Prevalence of Multidrug Resistant Bloodstream Bacterial Infections among Hospitalized COVID-19 Egyptian Patients and Evaluation of Predictors for Case Severity

Amal Ali El-Koa [1], Asmaa Shaaban Sleem[2], Sally Mohammed El-Hefnawy[3] , Nehad Badr Elsaid [4] and Mai Mahmoud El Kalashy[1]

[1] Chest Department, Faculty of Medicine, Menoufia University,
[2]Medical microbiology and immunology Department, Faculty of Medicine, Menoufia University,
[3]Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Menoufia University
[4]Public Health and Community Medicine Department, Faculty of Medicine, Menoufia University

Abstract

Background and Aim: Coronaviruses are dangerous human and animal pathogens. It is characterized by fast spread, starting as an epidemic through China, followed by a worldwide pandemic. This study aimed to determine the prevalence of laboratory proven blood stream bacterial co-infection in hospitalized adult COVID-19 Egyptian patients and to recognize antibiotic susceptibilities of identified pathogens together with evaluation of predictors for case severity.**Methods:** The study involved 142 adult COVID-19 Egyptian patients. The diagnosis was confirmed by quantitative or real time polymerase chain reaction (PCR) on nasopharyngeal swabs. For each case two blood cultures were taken after $\geq$ 3 days of hospital admission. **Results:**About 30% of positive blood cultures showed Gram positive staphylococci while Gram negative bacilli were detected by 70% (*Klebsiella* ;30%, *E.coli* ; 20% and *Pseudomonas* ; 20%). Variable resistance patterns were noticed in all bacterial isolates.Blood stream infections (BSI) were identified in 40 cases (28%). About 70% of them were males. The mean age significantly associated with BSI was 63.5±18.2 years old. Hypertension and diabetes had high significant association with BSI by 55% and 60% respectively. Significantly 68% of mechanically ventilated COVID cases were BSI complicated. Death was the fate of 57.5% of BSI positive COVID cases significantly with low O_2 saturation and prolonged hospital stay (21.6±3.52 days). **Conclusion:** All blood stream bacterial pathogens were multidrug resistant. Infections were detected among old aged, diabetic, hypertensive and mechanically ventilated patients. Prescribing antibiotics in COVID patients should be guided by careful clinical and laboratory assessment to improve their management and outcomes.

Corresponding author: Sally Mohammed El-Hefnawy, E-mail: doctor_sally@rocketmail.com. SALI.ALhefnawy@med.menofia.edu.eg.
ORCID: https://orcid.org/0000-0003-3090-0141

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by a positive-sense, single-stranded RNA (ssRNA) transforming virus. It is genetically related to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Corona viruses are common causes of severe community-acquired pneumonia *(1)*. COVID-19 is markedly infectious disease, with every case seeding more than two secondary cases. By the end of June 2021 the number of people identified with COVID-19 internationally crossed the 185 million with more than 4 million deaths since the beginning of the pandemic *(2)*. Egypt is one of the five countries recording the highest number of cases in Africa. *(3)*

Clinical pictures of COVID-19 are not specific. Diagnosis requires sufficient clinical, laboratory and radiological assessment of suspected cases. Treatment protocol according to the WHO includes home isolation for mild to moderate stable cases. Critical (respiratory failure, shock, multiple organ dysfunction or failure) and severe (dyspnoea, respiratory rate ≥ 30 breaths per min, oxygen saturation $\leq 92\%$) cases need to be hospitalized. *(2)*

Mortality in COVID-19 cases is usually related to older age, comorbidities as (hypertension, diabetes mellitus, cardiovascular disease, chronic lung disease and cancer), higher viral load, worse respiratory failure, higher d-dimer and C-reactive protein levels, lower WBCS count and secondary infections *(4).*

Bloodstream infections (BSIs) represent one of the commonest and life-threatening complications in patients with severe viral infections. The absence of an effective anti-viral agent against SARS-CoV2 combined with challenges in distinguishing secondary bacterial co-infection from severe COVID-19 infection alone, has fostered the widespread usage of empirical antibiotics in the immediate management of those patients that encourage multi drug-resistant secondary bacterial infections *(5)*. We concentrated here on BSIs because these represent sure infection events, whereas difference between colonization and infection is more difficult with other specimen types *(6)*. This study aimed to determine the prevalence of laboratory proven blood stream bacterial co-infection in adult COVID-19 Egyptian patients and to describe the demographic and laboratory characteristics of these patients and recognize antibiotic susceptibilities of identified pathogens, also to detect the impact of BSIs on the patient outcome together with evaluation of predictors for case severity.

