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Bacterial Co-infection among hospitalized patients with COVID-19 in Kirkuk city-Iraq

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ABSTRACT

Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (Covid-19), was first reported in China in late 2019 from a zoonotic source. The majority of Covid-19 cases either are asymptomatic or result in only mild disease. However, in a substantial percentage of patients, a respiratory illness requiring hospital care develops, and such infections can progress to critical illness with hypoxemic respiratory failure requiring prolonged ventilatory support. The prevalence, incidence, and characteristics of bacterial infection in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are not well understood and have been raised as a critical knowledge gap.

Aim of the study: To investigate the incidence of bacterial co-infection of (50) COVID-19 confirmed hospitalized patient with the exploration of demographic, laboratory and clinical features, descriptive observational study in AL-SHIFA 14 hospital in Kirkuk city, Iraq.

Methods: All 50 patients with a laboratory-confirmed critical (25 case) and severe (25 cases) COVID-19 were admitted to the wards and RCU in Al-Shiffa-14 Hospital from April 2021 to end of May 2021. Throat swabs were obtained from patients in RCU and care wards. The bacteria isolations diagnosis was confirmed using Vitek 2 analyser system in Azadi teaching hospital. In addition, the haematological and biochemical tests were performed for all the 50 patients at the Al-Shiffa-14 Hospital laboratory.

Results: Older people and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop severe and critical illnesses. Strong correlation of lymphopenia, increased CRP, D-Dimer, ferritin level and poor clinical outcome with the severity of the disease. Bacterial co-infection was identified, the high rate of bacterial co-infection registered in this study (94%) matches with other studies investigating the bacterial co-infection in COVID-19 sever infected patients who admitted in hospital wards and RCU units with the recording of *Staph. Haemolyticus* as the most common bacteria isolated from the critical and severe COVID-19 infected patients throat samples.

Conclusion: Secondary bacterial infection is common with COVID-19 patients and leads to significant morbidity and mortality, especially in the critical group patients.
Key words: COVID-19, risk factors, Secondary bacterial infection.

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Introduction

Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (Covid-19), was first reported in China in late 2019 from a zoonotic source. [(1).] Most of Covid-19 cases either are asymptomatic or result in only mild disease. However, intrinsic percentage of patients, a respiratory illness requiring hospital care develops, and such infections can progress to critical illness with hypoxemic respiratory failure requiring prolonged ventilatory support [(2).] A report from the Chinese Center for Disease Control and Prevention included approximately 44,500 confirmed infections with an estimation of disease severity [[3].]

- Mild disease (no or mild pneumonia) was registered in 81 percent.
- Severe disease (eg, with hypoxia, dyspnea, or >50 percent lung involvement on imaging within 24 to 48 hours) was reported in 14 percent.
- Critical disease (eg, with respiratory failure, shock, or multiorgan dysfunction) was registered in 5 percent.
- The overall case-fatality rate was 2.3 percent; no deaths were reported among non-critical cases.

The National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel suggests hospitalization for patients with any of the following: an oxygen saturation of <94 percent on room air, respiratory rate of >30 breaths/minute, PaO2/FiO2 <300 mmHg, or lung infiltrates >50 percent [4] While most patients with this presentation will require inpatient care, there are no fixed criteria for inpatient hospital admission with COVID-19; criteria vary by country, region, and availability of COVID-19 specific therapy.

The United States Centers for Disease Control and Prevention (CDC) has created a list of certain comorbidities that have been associated with severe disease (defined as infection resulting in hospitalization, admission to the intensive care unit [ICU], mechanical ventilation, intubation or death) [5]. Older people and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop severe and critical illnesses.

Bacterial co-pathogens are commonly identified in viral respiratory tract infections such as influenza and are an important reason of morbidity and mortality, necessitating timely diagnosis and antibacterial therapy [6,7). Bacterial co-infection in patients with severe influenza has been reported to be as high as 20-30% [(8)] and is associated with greater severity of illness, greater use of healthcare resources, and increased risk of death [(9).]

The incidence, prevalence, and characteristics of bacterial infection in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are not well understood and have been raised as an important knowledge gap [(10).] Understanding the percentage of COVID-19 patients with acute respiratory bacterial co-infection is important for treating patients with COVID-19 and to help ensure reliable use of antibiotics and to minimize negative consequences of antibiotics overuse [(11).] In addition, this knowledge could have a significant effect in refining empirical antibiotic management guidelines for patients with COVID-19.

