 53% | 0.421 |
| Cough | | 26 | 58% | 15 | 50% | 0.642 |
| Dyspnoea | | 25 | 56% | 18 | 60% | 0.521 |
| Anosmia | | 11 | 24% | 3 | 10% | 0.425 |
| Sore throat | | 12 | 27% | 6 | 20% | 0.141 |
| Hemoptysis | | 1 | 2% | 0 | 0% | - |
| Diarrhoea | | 3 | 7% | 3 | 10% | 0.038 |
| Chest pain | | 3 | 7% | 2 | 7% | 0.949 |
| Vomiting | | 2 | 4% | 1 | 3% | 0.368 |
| Rhinorrhea | | 7 | 16% | 1 | 3% | 0.053 |
| Myalgia | | 19 | 42% | 11 | 37% | 0.075 |
| Vaccination status | | 4 | 9% | 1 | 3% | 0.000 |
| Mode of O2 Delivery | Non-Invasive | 39 | 97% | 23 | 77% | 0.000 |
| | Invasive | 6 | 13% | 7 | 23% | |

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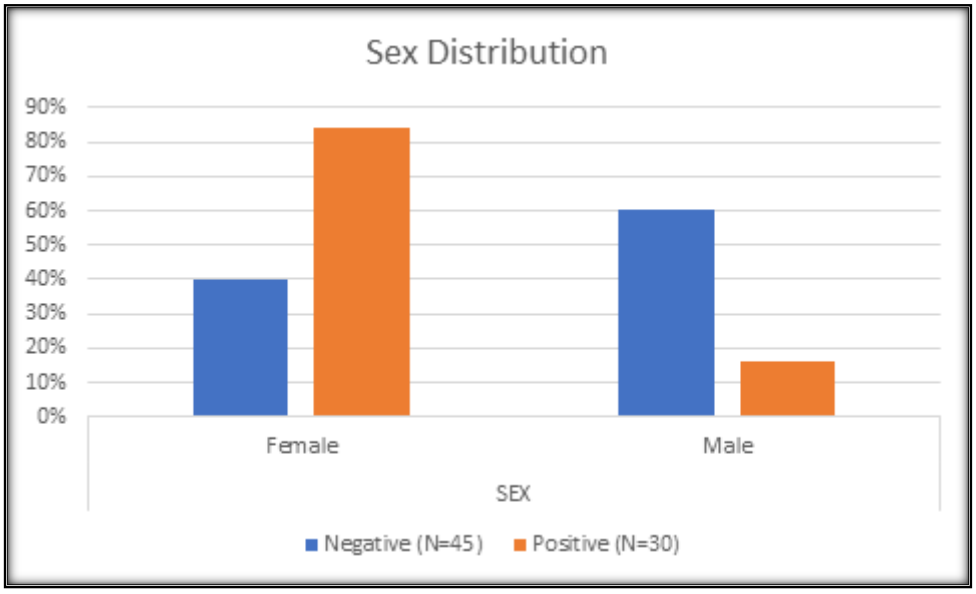
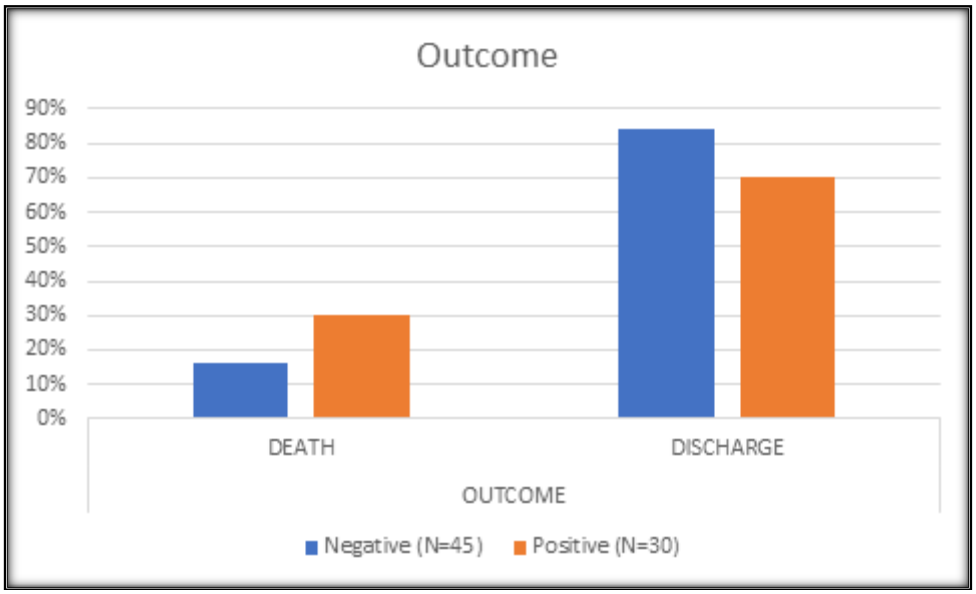