Patients and methods

The study involved 142 adult COVID-19 patients admitted to Menoufia fever hospital, Egypt from January to April 2021. The patients were diagnosed by real time PCR on nasopharyngeal swabs. For each case two blood cultures were taken after ≥ 3 days of admission. All patients had received empirical antibiotics in the form of a second- or third-generation cephalosporin plus azithromycin. Mortality was measured from the date of admission till the date of death. Data were assembled from hospital records including: demographics (age, sex, presence or absence of co-morbidity), and if need to be admitted in ICU or in ward. Laboratory investigations were done in the form of CBC, D

dimer, serum ferritin and CRP. The patients were categorized according to the previous CT presentations using a CORAD radiologic scoring system of the method previously reported by **Prokop et al** *(7)*.

Ethical Approval

The studied population was enrolled after obtaining written consent and approval from the university research ethics committee of the Menoufia Faculty of Medicine.

Specimen Collection and RNA isolation

Nasopharyngeal specimens were collected using sterile synthetic fiber swabs with thin plastic. Swabs were placed into the transport tube provided and stored at -80°C till PCR analysis. RNA was extracted from samples using Qiagen QIAamp Viral RNA Mini Kit, USA according to manufacturer instructions. The concentrations of RNA were assessed using the NanoDrop™ 2000 system (Thermo Scientific, USA).

cDNA synthesis and PCR amplification in one step method

The RNA extracts were kept at -80°C until the reverse transcription step. After extraction, RNA was reverse transcribed to cDNA and amplified in a Real-time PCR instrument using one step method. The kit includes primers/probes that are specific for the ORF1ab gene (probe labeled with FAM) and N gene (probe labeled with VIC) of SARS-CoV-2. In addition, the kit also contains primers and a probe (labeled with CY5) for the human RNase P gene as an endogenous internal control for specimen integrity, nucleic acid isolation, amplification and detection. The reactions were performed on ice in a 25µl total volume as follows: we added 7.5 µl of RT-PCR Buffer (Tris Hydroxy Methyl Aminomethan,

Potassium chloride, Magnesium chloride, Nucleotides mix), 5 µl of RT-PCR Enzyme Mix (Reverse transcriptase, RNase Inhibitor, Taq DNA polymerase) , 4.0 µL of reaction mix (Primers and probes of SARS-CoV-2 and RNase P), 3.5 µLof RNase-free water and 5 µl of RNA extract to each PCR well and 5 µL of extract from the positive control to one reaction well. The following primers were used: RdRP gene forward primer GTGARATGGTCATGTGTGGCGG, reverse CARATGTTAAASACACTATTAGCATA, E gene forward primer ACAGGTACGTTAATAGTTAATAGCGT, reverse ATATTGCAGCAGTACGCACACA, N gene forward primer CACATTGGCACCCGCAATC, reverse GAGGAACGAGAAGAGGCTTG. The thermal cycling conditions were modified as follows: 50°C, 10 min for one cycle at (hold stage), 97°C for 1 min for one cycle at (second hold stage). 45 cycle each one composed of: 97°C for 5s initial PCR stage, 58°C for 30s , 72°C for 30s. Data were analyzed by the software accompanying the ABI 7500 real-time PCR device, V.2.0.1.

Microbiological test and Blood Culture

Blood samples were taken under complete aseptic conditions from COVID patients hospitalized ≥ 3 days. Samples were immediately transferred to the bacteriology laboratory to be aerobically cultivated at 35-37°C (Becton Dickinson blood cultures instrument systems) for a maximum of 5 days. All clinically significant bacterial isolates were recognized by standard bacteriological methods (all contaminants were excluded). Antimicrobial susceptibility testing was performed and assessed by the standard disc diffusion methods. Also Multi-drug resistant (MDR) strains were

identified. All methods were done according to Clinical & Laboratory Standards Institute (CLSI) guidelines **(8)**.

