ORIGINAL ARTICLE

Pattern of Bacterial and Fungal Infections among Hospitalized Patients with COVID-19 versus non COVID-19 Community Acquired Pneumonia

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ABSTRACT

Background: *It is strongly believed that co-infections play an important role during COVID-19 outbreak. Furthermore, secondary bacterial pneumonia rates increase rapidly in intensive care unit patients.* ***Objectives:*** *This study aimed to elucidate the rate of bacterial and fungal contagions among the hospitalized COVID-19 patients and compares it with non-COVID-19 community acquired pneumonia (CAP) cases with documentation of the most common organisms to guarantee the responsible use of antibiotics among these cases.* ***Methodology:*** *100 patients were admitted with confirmed CAP and classified into 2 groups according to SARS-CoV-2 PCR results; the first group consisted of 52 COVID-19 positive patients. The second group included 48 patients with non- COVID-19 CAP.* ***Results:*** *COVID-19 group showed several negative sputum cultures than the non-COVID-19 group (p=0.023). Within the cases with positive cultures, COVID-19 patients had more (Staph. aureus, E. coli, Klebsiella pneumoniae and Candida albicans). While non-COVID-19 patients had more (Streptococcus, Pseudomonas aeruginosa, Enterococcus and Proteus) (p <0.05). COVID-19 cases had further resistant strains (p =0.031). Regarding the outcome findings, there were considerable increase in duration of the hospital stay (LHS), necessity of oxygen support and mechanical ventilation among COVID-19 group [p <0.05] with a higher decease rate among COVID-19 group.* ***Conclusions:*** *Critically ill COVID-19 patients exhibited a higher rate of bacterial co-infection detected in sputum (80.8%), PSI, LHS, necessity for oxygen, mechanical ventilation and mortality were higher in COVID-19 CAP compared with non-COVID-19 CAP PSI, LHS, necessity for oxygen, mechanical ventilation and decease rate which were higher among COVID-19 cases compared with non-COVID-19 CAP.*

INTRODUCTION

For a long time, it has been recognized that viral respiratory contagions predispose to bacterial contagions.[1] Microbial super-infection during Intensive Care Unit (ICU) admission has been pronounced in the other out-breaks of severe acute respiratory syndrome (SARS), but there is a circumscribed data available concerning COVID-19 cases. Numerous authors identify the importance of super-infection but absolute data is still deficient. [2,3]

Co-infections are thought to have a crucial role during COVID-19 infection, first of all, COPD (chronic obstructive pulmonary disease) is an important comorbid condition associated with severe COVID-19 [4]. Patients in COPD are inhabited by bacterial pathogens even at the stable phase, making it likely that SARS CoV-2 infection occurs in already bacterial infected patients. Furthermore, critically ill COVID-19 patients need hospitalization which increases their risk of acquiring secondary bacterial pneumonia. Garcia et al [5]. displayed that bacterial co-infection on admission has been reported in 3.1–3.5% of COVID-19 patients, while secondary bacterial contagions, following hospitalization, evolved in up to 15% of the cases.

The median hospital period of COVID-19 patients is 7 days but can reach up to 14 days or even more, and the risk of HAP (Hospital Acquired Pneumonia) increases considerably with prolonged hospitalization. Furthermore, more than 90% of HAP is associated with mechanical ventilation, which is used in management of COVID-19 patients admitted in the ICU [6]. Antibiotics are ineffective in the treatment of COVID-19. Several recommendations encourage the use of empirical antibiotics for patients with severe COVID-19 [7, 8]. However, these recommendations raise the concerns of antibiotic overuse and subsequent harm associated with bacterial resistance.

Therefore, this study aimed to elucidate the rate of bacterial and fungal contagions among hospitalized COVID-19 patients and compare it with non-COVID-19 CAP with the identification of the most common organisms included to guarantee responsible use of antibiotics.