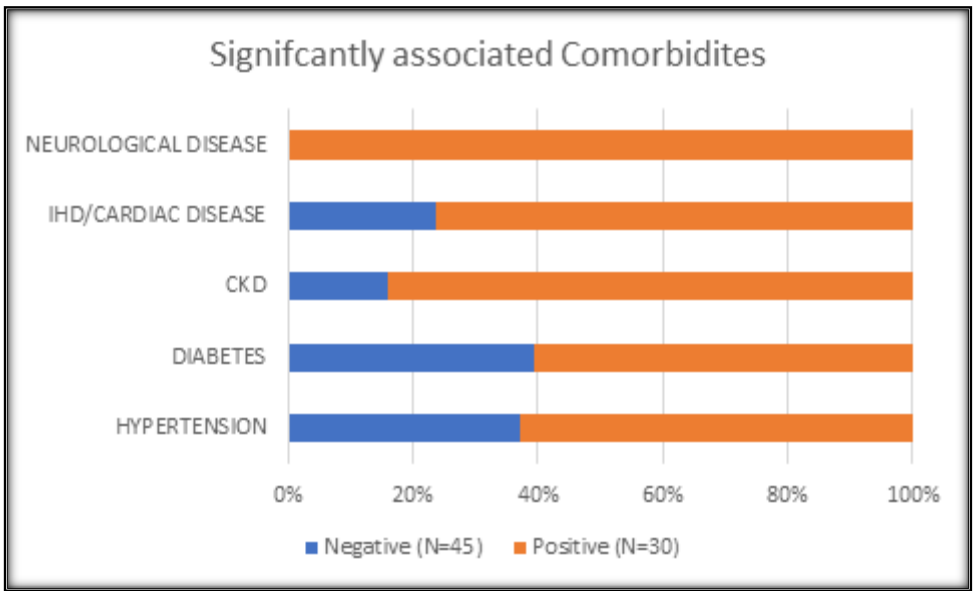
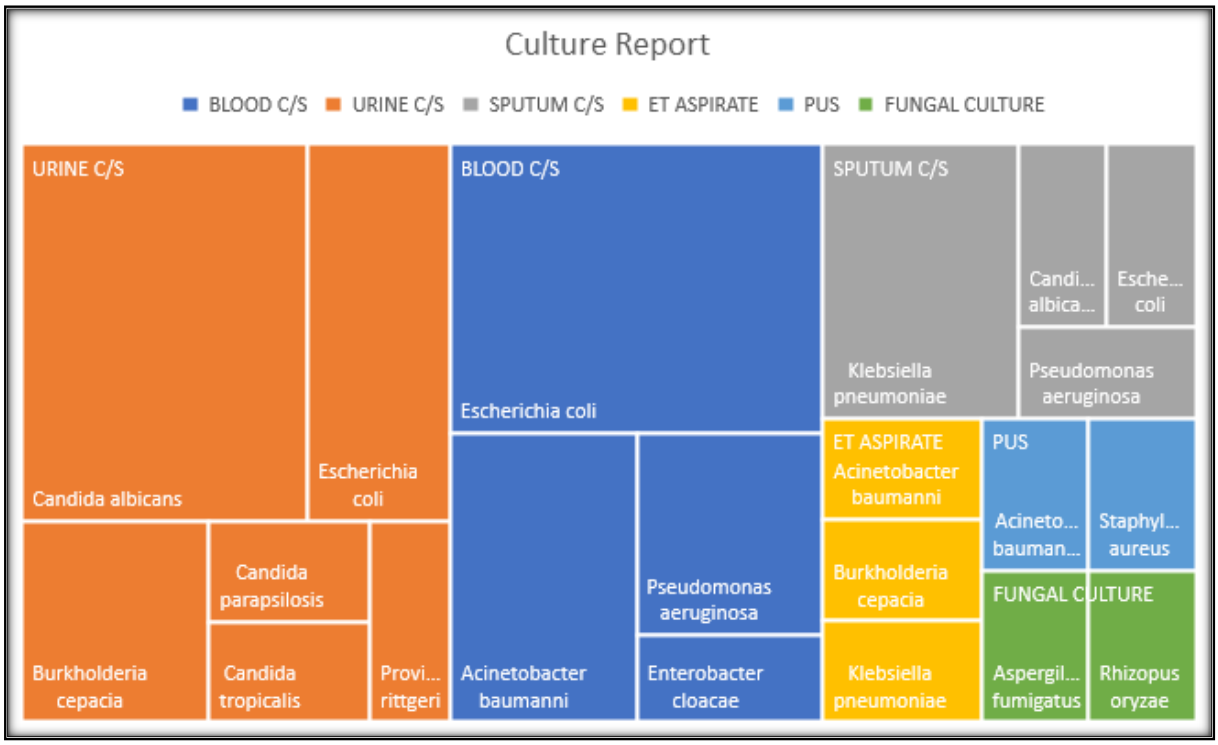