Detection of methicillin-resistant staphylococci was done by cefoxitin disk diffusion method (30μg). Screening for ESβLs production was performed by disk diffusion test using ceftazidime (30μg), cefotaxime (30μg), ceftriaxone (30μg) and aztreonam (30μg). Suspected ESβL producing Gram-negative bacilli were confirmed by clavulinate combined disk test. Screening for carbapenemase production was performed by disk diffusion test. Reduced susceptibility to one or more carbapenems (meropenem and etrapenem; 10μg) plus one or more of the indicator cephalosporins (cefotaxime, ceftriaxone, ceftazidime and cefoperazone) indicate carbapenemase production. Suspected carbapenemase producers were confirmed by modified carbapenem inactivation method (mCIM)**(8)**. **(Figure 1 a&b).**

Statistical analysis

Data were collected, tabulated, statistically analyzed using an IBM personal computer with Statistical Package of Social Science (SPSS) version 19 (SPSS, Inc, Chicago, Illinois, USA) quantitative data were displayed in the form of mean, standard deviation (SD), range, and qualitative data were presented in the form of number and percent. Chi-square test (χ^2) and Fisher exact test was used to study association between qualitative variables, Mann-Whitney test was used for comparison between quantitative variables. Univariate and multivariate regression analysis models were used to detect independent predictors for ICU admission. Significance level was at p value < 0.05.
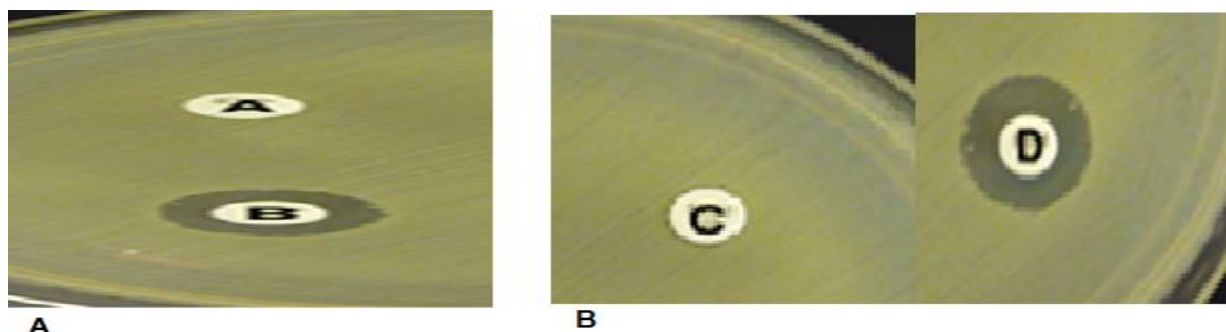

Figure (1): a- Detection of ESBL production using the clavulinate combined disc method) CLSI 2021). The A disc is ceftazidime (30 ug) and the B disc is ceftazidime/clavulinic acid (30/10 ug). There was an expansion of the bacterial growth inhibition zones around B disc > 5mm. **b-** Detection of carbapenemase production using the modified carbapenem inactivation method (mCIM) (CLSI 2021). Meropenem disc (10ug) was embedded in emulsified suspension of tested strain for carbapenemase production. Then this disc was placed on plate previously inoculated with carbapenem susceptible control strain. Tested carbapenemase producers were detected by growth inhibition zones of 6-15 mm around C & D meropenem discs.

Results

This study involved 142 COVID 19 PCR confirmed cases, their ages were ranged between (27 to 89 years), 82 of them (57.7%) was male and 68 (42.3%) was female gender. The most common comorbidities were diabetes mellitus (39.4%) and hypertension (38%). As regards the clinical findings, fever (93%), dyspnea (90.1%) and cough (84.5%) were the most common presenting symptoms while GIT symptoms (e.g., nausea, vomiting, abdominal pain and diarrhea) represented (39.4 %) (**Table I**).