METHODOLOGY

Study design:

It is a prospective cross-sectional study that was accomplished in Aswan university hospital in the period from January 2022 to January 2023 in 100 hospitalized adult patients.

Ethical consideration:

This study was approved by the ethical committee of Faculty of Medicine, Aswan University (592/1/22), and all subjects gave written informed consent prior to participating in the study.

Eligible participants:

Inclusion criteria:

- Pneumonia evidence at High Resolution Computed Tomography (HRCT) scan
- Accessibility of the whole laboratory data and a thorough clinical history
- Availability of complete outcome data (discharge/decease) and length of hospital stay.

Exclusion criteria:

- Inadequate clinical records, non-existence of laboratory or imaging information.

All the included cases were subjected to:

- **A through history taking**
- **Clinical examination**
- **PCR testing of nasopharyngeal swabs for SARS-CoV-2;** Automated QIAcube RNA extraction was performed using QIAmp DSP Virus Spin kit (Qiagen, Hilden, Germany, Cat.61704). The extracted RNA was then amplified using the Rotor-Gene Q thermal cycler and the Coronavirus COVID-19 (CE IVD) genesig® Real-Time PCR kit according to the manufacturer's instruction.
- **Sputum culture;** Samples were transported within 2 hours and inoculated on blood agar and MacConkey agar then incubated aerobically at 37°C for 24 hours. Identification of the isolates was done by using standard microbiological techniques which involved the morphological appearance of the colonies, gram staining properties, and biochemical reactions e.g. catalase production test, coagulase production test by tube method, indole production test, Methyl red test, Voges-Proskauer (VP) test, citrate utilization test, triple sugar iron (TSI) agar test, oxidase test and urease test. For the fungal documentation, Gram staining and culture on Sabouraud`s dextrose agar was done.
- **Antibiotic susceptibility** pattern of all the isolated strains was done by modified Kirby Bauer disc diffusion method [Microorganisms were clarified as multi-drug resistant (MDR) if they were refractory to one or more drug in at least three categories of antibiotics. [9]
- **Laboratory Investigations:** comprising (CBC, CRP, ESR, D-dimer, serum ferritin, pro-calcitonin, ABG, Na, K, renal and liver function tests),
- **Imaging** including chest x-rays and CT
- **Pneumonia severity scores** comprising [PSI (pneumonia severity index), CURB-65 (confusion, urea nitrogen, respiratory rate, blood pressure) scale, and SOFA score (The sequential organ failure assessment score)].
- The **outcomes** of the cases comprising [length of stay, ICU admission, complications, need for invasive or non-invasive mechanical ventilation and decease].

Statistical analysis:

Data analysis were done using SPSS (Statistical Package for Social Science) software program version 21.0 (SPSS Inc., Chicago, IL).

RESULTS

This study included 100 cases diagnosed as CAP and were divided into 2 groups according to SARS-CoV-2 PCR results; First group consisted of 52 COVID-19 positive patients. Second group consisted of 48 patients with non- COVID-19 CAP.

Table (1) showed the demographic and clinical features of the study groups. No considerable variance in demographic data was found between the two groups. Regarding the pneumonia severity scores, there was only considerable increase in PSI score among COVID-19 cases. There was an ominous increase in inflammatory markers including (ESR, CRP, D-dimer and ferritin) among COVID-19 cases**.**

Table 1: Demographic, clinical topographies and the inflammatory markers of the study population