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Aim of study

To investigate the incidence of bacterial co-infection of [50] COVID-19 confirmed hospitalized patient with exploration of demographic, laboratory and clinical features, descriptive observational study in AL-SHIFA 14 hospital in Kirkuk city, Iraq.

Methods

All 50 patients with a laboratory-confirmed critical (25 case) and severe (25 cases) COVID-19 were admitted to the wards and RCU in Al-Shiffa-14 Hospital from April2021 to end of May 2021. Throat swabs were obtained during the first 72 hours of hospital admission. Throat swabs are directly cultured into (Blood, MacConkey, and Chocolate agar) which were prepared at the Central public laboratory in Kirkuk city. The bacteria isolations diagnosis was confirmed using Vitek 2 analyzer system in Azadi teaching hospital. In addition, the hematological and biochemical tests were performed for all the 50 patients at the Al-Shiffa-14 Hospital laboratory.

Results

A total of 50 patients with a PCR confirmed covid-19 were enrolled in this study. Male to Female ratio was 1:1 and divided in to two groups: critical (25 patients) and severe (25 patients) Based on the Chinese CDC clinical society for SARS-Cov-2 infection. Median age of sever and critical patients were 50-60 and 50-80 respectively.

Among COVID-19 patients in critical group, 12 (24%) of them had hypertension, 11 (22%) had Diabetes Mellitus, 9 (18%) had cardiovascular disease and 11 (22%) had chronic lung disease. While in severe cases group patients, 5 (10%) had hypertension, 6 (12%) had Diabetes Mellitus, and 1(2%) had cardiovascular disease. All 25 patients of critical groups were on antibiotics while only 15 (30%) were on severe group. The length of hospitalization for sever group were between 3-7 days while it was more than 7 days for critical group.

All CT scan images were analyzed and reviewed by a specialist radiologist. The severity score was calculated based on lung involvement percentage for each patient (12). From critical group patients 10(20 %) and 8 (16%) were with score 4 and score 5 respectively, while most of the patients 4 (%) and 14 (%)in sever group were in score 2 and 3 respectively.

Clinical outcome of patients with covid-19 in both critical and sever group demonstrated significant cure rate 19 (38%) in sever group in comparison to critical group, while 7 (14) of patients died in critical group in comparison to 1 (2%) in sever group.

In table 2 high WBC count were registered in the most of the cases and seen in 48 (96%) of the patients, and the study showed strong correlation of lymphopenia (low lymphocyte count less than 0.5%) with the severity of the disease were 36 (72%) of patients reported with lymphocytopenia, and only 10 (20%) of patients in severe group had normal lymphocyte count (1-1.5%).

Strong correlation was seen between increased CRP, D-Dimer and ferritin level and the severity of infection, CRP level ≥ 10 mg/ml found in 13 (26%) and CRP ≥30 seenin 36 (72%). D-Dimer levels ≥ 500 ng/ml were found in 30 (60%) patients. Serum ferritin ≥250 U/L seen in 35 (70%) patients as summarized in table 3.

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Regarding LDH, there was no significant increasing level when 27 (54%) of patients founded with level ≥ 440 U/L. In the present study S.GPT, S.GOT and S. alkaline phosphatase level were increased ≥ 40 U/L (in S.GPT, S.GOT) and (≥ 240 U/L for S. Alkaline Phosphatase) in only 25(50%), 25(50%) and 16 (32%) of patients respectively.

In this study we established that COVID-19 can cause co-infection with bacteria. Bacterial culture identified positive in 47 (94%) of patients and ranged between pathogenic, opportunistic growth which might contribute to the severity of the infection. The most common bacteria reported was *Staph. Haemolyticus* in 13 (26%); (10) in the critical and (3)in severe cases. *Str. Viridans* reported in 9 (18%) patients (6 in critical and 3 in severe cases). *Str. Mitis* registered in 6 patient culture 3 for each of critical and severe cases. Moraxella spp. Reported in 6 patients culture (2 in critical and 4 in severe cases) while *Granuli adiacens* identified in 5 patients culture (4 in critical and 1 in severe group patients. *Entero raffinosus* reported in 3 patients (2 critical and 1 severe), *Rothia muciaginosa* and *str. Sanguinis* in 2patients from each group and *Leuco lactis* reported in 1 patient from critical group.