The CT examination of the studied cases showed 2 cases (1.4%) with CORAD I and another 2 cases (1.4%) with CORAD II, 24 cases (16.9%) with CORAD III, 70 cases (49.3%) with CORAD

IV and 44 cases (31%) with CORAD V. The mean oxygen saturation among cases was 88.2±7.35. The cases that needed mechanical ventilation were 50 cases (35.2%). The passed away cases were 28 (19.7%) cases. The mean hospital stay days were 8.86 ± 8.30 days (**Table II**).

Table **III** shows highly significant differences between ventilated and non-ventilated patients regarding age, dyspnea and cyanosis at their initial presentation and diabetes as a comorbidity. In contrast there were non-significant differences between the two groups regarding sex, other comorbidities and fever, cough and GIT symptoms as presenting symptoms.

Also, there were highly significant differences between ventilated and non-ventilated patients regarding CT scoring, mean oxygen saturation on presentation and fate of the disease.

There was a positive correlation between age and hospital stay and a negative correlation between age and O_2 saturation (**Table IV**).

Blood stream infections (BSI) were detected in 40/142 cases (28%). About 70% were males. The mean age of 63.5±18.2 years old was significantly associated with BSI. Hypertension and diabetes showed high significant association with BSI by 55% and 60% respectively.

Significantly 34\50 (68%) of mechanically ventilated cases had multi drug resistant BSI, while 6/92(6.5%) of non ventilated cases had BSI. Eighty five percent of COVID patients with positive BSI (34/40) were mechanically ventilated of whom 88.2% (30/34) were badly deteriorated. About 30% of (40) positive blood cultures showed Gram positive staphylococci while Gram negative bacilli were detected by 70% (*Klebsiella* spp;30%, *E.coli* ; 20% and *Pseudomonas* spp; 20%). Variable resistance patterns were detected in all bacterial isolates as shown in **figure (2 a&b).**

Twenty eight COVID 19 included patients in concurrent study died by 19.7% mortality rate. About 85.7% of non survivors were mechanically ventilated and needed ICU care. Death was the fate of 57.5% (23/40) of BSI positive COVID cases mainly with low O2 saturation and prolonged hospital stay (21.6±3.52 days) with high significance, while only 4.9% (5/102) of BSI negative COVID cases died with chronic diseases (**Table VI**).

High CT score, O2 desaturation and secondary bacterial blood stream infection are independent predictors for need for mechanical ventilation (P values 0.013, 0.023 and 0.001 respectively) as shown in **table VII**.

Table (I): Socio demographic and clinical data of the studied group (N=142):

Studied variables	No.	%
Age / years		
Mean ±SD	58.8±15.5	
Range	27 – 89	
Sex		
Male	82	57.7
Female	60	42.3
Co morbidities		
Hypertension	54	38.0
Diabetes mellitus	56	39.4
Cardic disease	8	5.60
Renal disease	2	1.40
Chronic lung disease	10	7.00
Neurological	7	4.90
Clinical presentation		
Fever	132	93.0
Cough	120	84.5
Dyspnea	128	90.1
Cyanosis	62	43.7
GIT symptoms	56	39.4

Table (II): Radiological finding, O2 saturation, O2 therapy, need for mechanical ventilation, fate and hospital stay/days among the studied group (N=142):

Studied variables	No.	%
CT		
CORAD I	2	1.40
CORAD II	2	1.40
CORAD III	24	16.9
CORAD IV	70	49.3
CORAD V	44	31.0
O2 saturation		
Mean ±SD	88.2±7.35	
Range	45 – 98	
Need for mechanical ventilation	50	35.2
Fate		
Died	28	19.7
Alive	114	80.3
Hospital stay /days		
Mean ±SD	8.86±8.30	
Range	3 – 28	

Table (III): Relation between need for mechanical ventilation and clinical, radiological parameters and outcome of the studied group (N=142):