	COVID-19 Negative (n = 48)	COVID-19 Positive (n = 52)	P-value
Age/years	61.60 ± 11.5	59.06 ± 13.6	0.315*
Sex: F/M	17 (35.4%) / 31 (64.6%)	26 (50%) / 26 (50%)	0.141**
BMI	28.25 ± 2.8	27.75 ± 2.3	0.234*
Smoking Status			
Non-smoker	22 (45.8%)	26 (50%)	**0.779****
Ex-smoker Smoker	17 (35.4%) 9 (18.8%)	15 (28.8%) 11 (21.2%)	
Pneumonia scores			
CURB-65	2.27 ± 0.1	2.50 ± 0.2	0.370*
PSI	96.10 ± 3.5	110.54 ± 6.5	**0.020***
SOFA	4.46 ± 0.3	4.88 ± 0.4	0.321*
Inflammatory markers			
CRP	31.40 ± 1.7	36.44 ± 1.4	**0.020***
ESR	27.30 ± 1.2	31.93 ± 1.1	**0.013***
D-Dimer	134.26 ± 76.1	431.26 ± 58.2	**< 0.001***
Ferritin	510.07 ± 49.3	724.70 ± 66.7	**0.012***
PT Outcome			
LHS (Days)	9.06 ± 1.3	11.12 ± 1.9	**0.045***
Need for ICU	34 (70.8%)	39 (75%)	**0.639****
Need for Oxygen	25 (52.1%)	41 (78.8%)	**0.005****
Need for MV	15 (31.3%)	30 (57.7%)	**0.009***
Improved / Died	34 (70.8%) /14 (29.2%)	21 (40.4%) /31 (59.6%)	**0.040****
COVID-19 Vaccination			
Type of Vaccine			
AstraZeneca	5 (10.4%)	4 (7.7%)	
Pfizer	0 (0%)	2 (3.8%)	0.141*
Sinopharm	6 (12.5%)	1 (1.9%)	

Concerning the outcome data, there were a considerable increase in length of hospital stay (LHS), need for either oxygen support or mechanical ventilation in COVID-19 group [p <0.05]. Moreover, the death rate was also higher among COVID-19 patients. There was no considerable variance in the vaccination history between the two groups (p <0.05). However, unvaccinated group has worse prognosis [as there was a substantial rise in number of patients who required ICU admission, O2 support and mechanical ventilation in the unvaccinated group (p <0.05)]. The result was shown in **(Table 2).**

Table 2: The relations between vaccination status and outcome among the study cohort

	Unvaccinated (n = 82)	Vaccinated (n = 18)	P-value
Need for ICU	70 (85.4%)	3 (16.7%)	**< 0.001***
Need for O_2	59 (72%)	7 (38.9%)	**= 0.007***
Complication	26 (31.7%)	1 (5.6%)	**= 0.024****
MV	44 (53.7%)	1 (5.6%)	**< 0.001****
Improvement	39 (47.6%)	18 (100%)	**< 0.001***

Regarding the sputum culture results among the two studied groups, COVID-19 group had more negative cultures than the other group (p = 0.023). Amid the positive culture results, COVID-19 patients had more (*Staph. aureus, E. coli, Klebsiella pneumoniae and Candida albicans)* and non-COVID-19 patients had more *(Streptococcus, Pseudomonas aeruginosa, Enterococcus and Proteus)* (p <0.05). COVID-19 cases had further resistant strains with (p = 0.031). The result was shown in **(Table 3).**

Table 3: Sputum culture results and their Antibiotic sensitivity among the study cohort

	COVID-19 Negative (n = 48)	COVID-19 Positive (n = 52)	P-value
Organism (n / %)			
No Growth	5 (10.4%)	10 (19.2%)	**0.023****
Candida albicans	2 (4.2%)	4 (7.7%)	0.108*
E. Coli	5 (10.4%)	9 (17.3%)	**0.042***
Klebsiella pneumoniae	2 (4.2%)	10 (19.2%)	**0.005****
Staph. aureus	22 (45.8%)	14 (26.9%)	**0.015***
Streptococcus pneumoniae	6 (12.5%)	3 (5.8%)	0.224**
Pseudomonas aeruginosa	3 (6.3%)	2 (3.8%)	0.706**
Enterococcus	2 (4.2%)	0 (0%)	0.881**
Proteus	1 (2.1%)	0 (0%)	0.994**
Antibiotic Sensitivity			
Multi-drug resistance	1 (2.1%)	6 (11.5%)	**0.031****
Amox-Clav.	5 (10.4%)	3 (5.8%)	0.337**
Amphotericin	2 (4.2%)	4 (7.7%)	0.398**
Cefazoline	2 (4.2%)	0 (0%)	0.369**
Cefoprazone	4 (8.3%)	0 (0%)	**0.047****
Ceftriaxone	0 (0%)	4 (7.7%)	**0.047****
Chloramphenicol	5 (10.4%)	3 (5.8%)	0.198*
Ciprofloxacin	4 (8.3%)	3 (5.8%)	0.258**
Clindamycin	3 (6.3%)	2 (3.8%)	0.402**
Gentamycin	3 (6.3%)	0 (0%)	0.144**
Levofloxacin	11 (22.9%)	7 (13.5%)	**0.046****
Meropenem	2 (4.2%)	6 (11.3%)	**0.044****
Ofloxacin	0 (0%)	4 (7.7%)	**0.047****
Vancomycin	1 (2.1%)	0 (0%)	0.527**

