The Relationship of Comorbid Diseases and Empirical Antibiotic Usage with Superinfection in COVID-19 Patients

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ABSTRACT

Objective: To identify the microorganisms responsible for superinfections in patients admitted with COVID-19 and evaluate the impact of empirical antibiotic regimen and comorbid disease on superinfections comparing COVID-19 patients with and without secondary infection.

Study Design: A descriptive study.

Place and Duration of the Study: Department of Microbiology, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkiye, from March to July 2020.

Methodology: This study was conducted with patients diagnosed with COVID-19 disease based on radiological or quantitative RT-PCR test results. Culture results, demographic characteristics, clinical variables, and therapeutic regimen were collected from medical records.

Results: Superinfection developed in 48 (26.96%) of 178 cultures (24 of 101 patients) followed up in the COVID-19 clinics. Infections were determined as 25 (52.08%) bloodstream, 11 (22.9%) urinary tract, 10 (20.8%) respiratory tract and 2 (4.16%) soft tissue infections, respectively. Secondary infectious agents were *E.coli* in 11 (22.9%), *A.baumannii* in 8 (16.7%), *S.homminis* in 7 (14.6%), *S.epidermidis* in 6 (12.5%), *K.pneumoniae* in 4 (8.3%), *C.albicans* in 2 (4.1%), and other bacterial and fungal agents in 10 (20.8%). The median range from admission to the hospital to detecting microorganism growth was the longest with piperacillin/tazobactam with moxifloxacin and azithromycin. Secondary microorganism detection was delayed, mostly due to the empirical use of moxifloxacin, azithromycin, and piperacillin/tazobactam.

Conclusion: Demographic characteristics, comorbidity and antibiotic use of patients were not directly related to secondary infections. In addition, the empirical use of azithromycin and moxifloxacin with piperacillin/tazobactam appeared to delay the development of superinfection.

Key Words: *Superinfection, COVID-19, Comorbidity*.

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INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) and the elderly are at risk of contracting COVID-19 disease.[1-3] The risk of illness increases 4-fold in patients with COPD.[4] A retrospective study concerning middle-aged and elderly patients with COVID-19 showed that the elderly population is more susceptible to this disease, has a higher mortality rate and has a higher probability of admission to the ICU.[5] One of the factors reflecting the severity of COVID-19 patients is superinfection or co-infection. Secondary pulmonary bacterial infection may have an unfavourable outcome in COVID-19 patients, in comparison with those without it.[6]

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Information on factors affecting superinfection in COVID-19 patients is limited and needs to be studied in detail. Preventing secondary infection in critically ill patients may reflect the outcome. Therefore, national guidelines recommend the initiation of empirical antibiotic therapy up to the microbiological documentation of secondary pathogens.[7]

Although patients have similar demographic characteristics, superinfection does not develop in every patient during the course of COVID-19 disease. This study will help to investigate the effect of these risk factors on superinfections during COVID-19 disease.

The aim of this study was to investigate the impact of demographic characteristics, comorbidities, and empirical antibiotic use on the development of superinfection in COVID-19 patients.

METHODOLOGY

A descriptive study was conducted on patients diagnosed with COVID-19 disease based on radiological or quantitative RT-PCR (qRT-PCR, Biospeedy, Istanbul) test results. Patients hospi-

talised for more than 48 hours with the diagnosis of COVID-19 between March 2020 and July 2020 at Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkiye, were included in the study. Outside of these dates, patients with a pre-diagnosis of COVID-19, and no growth in their routine cultures were excluded from the study.

The Helsinki Declaration was compiled with the Ethics Committee of the University and ethical approval was obtained (CAAE No. 26 /08/2020/16-13).

Power analysis was used to determine the number of samples. To do so, α: 0.05 for the first type error level and β: 0.10 for the second type error level 0.90 test power of the reference study,[8] the calculation was made by considering bacterial growth rates of p1: 0.75 and p2: 0.333. A total of 101 patients were included in the study. There were 77 patients in the control group and 24 patients in the superinfection group.

Data of hospitalised patients with COVID-19 about demographic characteristics (age, gender) of all patients with, epidemiology, comorbidities, culture results (blood and urine cultures, endotracheal aspirate, sputum, and soft tissue cultures), type of empirical antibiotic regimen used were collected directly from the University Hospital electronic health record system.