Table 1: Table 1: Characteristics of Covid-19 patients

Parameter	Critical no (%)	Severe no (%)
Ages (yrs)		
25-30	0	1 (4%)
40-50	3 (12%)	6 (24%)
50-60	8 (32%)	2 (8%)
60-70	16 (64%)	1 (4%)
> 70	13 (52%)	0
Gender		
Male	14	11
Female	15	10
Comorbidities		
Hypertension	12	5
Diabetes mellitus	11	6
Cardiovascular disease	9	1
Tumors	1	0
Chronic lung disease	11	1
Antibiotic use	25	15
Hospital admission (days)		
1-3 days	0	5
3-7 days	20	
> 7 days	25	
Chest radiology (lung involvement)		
Score 1: 5%	0	0
Score 2: 5-25%	2 (8%)	4 (1%)
Score 3: 26-50%	5 (20%)	14 (56%)
Score 4: 51-75%	10 (40%)	7 (28%)
Score 5: >75	8 (32%)	0
Outcome		
Death	7 (28%)	1 (4%)
Cure	6 (24%)	19 (76%)
Discharge on responsibility or sent to other hospitals	12 (48%)	5 (20%)

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Table 2- A: Total WBC (3.5 - 10000 x 10^9/l)

Count	Total	%
Low	0	0
Normal	2	4
High	48	96

Table 2: B lymphocyte count (0.9-5 x10^9/l)

Count	Total	%
Low 0.5-0.9	36	72
Normal 0.9-1.5	11	22
High > 1.5	3	6

Table 3: Laboratory Finding - Biochemical parameters

Parameters	Results
CRP	
Low <10	1
High (10-30)	13
Extremely high > 30	36
D-Dimer	
Low 1-500	20
High 500-1000	25
Extremely high >1000	5
S. Ferritin (20-250 Ug/L)	
Low 20-250	15
High 250-500	25
Extremely high >500	10
S.LDH (225-450 U/L)	
Low 225-440	24
High 440-640	15
Extremely high >640	12
S.GPT (UP TO 40 U/L)	
(1- 40)	25
40-60	10
>60	15
S.GOT (UP TO 40 U/L)	
(1- 40)	25
40-60	15
>60	10
S.Alkaline Phosphatase (up to 270 u/L)	
1-270	34
270-370	13
>370	3

Table 4: Microbial isolates from critical and severe covid-19cases

Culture results	Total	%
Staph haemolyticus	13	26%
Str. Viridans	9	18%

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str. Mitis	6	12%
Moraxella spp.	6	12%
Granuli adiacens	5	10%
Entero raffinosus	3	6%
Rothia muciaginosa	2	4%
Leuco lactis	1	2%
str. Sanguinis	2	4%
	47	94%

Discussion

The outbreak of COVID-19 is considered a new public health concern threatening the world. The studies showed the animal origin of COVID-19 to infect humans[22]. Recently, more attention has been paid to hospital-acquired infection, including pathogenic and opportunistic bacterial infection, which might be attributed to long-term patient hospitalization and the high workload on healthcare workers. In our study mean age of the critical group patients were (50-80yrs) while it was (50-60yrs) in severe group patients. Additionally, most of the patients in this study, especially in critical group, had one or more chronic underlying diseases, mainly hypertension, diabetes mellites, and cardio vascular disease matching the same results recorded in CDC guidance. [13] The age-dependent defects in T-cell and B-cell function and the excess production of type 2 cytokines could lead to a deficiency in control of viral replicationprolonged proinflammatory responses, potentially leading to poor outcomes. [14]

Infection with the SARS-CoV-19 virus may cause catastrophic infection in any patient even among those without any risk factor. The reason of this finding is unclear but are most likely related to inequalities in the social determinants of health (e.g access to health care, economic stability, living environment, community experience, education) [15][16]

In current study major laboratory marker performed at hospital revealed significant lymphopenia and leukocytosis in most of the patients in severe and critical groups and these matching other studies result [17]. Levels of D-dimer, C reactive protein and lactate dehydrogenase where clearly elevated in both study groups similar to (Fei zhou et.al) study. [14]. This result suggested that SARS-CoV-19 act on lymphocytes, especially T-lymphocytes, spread through respiratory mucosa and infect other cells pro-inflammatory and inflammatory mediators increased induce cytokine storm, leading to damage of T-lymphocytes which is a vital factor that plays a role in the worsening of the patient clinical condition. [14].