Staph. aureus positive cases had a substantial increase in CURB-65, PSI and SOFA scores among COVID-19 group, while *Klebsiella pneumoniae* positive cases disclosed only a substantial decrease in CURB-65 among the same group. The result was shown in **(Table 4).**

Table 4: Relation between Culture Results and Pneumonia scores among the study cohort

	COVID-19 Negative (n = 48)	COVID-19 Positive (n = 52)	P-value
CURB-65 (Mean ± SD)			
No Growth	1.60 ± 0.5	1.40 ± 0.4	= 0.677
Candida albicans	3.01 ± 0.1	2.01 ± 0.1	= 0.391
E. Coli	2.40 ± 0.2	2.67 ± 0.4	= 0.630
Klebsiella pneumoniae	4.01 ± 0.3	2.50 ± 0.6	**= 0.026**
Pseudomonas aeruginosa	2.33 ± 0.3	3.01 ± 0.2	= 0.696
Staph. auras	1.91 ± 0.2	3.07 ± 0.3	**= 0.004**
Streptococcus pneumoniae	2.50 ± 0.5	3.33 ± 0.6	= 0.208
PSI (Mean ± SD)			
No Growth	75.20 ± 4.9	83.10 ± 12.1	= 0.568
Candida albicans	90.01 ± 9.1	93.25 ± 13.3	= 0.928
E. Coli	106.01 ± 4.6	120.22 ± 12.1	= 0.331
Klebsiella pneumoniae	83.50 ± 13.1	115.80 ± 17.5	= 0.201
Pseudomonas aeruginosa	98.01 ± 11.3	126.50 ± 16.6	= 0.106
Staph. auras	93.95 ± 5.9	135.01 ± 10.1	**= 0.001**
Streptococcus pneumoniae	107.01 ± 12.5	107.67 ± 7.4	= 0.973
SOFA (Mean ± SD)			
No Growth	3.60 ± 0.8	2.40 ± 0.7	= 0.361
Candida albicans	4.01 ± 0.1	3.50 ± 1.3	= 0.809
E. Coli	4.40 ± 0.4	5.33 ± 0.3	= 0.080
Klebsiella pneumoniae	7.01 ± 0.3	5.40 ± 0.8	= 0.100
Pseudomonas aeruginosa	6.33 ± 0.7	5.01 ± 0.4	= 0.259
Staph. auras	4.05 ± 0.5	6.36 ± 0.5	**= 0.002**
Streptococcus pneumoniae	4.17 ± 0.4	5.01 ± 0.4	= 0.474

Table (5) disclosed the correlates of growth among the studied cohort where, the positive culture group had a considerable increase in the mean age, number of smokers, comorbid disorders [hypertension and kidney diseases], laboratory investigations [WBCs, HGB and platelets, liver functions, Urea, and D-dimer], all pneumonia scores, need for mechanical ventilation and length of hospital stay ($p < 0.05$).