Blood cultures (BacT/ALERT, France), urine, endotracheal aspirate, sputum and soft tissue specimens had been cultured on 5% sheep blood agar (BD, USA), chocolate agar (BD, USA) and eosin-methylene blue agar (BD, USA) plates and incubated at 37°C for 18–24 hours. Isolates in yeast morphology had been cultured on Saborauds' dextrose agar. Identification was made by conventional methods and BD Phoenix automated bacterial identification system (Becton Dickinson, USA).

Secondary infections were categorised as bloodstream infection, respiratory tract infection, urinary tract infection, and soft tissue infection based on laboratory-confirmed bacterial and fungal growths. Definition of culture growth results as pathogen was made according to the decision of physicians. This depended on variables such as the patient's clinical condition and inflammatory markers (white blood cell count, C-reactive protein levels, neutrophil ratio, and lymphocyte ratio, etc.).

The compliance of data variables to normal distribution was examined using the Shapiro-Wilk test. Mann-Whitney U test was used for group comparisons of variables that did not show normal distribution. Group comparisons were analysed by independent samples t-test for variables with normal distribution. Statistical parameters of non-parametric variables were expressed as median (minimum-maximum) and parametric variables were expressed as mean and SD. Chi-square test and Fisher's exact test were used to examine the distributional relationship of categorical variables. The results were expressed in ratio (%) and frequency (n). Data evaluation was carried out with IBM SPSS version 22 (IBM SPSS for Windows version 22, IBM Corporation, Armonk, New York, United States). Statistical significance was accepted as $p<0.05$.

RESULTS

Of the superinfected patients 14 (58.33%) were females and 10 (41.6%) were males; the mean age was 31.29±18.34 years. There was no statistically significant difference in group comparisons in terms of age, gender, and death results. Superinfection developed in 24 (23.76%) of 101 patients followed up in the COVID-19 clinics. Microorganism growth was detected in a total of 178 cultures. Fourty-eight (26.96%) of these were evaluated as pathogen *E.coli* with 22.91% (n:11), *A.baumannii* 16.6% (n:8), *S.homminis* 14.5% (n:7), *S.epidermidis* 12.5% (n:6), *K.pneumoniae* 8.3% (n:4), *C.albicans* 4.1% (n:2), and other bacterial and fungal agents 20.8% (n:10) were isolated as causative agents. Of the detected infections, 52.10% (n:25) were bloodstream infections, 22.9% (n:11) were urinary tract infections, 20.8% (n:10) were respiratory tract infections and 4.2% (n:2) were soft tissue infections (Figure 1).

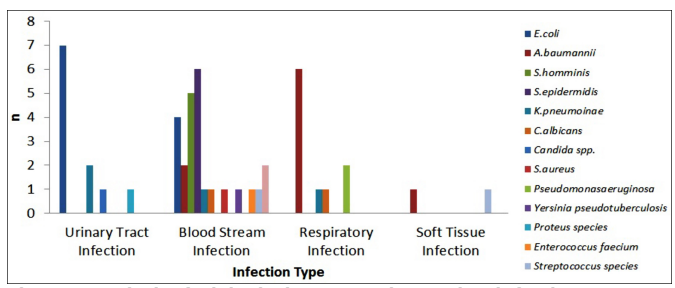

Figure 1: Analysis of etiological agents and secondary infections.

The most common comorbidities were hypertension (n:10, 41.7%), diabetes mellitus (n:5, 20.8%), chronic renal failure (n:3, 12.5%), chronic obstructive respiratory disease (n:3, 12.5%), asthma (n:1, 4.2%), and cerebro-vascular disease (n:2, 8.3%, Table I).

The overall mortality rate in hospitalised patients was 29.1% (n: 30) and there was no statistically significant difference in group comparisons (31% *vs.* 30.9%).

Median time from admission to detection of microorganism growth in culture did not differ in group comparisons (2.0 *vs.* 1.0 days, p:0.234). However, the duration of protection from secondary infection was the longest with empirical use of azithromycin (12 days) and piperacillin/tazobactam with moxifloxacin (11 days) empirical usage.