According to the scoring system used to assess the lung changes and the involvement by the COVID-19 (CT severity score index); 36% of critical group patients were with scores 4 and 5, where 36% of severe group patients were with score 2 and 3. Consequently, the study showed a strong correlation of increment of CT chest score with disease severity short term prognosis matching to most patients in critical and severe group were on single or combination antibiotic therapy which covered common and some atypical pathogen. [12] Empirical treatment may indicate with COVID-19 disease if there is clinical suspicion (new fever after regression with new consultation in chest image) based on the data from previous studies on the other types of viral pneumonia, particularly influenza. [18] Although the infectious disease society of America guidelines did not mention this issue [19].

In the current study, seven patient (14%) from critical group died ;other patients transferred to other hospital or discharged on their responsibility.one patient died in sever group and others discharged to home in stable clinical condition .The study of(Fei zhou et.al)[14]support our

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finding which record that half of non-survivors experienced a secondary infection, and ventilator-associated pneumonia occurred in ten (31%) of 32 patients requiring invasive mechanical ventilation. The frequency of complications was higher in non-survivors than survivors.

Most bacterial co-infection in patients with viral lower respiratory tract infection (specially influenza virus infection) seem to be acquired in the community specially in patients who undergo mechanical ventilation [20,21]. In this study the bacterial co-infection was identified, with the recording of *Staph. Haemolyticus* as the most common bacteria isolated from the critical and severe COVID-19 infected patients throat samples (13 patients) followed by *Str.Viridans* (9 patients), *Str. mitis* and Moraxella spp. (6 cases each), Granuli adiacens (5 patients), *Entero raffinosus* (3 patients), *Rothia muciaginosa* and *str. Sanguinis* (2 patients each) and *Leuco lactis* isolated from 1 patient sample. The high rate of bacterial co-infection registered in this study (94%) is matching with other studies investigated the bacterial co-infection in COVID-19 sever infected patients who admitted in hospital wards and RCU units [22], 100% bacterial co-infection of all patients involved in this study). Although this co-infection percentage consider high in comparison to another study held in the UK when only 27 out of 836 (3,2%) COVID-19 patients were confirmed to have bacterial co-infection at the first admission into the hospitals but this percentage raised into 6.1% throughout admission (0-5 days after admission) [23]. *Staph. Haemolyticus* gram positive cocci[24]. *Strp. Viridans*gram positive cocci can cause pyogenic infection. *Strpt. Mitis* are the predominant bacteria in human oropharynx causes wide spread of infections in human including bacteremia in patients with neutropenia, infective endocarditis and orbital cellulitis [26]. Moraxella spp. coccobacilli colonize the upper respiratory tract, the pathogenicity of this bacteria associated with weaken immune system, it also can cause pneumonia or bronchitis [27].

Granuli adiacens are gram positive cocci difficult to identify normally inhibit the oral cavity and mucosal surface and rarely causes disease. *G. adiacens* can cause endocarditis or bacteraemia[28]. *Entero raffinosus* cause rare infection in human with few cases reported with endocarditis in elderly patients, it is also reported to cause haematoma infection in immunosuppressed old patients which approves a potential pathogenic role of this bacteria [29]. *Rothia mucilaginosa* isdifficult to identify, causes rare lower respiratory tract infection and usually occur in immunocompromised patients[30]. *Leuconostoc lactis* gram positive cocci associated with multiple risk factor, it is presence in human associate with the use of central venous catheter it is also identified as a part of polymicrobial infection. Bacteraemia associated with *L lactis* reported in immunodeficient/ immunocompromised patients and patients with endocarditis associated with intravenous drug administration [31]. *Strpt. Sanguinis* gram positive cocci can cause disseminated human infection such as infective endocarditis[25]. The reporting of *Strpt. Sanguinis,* Rothia muciaginosa and Leuco lactis in this research consider novel finding in samples collected from COVID-19 patients in Kirkuk city and in Iraq.

Conclusion

Secondary bacterial infection is common with COVID-19 patients and lead to significant morbidity and mortality, especially in the critical group patients.

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