Studied variables	need for mechanical ventilation				Test of sig.	P value
	Yes (N=50)		No (N=92)			
Age / years Mean ±SD	64.8±18.4		55.5±12.7		U 3.56	**0.001****
Sex					X^2	
Male	30	60.0	52	56.5	0.161	0.689
Female	20	40.0	40	43.5		
Co morbidities					X^2	
Hypertension						
Diabetes mellitus	22	44.0	32	34.8	1.16	0.280
Cardic disease	26	52.0	30	32.6	5.10	**0.024***
Renal disease	5	10.0	3	3.30	2.83	0.092
Chronic lung disease	0	0.00	2	2.20	1.10	0.293
Neurological	6	12.0	4	4.30	2.90	0.088
	4	8.00	3	3.30	1.55	0.212
Clinical presentation					X^2	
Fever	48	96.0	84	91.3	1.09	0.296
Cough	44	88.0	76	82.6	1.91	0.383
Dyspnea	50	100.0	78	84.8	8.44	**0.002****
Cyanosis	40	80.0	22	23.9	41.4	**0.001****
GIT symptoms	15	30.0	41	44.6	2.88	0.089
CT					X^2	**0.001****
CORAD I	0	0.00	2	2.20	31.4	
CORAD II	0	0.00	2	2.20		
CORAD III	4	8.00	20	21.7		
CORAD IV	16	32.0	54	58.7		
CORAD V	30	60.0	14	15.2		
O2 Saturation Mean ±SD	82.3±10.1		90.6±4.02		U 6.25	**0.001****
Fate					X^2	
Died	24	48.0	4	4.30	38.9	**0.001****
Alive	26	52.0	88	95.7		
Hospital stay /days Mean ±SD	16.1±8.86		4.91±4.44		U 7.14	**0.001****

*U: Mann Whitney test   #: Fisher exact test   *Significant   **High significant*

Table (IV): Correlation between age / years and O2 saturation and hospital stay among the studied group (N=142):

Studied variables	Age/ years	
	r	P value
O2 saturation	-0.224	**0.007****
Hospital stay	0.274	**0.001****

Table (V): Relation between need for need for mechanical ventilation and blood culture results of the studied group (N=142):

Studied variables	need for mechanical ventilation				Test of sig.	P value
	Yes (N=50)		No (N=92)			
Culture					X^2	
Positive	34	68.0	6	6.50		**0.001****
Negative	16	32.0	86	93.5	60.5	
Type of bacteria	N=34		N=6			
Staph aureus	8	23.5	4	66.7	X^2	
Klebsiella	12	35.3	0	0.00		0.062
Pseudomonas	6	17.6	2	33.3	7.32	
E-Coli	8	23.5	0	0.00		
Drug resistance	N=34		N=6			
Carbapenem resistance	6	17.6	0	0.00		
ESBL+Carbapenem resistance	6	17.6	0	0.00	X^2	
Extended spectrum B lactamase	8	23.5	0	0.00		0.125
					7.20	
Methicillin resistance	8	23.5	3	50.0		
MDR	6	17.6	3	50.0		

**High significant

Table (VI): Relation between blood stream infection and clinical parameter of the studied group (N=142):

Studied variables	Blood Culture				Test of sig.	P value
	Positive (N=40)		Negative (N=102)			
Age / years Mean ±SD	63.5±18.2		56.9±14.1		U 2.23	**0.026***
Sex					X^2 3.42	
Male	28	70.0	54	52.9		0.064
Female	12	30.0	48	47.1		
Co morbidities					X^2	
Hypertension	22	55.0	32	31.4	6.80	**0.009****
Diabetes mellitus	24	60.0	32	31.4	9.85	**0.002****
Cardic disease	3	7.50	5	4.90	0.360#	0.545
Renal disease	1	2.50	1	0.98	0.480#	0.489
Chronic lung disease	4	10.0	6	5.90	0.740#	0.388
Neurological	3	7.50	4	3.90	0.790#	0.375
Clinical presentation					X^2	
Fever	38	95.0	94	92.2	0.355#	0.725
Cough	32	80.0	88	86.3	0.860#	0.352
Dyspnea	38	95.0	90	88.2	1.47#	0.350
Cyanosis	30	75.0	32	31.4	22.2	**0.001****
GIT symptoms	16	32.0	40	43.5	1.79	0.181
Fate					X^2	
Died	23	57.5	5	4.90	50.2	**0.001****
Alive	17	42.5	97	95.1		
Hospital stay /days Mean ±SD	21.6±3.52		3.84±1.07		U 9.51	**0.001****
O2 Saturation Mean ±SD	82.3±10.1		90.6±4.02		U 6.25	**0.001****