Table 5: Correlates of Growth among the study population

	No-Growth (n = 15)	Growth (n = 85)	P-value
Demographic data			
Age/years	46.80 ± 12.1	62.66 ± 11.2	< 0.001*
Sex (Female/Male)	6/9	37/48	0.799**
Number of smokers	2 (13.3%)	18 (21.2%)	0.021**
Comorbidity			
DM	4 (26.7%)	25 (29.4%)	0.829**
HTN	4 (26.7%)	48 (56.5%)	**0.033****
Hepatic	1 (6.7%)	10 (11.8%)	0.561**
Renal	0 (0%)	13 (15.3%)	**0.047*****
Cardiac	2 (13.3%)	10 (11.8%)	0.863***
Chest	3 (20%)	37 (31.8%)	0.157**
Pneumonia Scores			
CURB-65	1.47 ± 0.3	2.55 ± 0.1	**0.002****
PSI	80.44 ± 8.3	109.60 ± 4.2	**0.005****
SOFA	2.80 ± 0.8	5.01 ± 0.2	**0.003****
LHS (Day)	8.27 ± 1.9	10.45 ± 1.8	**0.009****
Need for ICU	10 (66.7%)	63 (74.1%)	0.541*
MV	3 (20%)	42 (49.4%)	**0.036***
COVID-19 Positive	10 (66.7%)	42 (49.4%)	0.217*
CBC			
HGB	12.31 ± 1.9	10.82 ± 2.1	**0.015****
WBCs	11.79 ± 4.2	13.98 ± 1.8	0.179**
Platelet	257.47 ± 19.1	224.49 ± 14.1	**0.042****
Liver & Kidney Function			
ALT	30.53 ± 6.5	46.09 ± 13.1	**0.032****
AST	29.33 ± 6.3	73.88 ± 10.8	**0.044****
Total Bilirubin	0.94 ± 0.2	1.02 ± 0.3	0.277**
Albumin	2.89 ± 0.4	3.96 ± 0.6	**0.062****
B. Urea	50.60 ± 7.7	89.80 ± 9.6	**0.043****
S. Creatinine	1.13 ± 0.4	2.06 ± 0.3	**0.062****
Inflammatory markers			
CRP	31.01 ± 1.7	34.55 ± 1.2	0.108**
ESR	28.53 ± 3.7	29.56 ± 2.6	0.579**
D-Dimer	630.83 ± 46.9	1285.36 ± 83.1	**0.011****
Ferritin	519.25 ± 45.2	666.26 ± 52.1	0.210**

HGB: haemoglobin ESR: erythrocyte sedimentation rate WBC: white blood cells
ALT: alanine transaminase CRP: C reactive protein AST: aspartate transaminase

DISCUSSION

It is strongly believed that co-infections play an important role during COVID-19, We aimed in this study to elucidate the frequency rate of bacterial and fungal contagions among hospitalized COVID-19 patients and compare it with non-COVID-19 community acquired pneumonia (CAP) cases. We found that there was a remarkable increase in PSI, inflammatory markers including (ESR, CRP, D-dimer and ferritin) among COVID-19 cases. Moreover, concerning the outcome data, there was a considerable increase in length of hospital stay (LHS), need for either oxygen support or mechanical ventilation among COVID-19 group [$p < 0.05$]. In harmony, Sheikh et al. [10] reported that in COPD patients with CAP, the existence

of COVID-19 infection is associated with greater ICU admission rates, higher necessity for mechanical ventilation, higher length of hospital stays, and seven-folds increase in hospital decease. However, Di Mitri et al. [11] reported that in areas or periods with a low frequency of COVID-19 contagion, the outcomes of COVID pneumonia can be indistinguishable in severity from the non-COVID pneumonia.