**Table 3: Distribution of organisms in patients with secondary infection**

| | | Count | % |
|---|---|---|---|
| Blood C/S | Acinetobacterbaumanni | 3 | 10% |
| | Enterobacter cloacae | 1 | 3% |
| | Escherichia coli | 6 | 20% |
| | Pseudomonas aeruginosa | 2 | 7% |
| Urine C/S | Burkholderiacepacia | 2 | 7% |
| | Candida albicans | 6 | 20% |
| | Candida parapsilosis | 1 | 3% |
| | Candida tropicalis | 1 | 3% |
| | Escherichia coli | 3 | 10% |
| | Providenciarittgeri | 1 | 3% |
| Sputum C/S | Candida albicans | 1 | 3% |
| | Escherichia coli | 1 | 3% |
| | Klebsiella pneumoniae | 3 | 10% |
| | Pseudomonas aeruginosa | 1 | 3% |
| ET Aspirate | Acinetobacterbaumanni | 1 | 3% |
| | Burkholderiacepacia | 1 | 3% |
| | Klebsiella pneumoniae | 1 | 3% |
| PUS | Acinetobacterbaumanni | 1 | 3% |
| | Staphylococcus aureus | 1 | 3% |
| Fungal culture | Aspergillus fumigatus | 1 | 3% |
| | Rhizopusoryzae | 1 | 3% |

Blood C/S reports reveled that the most prevalent organism was Escherichia coli 6 (20%), in Urine C/S most prevalent organism was Candida albicans 6(20%). Sputum C/S showed Klebsiella pneumoniae was present in 3(10%) subjects.



## DISCUSSION

Secondary infection is a serious complication in patients hospitalized with COVID-19, which is associated with worse outcomes and high mortality.[6,14,15] So far, many studies have been published reporting frequency and the features of these infections from different countries around the world.[7,11]As stated in some studies,[16,17] we also observed that patients with secondary infections were older and had multiple underlying comorbidities, mostly hypertension and coronary heart disease, compared to those without secondary infection. Out of all 75 subjects 7 (16%) without secondary infection died whereas 9(30%) with secondary infection died in this study. It was found that patients with secondary infection had significantly prolonged length of hospital stay and a higher mortality rate, compared to those without infection, which was consistent with previous studies.[2,18]

In the current literature, the rate of secondary infection in hospitalized COVID-19 patients varies widely between 3.8% and 83.3%, by emphasizing that it is noticeably more often in ICU-patients than those in the general service.[2,6,11,18] In accordance with this data, we found the secondary infection rate to be 40% among all 75 hospitalized COVID-19 patients. Compared with patients without secondary infection, use of mechanical ventilation were more common in patients with secondary infections (23% vs 13%). Given that secondary infections closely related with the use of mechanical ventilation, it is expected that the majority of secondary respiratory infections reported in critically ill COVID-19 patients are ventilator-associated pneumonia.[11,16,18-24]

In our study, when laboratory values examined, it was found that DBP (77.2±11.4 vs 69.5±13.4), TC (13582.4±6305.7 vs 18550.0±8700.8), NLR (15.8±14.3versus 19.1±13.51), APTT (23.1±3.6 vs 27.7±9.5), FERRITIN (607.1±504.0vs1100.6±645.4),PROCALCITONIN(6.3±16.5 vs 9.3±6.9) levels were significantly higher among patients with secondary infection compared to those without ($p<0.05$). Thus, the fact that these parameters can help the clinician to predict that patients are unlikely to have secondary infection, even if it cannot be completely ruled out.

## CONCLUSION

In conclusion, higher levels of TC, NLR, APTT, FERRITIN and PROCALCITONIN can be used as determinants of secondary infection in hospitalized COVID-19.Blood C/S reports reveled that the most prevalent organism was Escherichia coli6 (20%), in Urine C/S most prevalent organism was Candida albicans6(20%). SPUTUM C/S showed Klebsiella pneumoniae was present in 3(10%) subjects. Duration of stay in hospital and mortality rate was significantly higher in subjects with secondary infection compared to subjects without secondary infection.

### Limitation:

The present study limitations such as. First, it was performed in a single-centre with a small sample size, which may limit generalizability. It is known that the use of steroids increases the risk of secondary infection, and since the subjects in this study were under steroid use, it could have an effect on incidence of secondary infection.