U: Mann Whitney test   FE: Fisher exact test   *Significant   **High significant

Table (VII): Univariate and multivariate regression analysis for detection of predictors for need for mechanical ventilation

Studied variables	Univariate regression		P value	Multivariate regression		P value
	OR	95%CI		OR	95%CI	
Age / years	1.46	1.23 – 2.23	**0.001****	0.982	0.936 – 0.983	0.237
Diabetes mellitus	2.23	1.10 – 4.53	**0.025***	0.817	0.248 – 2.69	0.741
Dyspnea	1.03	1.04 – 1.06	0.998	-	-	-
Cyanosis	12.7	5.48 – 29.5	**0.001****	1.02	0.606 – 2.82	0.187
CT score	0.225	0.120 – 0.424	**0.001****	0.303	0.118 – 0.776	**0.013***
O2 Saturation	1.43	1.26 - 1.62	**0.001****	1.25	1.03 – 1.53	**0.023***
Bacterial infection	3.41	1.23 – 5.67	**0.001****	2.38	2.01 -4.63	**0.001****

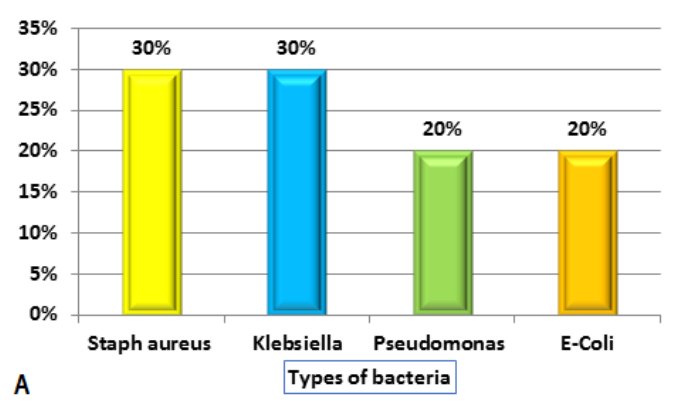**OR: Odds ratio CI: Confidence interval**
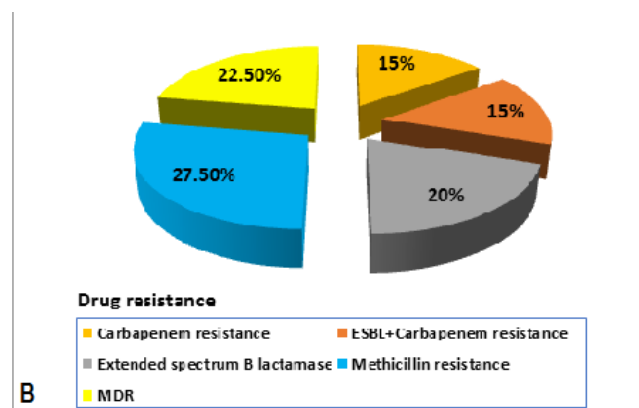
Figure (2): a- Distribution of types of bacteria among positive culture patients. **b-** Distribution of drug resistance among bacterial isolates.

Discussion

In this study, percentage of infected males was more than females, coincided with multiples studies as shown in met analysis study of **Li et al. (9)**. This could be clarified by the high expression of angiotensin-converting enzyme-2 (ACE 2; receptors for coronavirus) in male than female, immunological factors driven by sex hormone and X chromosome and also gender behaviour (lifestyle) **Bwire, (10).** Diabetes mellitus and hypertension were the commonest comorbidities reported that agreed with previous studies **Yang et al., (11)** & **Huang et al., (12)** & **Liu et al., (13)**. Our results are in line with previous studies shown in meta-analysis of **Li et al. (9) and Yang et al. , (11)**, we found that fever, dyspnoea and cough,

were the most common presenting symptoms, while GIT symptoms were less common.