In our study, we found that COVID-19 cases exhibited high rates of bacterial and fungal co-infection in sputum (80.8%), Bazaid et al. [12] revealed a similar result where the rate (74%). In contrast, Hughs et al. [13] reported a lower frequency of bacterial co-infection in earlier COVID-19 hospital exhibition, with no signs of con-comitant fungal contagion, at least in the initial phase of COVID-19. Moreover, a previous study displayed a 23% incidence rate of bacterial co-infections. [11] Our result was also higher than other reports. [14,15] This discrepancy in the results was attributed to variation in the characterization criteria, the heterogeneity of cases involved, and the analytical approaches used [16].

The phenomenon of secondary bacterial infection often occurs in COVID-19 cases, specifically in severe and critical cases.[17] The incidence rates of micro-organisms vary between studies. *Staph. aureus* was the most common isolated organism in this study which was consistent with previous results. [18,19] In contrast, Wijaya et al. [20] reported different pathogenic profiles as the commonest bacteria among their COVID-19 cases were [normal flora 42.16%, Klebsiella pneumonia 22.55%, no growth of bacteria 10.78%, *Acinetobacter baumannii 6.37%, Staph. aureus 5.39%, Pseudomonas aeruginosa 3.43%, Staphylococcus maltophilia, E. coli, Enterobacter cloacae 2.45% each]*. [20] Some reports have revealed that the commonest micro-organisms were *Mycoplasma pneumoniae and Pseudomonas aeruginosa* [21]. This discrepancy among the studies was attributed to the variances in the incidence and the trend of microbial contagions before COVID-19 outbreak and the variances in the efficiency of the infection prevention and control measures employed during the outbreak.

Anti-microbial resistance was one of the major communal health trials in the twenty first century.[22,23] We demonstrated antimicrobial resistance in about 11.6% of bacterial isolates among COVID-19 group which was ominously higher than the non-COVID group (2.1%); this had been predicted in a previous review. [24] Moreover, Bardi et al. [25] detected a high frequency of multi-drug resistant bacteria (30%) but also it has been a topic of considerable debate [26,27]. Upsettingly, there is also evidence suggesting that this empirical inadequate broad spectrum antibiotic use could be associated with higher fatality, at least in the case of sepsis. [28]

Staphylococcus aureus growth cultures showed a significant increase in all pneumonic scores (CURB-65, PSI and SOFA) among COVID-19 positive group compared with the other group, a result consistent with a previous report. [29]

Our study, comparable to Jara et al. [30] revealed that the hazard of ICU admission for cases vaccinated against COVID-19 was considerably lower than unvaccinated cases (16.7% versus 85.4% correspondingly) denoting that being un-vaccinated resulted in almost 5-times higher hazard of being admitted to an ICU.

In the current study, when we compared cases with positive and negative sputum cultures, the growth group had considerable increase in all pneumonic scores, WBCs, liver functions, urea & D-dimer. Moreover, the outcome measures were considerably increased among the positive growth group with subsequent higher mortality rate, in harmony, Meawed et al. [31] confirmed a similar result.

In conclusion, our study results were consistent with previous studies displaying that bacterial co-infections or 2ry infections among COVID-19 cases seem to be allied with both higher severity of COVID-19 as well as worse outcomes. [32]

However, this study had several limitations including: First: No distinction was made between secondary bacterial infection and co-infection. Second: The survival status of the cases as a result of their medical course was not comprised in this study. Third: the resistance genes of the isolated bacterial mediators were not considered. Fourth: the varying treatment protocol and admission policy during the study period. Fifth: the follow up laboratory statistics and linear fluctuations in alliance with the medical condition of the patients were not appraised and the other bio-markers such as IL-6 level, LDH, CK-MB, troponin, and procalcitonin were not evaluated. Lastly: it is a single center study.

CONCLUSION

Critically ill COVID-19 patients exhibited a higher rate of bacterial co-infection detected in sputum (80.8%), in order of frequency *[Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli, Candida albicans, Streptococcus pneumoniae and lastly Pseudomonas aeruginosa]*. PSI, LHS, necessity for oxygen, mechanical ventilation and mortality were higher in COVID-19 CAP compared with non-COVID-19 CAP.

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