DISCUSSION

Secondary infections and comorbidities are thought to have a significant impact on the course of COVID-19 disease. The causes of secondary infections detected in the *SARS-CoV-2* disease and their relationship have not been studied in detail to date.

This study focused on the demographic characteristics, comorbidities of COVID-19 patients, and the impact of empirical antibiotic therapy on secondary infections.

Group comparisons were made according to the development of superinfection in patients hospitalised for more than 48 hours. Secondary infections were detected in 24 (23.76%) of 101 COVID-19-diagnosed patients.

Table I: Group comparisons for comorbidities.

	Control (n:77)		Superinfection (n:24)		p
	n	%	n	%	
Hypertension	22	28.6	10	41.7	
Diabetes mellitus	17	22.1	5	20.8	
Chronic renal failure	6	7.8	3	12.5	
Chronic obstructive pulmonary disease	6	7.8	3	12.5	
Asthma	8	10.4	1	4.2	
Cerebro-vascular disease	9	11.7	2	8.3	0.936
Liver disease	1	1.3	0	0.0	
Pulmonary malignancy	1	1.3	0	0.0	
Alzheimer's disease	4	5.2	2	8.3	
Others	41	53.2	11	45.8	
No disease	22	28.6	7	29.2	

Exact test: α: 0.05; since multiple comorbidities were present, the number of diseases is higher.

The results revealed that men [58% (n:11)] are more affected by the disease than women, as reported previously.[2,9,10] In a retrospective study of 168 patients, mortality (12.8% *vs.* 7.3%) rates were higher among men than women.[11] Concerns have been raised about the potential for high mortality rates from bacterial and fungal co-infections in previous respiratory viral pandemics such as influenza.

The present study detected bloodstream infection in 25 (52.08%), urinary tract infections in 11 (22.9%) and respiratory tract infection in 11 (22.9%) patients. This was compatible with other studies.[6,12] According to researchers, superinfection rates vary between 5% and 27%.[6,9,12,13] This ratio increases mainly with hospitalised patients in intensive care unit (ICU)'s from 13.5% to 44%. Secondary infections detected are mainly respiratory infections such as bacterial or fungal pneumonias; meanwhile, in another study, urinary tract infection was detected most frequently in 10 (72%) patients and bacterial pneumonia in 13 (12.2%) patients; with two cases of each methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *Staphylococcus aureus* (MSSA), *Corynebacterium striatum*, and *P.aeruginosa*; one case each of *Legionella*, *Serratia marcescens*, and *K. pneumoniae*.[9,13] Two had other respiratory tract virus infections (ICU).[9,13]

Mostly identified infectious agents were mainly *Entero-bacterales* such as mutidrug resistant (MDR) *A.baumannii*, carbapenemase producing *K.pneumoniae*, extended spectrum beta-lactamase producing *K.pneumoniae*, *Pseudomonas aeruginosa, E.cloacae, Serratia marcescens, Aspergillus fumigatus, Aspergillus flavus, Candida albicans,* and *Candida glabrata.*[6,9,10] Influenza-associated seconder pathogens such as *S.aureus*, *Mycoplasma pneumoniae*, *Streptococcus pyogenes* and *Streptococcus pneumoniae* are rarely detected and usually cause co-infections.[11,12] Garcia-Vidal *et al*. found that seven (0.7%) of the secondary infections were hospital-acquired fungal infections; three cases were *A.fumigatus* and four *C.albicans.*[9] Another researcher identified one *Aspergillus fumigatus* infection among fungal pathogens.[12] There was only one (4%) *C. albicans* isolate from a blood culture and one (10%) from a respiratory tract specimen in this series. *Aspergillus* was not detected. It has been suggested that fungal infections are associated with corticosteroid use.[14] In this study, there was only one patient on corticosteroids.