## REFERENCES

1. Sharifipour E, Shams S, Esmkhani M, et al. Eva- luation of bacterial co-infections of the respira- tory tract in COVID-19 patients admitted to ICU. BMC Infect Dis.2020;20(1):646.
2. Zhang H, Zhang Y, Wu J, et al. Risks and featu- res of secondary infections in severe and critical ill COVID-19 patients. Emerg Microbes Infect. 2020;9(1):1958-1964.

3. Nori P, Cowman K, Chen V, et al. Bacterial and fungal coinfections in COVID-19 patients hospi- talized during the New York City pandemic sur- ge. Infect Control Hosp Epidemiol.2021;42(1):84-88.
4. Póvoa HCC, Chianca GC, Iorio NLPP. COVID- 19: An Alert to Ventilator-Associated Bacterial Pneumonia. Infect Dis Ther.2020;9(3):417-420.
5. Crotty MP, Akins R, Nguyen A, Slika R, et al. Investigation of subsequent and co-infections associated with SARS-CoV-2 (COVID-19) in hospitalized patients. medRxiv. 2020. doi:05.29.20117176.
6. Li J, Wang J, Yang Y, et al. Etiology and antimic- robial resistance of secondary bacterial infections in patients hospitalized with COVID-19 in Wu- han, China: a retrospective analysis. Antimicrob Resist Infect Control.2020;9(1):153.
7. Lansbury L, Lim B, Baskaran V, Lim WS. Co- infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81 (2):266-275.
8. World Health Organization (WHO). COVID-19 Clinical management: livingguidance.25.01.2021.Available from: https://www.who.int/ publications/i/item/WHO-2019-nCoV-clinical- 2021-1. Accessed March15,2021.
9. Sieswerda E, de Boer MGJ, Bonten MMJ, et al. Recommendations for antibacterial therapy in adults with COVID-19 - an evidence based guide- line. ClinMicrobiol Infect.2021;27(1):61-66.
10. 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.
11. Langford BJ, So M, Raybardhan S, et al. Bacte- rial co-infection and secondary infection in pati- ents with COVID-19: a living rapid review and meta-analysis. ClinMicrobiol Infect. 2020;26 (12):1622-1629.
12. Rawson TM, Moore LSP, Zhu N, et al. Bacterial and Fungal Coinfection in Individuals With Coro- navirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. Clin Infect Dis. 2020;71(9):2459-2468.
13. Infectious Diseases Society of America (IDSA). Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clini- cal Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society.Availablefrom: https://www.idsociety.org/practice-guideline/hap_vap/. Accessed March1,2022.
14. European Committee on Antimicrobial Suscepti- bility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Ver- sion 10.0.Availablefrom:https://www.eucast.org/fileadmin/src/media/PDFs/ EUCAST_files/Breakpoint_tables/ v_9.0_Breakpoint_Tables.pdf; 2020. Accessed March1,2022.
15. Fu Y, Yang Q, Xu M, et al. Secondary Bacterial Infections in Critical Ill Patients WithCoronavi- rus Disease 2019. Open Forum Infect Dis. 2020;7 (6):ofaa220.
16. Lee SI, Koh JS, Kim YJ, et al. Secondary infec- tion among hospitalized COVID-19 patients: A retrospective cohort study in a tertiary care set- ting. Respirology. 2021;26(3):277-278.
17. Goncalves Mendes Neto A, Lo KB, Wattoo A, et al. Bacterial infections and patterns of antibiotic use in patients with COVID-19. J Med Virol. 2021;93(3):1489-1495.
18. Garcia-Vidal C, Sanjuan G, Moreno-García E, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retros- pective cohort study. ClinMicrobiol Infect. 2021;27(1):83-88.

19. MorettiM,VanLaethemJ,MininiA,PierardD,Malbrain MLNG. Ventilator-associated bacterial pneumonia in coronavirus 2019 disease, a retros- pective monocentric cohort study. J Infect Che- mother. 2021;27(6):826-833.
20. Ripa M, Galli L, Poli A, et al. Secondary infecti- ons in patients hospitalized with COVID-19: inci- dence and predictive factors. ClinMicrobiol Infect.2021;27(3):451-457.
21. Dudoignon E, Caméléna F, Deniau B, et al. Bac- terial Pneumonia in COVID-19 Critically Ill Pati- ents: A Case Series. Clin Infect Dis. 2021;72 (5):905-906.
22. Bardi T, Pintado V, Gomez-Rojo M, et al. Noso- comial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome. Eur J ClinMicrobiol Infect Dis. 2021;40(3):495-502.
23. Koehler P, Bassetti M, Chakrabarti A, et al. Defi- ning and managing COVID-19-associated pulmo- nary aspergillosis: the 2020 ECMM/ISHAM con- sensus criteria for research and clinical guidance. Lancet Infect Dis.2021;21(6):149-162.
24. Hughes S, Troise O, Donaldson H, Mughal N, Moore LSP. Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting. ClinMicrobiol Infect. 2020;26(10):1395- 1399.