Rynda-Apple *et al*. supposed that the decrease in interferon I (IFN I) levels was associated with secondary bacterial infections.[15] Conversely, increased IFN I and III production after bacterial infection may facilitate *SARS-CoV-2* exposure through ACE2 receptor stimulation.[16] Buckley *et al*. suggested that treatment with IL-1 blokers, IFN I and III could promote bacterial infections.[17] The host-virus interactions and inflammatory responses may facilitate the occurrence of bacterial infections. The H1N1 Influenza pandemic in 2009 was complicated by bacterial pneumonia in 4-33% of hospitalised patients with a mortality rate of 30-55%.[18,19] In Brazil, the confirmed death rate attributable to superinfection among hospitalised COVID-19 patients was 34.7%.[20] Some researchers noted that deaths were associated with bacterial co-infection or superinfection and this increased when admitted to ICU.[9,10]

In this study, no significant difference was observed when groups were compared. The overall mortality rate in hospitalised patients was 29.1% (n = 30) and secondary infections do not appear to directly affect mortality according to group comparisons (31% *vs.* 30.9%).

Since the beginning of the pandemic, there is no consensus on the treatment of COVID-19 patients. It has been suggested that excessive use of antimicrobial soaps, disinfectants, and antimicrobials may increase health-related infections and even transmission of MDR organisms.[6] It was reported during the data collection periods of seventeen studies that more than 90% of patients were receiving empirical antibiotics.[19] Numerous types of antibiotics such as azithromycin have been used to prevent bacterial infection. Almost all patients received empirical antibiotics although it is thought to result in microbial resistance in the future. In this study, azithromycin and levofloxacin were used mainly in the first

two months. A second antibiotic was started for some patients with C-RP values above 50 mg /dl. The type of antibiotic used and median time from admission to microbial growth detection were not statistically significant. However, the authors detected that the use of azithromycin and piperacillin / tazobactam delayed the occurrence of secondary infection from 11 to 12 days. The duration of prophylaxis ranged from 1 to 35 days (median: 1 day). One researcher recorded the time as 10.6 (6.6) days and another study recorded 5 days.[9,10]

It has also been stated that underlying uncontrolled comorbidities such as diabetes mellitus and hypertension are associated with the progression of COVID-19.[2,21,22] A study conducted in China examined 633 COVID-19 patients, of whom 247 were elderly individuals over 60 with at least one comorbidity, concluded that older patients were more likely to succumb to COVID-19 disease.[12] It has been established that *SARS-CoV-2* binds to ACE2 receptors and enters host cells. The ACE2 receptors are located in cells of human airway epithelia as well as lung parenchyma, arteries, heart, kidney, and intestines.[23,24] This could seem to explain why diabetes mellitus, hypertension, and chronic renal diseases are risk factors. Interestingly, in Canada, dementia or Alzheimer's was the most listed comorbidity in deaths caused by COVID-19.[25] However, no association with Alzheimer's disease and secondary infections has been reported.

Alzheimer's diseases were seen in the superinfection group with only 2 (8.3%) *versus* 4 (5.2%) in the control group. Poor personal care and hygiene conditions could make Alzheimer's patients susceptible to infections. Almost all hospitalised patients had multiple comorbidities, mostly suffering from hypertension (41.7%) and diabetes mellitus (20.8%). The underlying conditions do not directly predispose the patient to superinfection.

This study will help identify common infections among COVID-19 patients and predict risk factors and treat superinfections in the early stages of the disease.

The limitation of the study is the low number of super-infections in patients diagnosed with COVID-19 during the study period. In addition, patients with superinfection in the normal population were not compared with the period of the study.

CONCLUSION

The development of secondary infections should not be referred to as the main cause of death in COVID-19 patients. The infection profile can guide physicians in choosing empirical therapeutic protocols to increase the survival rates of COVID-19 patients. In addition, special care should be taken to initiate appropriate antibiotics and to prevent antimicrobial resistance.

ETHICAL APPROVAL:
The Helsinki Declaration was compiled with the Ethics Committee of the University and ethical approval was obtained (CAAE No. 26 /08 /2020 /16-13).

PATIENTS' CONSENT:
Patients' consents were not required in this study as the data were taken from the patients' records without mentioning patient's personal details or pictures.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
FO: Conception, design and manuscript writing.
SN, SA: Conception, data collection and supervision.
KTY: Conception, design, data collection and manuscript correction.
MA: Supervision and manuscript correction.
AD: Statistical analysis and data interpretation.
All the authors have approved the final version of the manuscript to be published.

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