In this current study, there was a highly significant difference between mechanically ventilated and non-ventilated patients regarding age together with positive correlation between age and hospital stay and a negative correlation between age and O_2 saturation. This was in line with multiple studies showed that older age was the strongest risk factor associated with hospitalization, mechanical ventilation, and mortality **(14) , (15) , (16).**

The defects in T-cell and B-cell function with age together with extra production of type 2 cytokines could lead to decrease in the control of viral replication and more extended pro-inflammatory

responses that lead to high infection rate & poor outcome **(17).** More than 50% of diabetic patients were admitted in ICU with a highly significant difference. Multiple studies showed that diabetes mellitus increases the risk of infection, together with the rates of intensive care unit (ICU) admission, respiratory support, and mortality **(18)**, **(15).**This could be explained by the advanced risk of severe pneumonia, the higher levels of enzymes linked to tissue injury, hysterical inflammatory response, increased level of inflammatory markers, and hypercoagulable state in diabetic compared to non-diabetic patients, suggesting that diabetes increases the susceptibility to an inflammatory storm that worsen COVID-19 **(19).**

Suleyman et al (20) found that dyspnea and hypoxia at presentation was associated with hospitalization and the need for ICU management. However, fever and headache at presentation were more in patients presented in the general practical unit than patients in the ICU on univariable analysis. Gastrointestinal symptoms were presenting symptoms in a substantial proportion of patients required hospitalization, similar to the data reported in the COVID-19–Associated Hospitalization Surveillance Network. Also, in the initial reports from Wuhan, China, during the pandemic; dyspnea was recorded in 54% of patients and was linked to complex end point of admission to an ICU, mechanical ventilation management, and death **(21)**. A similar prevalence of dyspnea was recorded in 21 critically ill patients in Washington State and in the COVID-19–Associated Hospitalization Surveillance Network database **(22), (23).**

Multiple studies were in line with this current study regarding chest CT finding. Guan et al **(24)**

found that the most common patterns on CT chest were ground-glass opacity (56.4%) and bilateral patchy shadowing (51.8%). The median duration of hospitalization was 12.0 days (mean 12.8**).**Also, the study of Ramadan et al **(25)** that reported that the frequency of bilateral peripheral multilobar ground-glass opacities was the characteristic CT patterns in COVID-19 infection as reported by systematic review done by **(26).**

Li et al , (27) found that consolidation was significantly more common in severe and critical patients in comparison with ordinary groups and the CT scores of the severe and critical patients were significantly higher than those of the ordinary patients ($P < 0.001$).This shows that the alveoli are completely full with inflammatory exudate which means that the virus diffuses into the respiratory epithelium, ending in necrotizing bronchitis, extensive alveolar damage and finally death**(28).**

The blood culture results and the characteristics of COVID-19 patients vary greatly between centers and geographic sites **(5)**. Among COVID-19 patients we detected an increased incidence of hospital-acquired BSIs, mostly due to multidrug-resistant pathogens. Our results match studies conducted by **Kokkoris et al.(29)** and **Giacobbe et al. (30)** studies with 40% and ≥25% respectively for hospital-acquired BSIs.

In current study Blood stream infections caused by Methicillin resistant *Staphylococci* (MRSA) were represented by 27.5% while MDR Gram negative bacilli recorded 72.5%. Other studies **(31)** had limited their analysis only to the first 48 h of hospital admission & reported lower BSI rate than ours. However our data are in agreement with **Wang et al.(32)** with 20% for MRSA and 80% for MDR Gram negative bacilli. Also **Bogossian et**

al.(33) reported BSI rates with 10% for MRSA, 77% for MDR Gram negative bacilli (29% for ESBL and 48% for MBL producers). Old age, Hypertension, Diabetes, Assisted ventilation with prolonged hospital stay were significant risk factors for BSI in COVID 19 patients as shown in different researches **(3, 6 , 32).**

The COVID 19 infection & mortality rates are multifactorial issues that reflect; COVID strain virulence and infectivity, demographic characters-associated infections and presenting co-morbidities of patients as well as availabilities of health care personnel-protocols and facilities. The rates vary significantly between different countries **(2).** All previously mentioned factors could explain morbidity & mortality rates reported in this study especially as more than 80% of ventilated cases with MDR blood stream infections died during hospitalization.

Conclusion

Egypt is among the countries that reported high rates of antimicrobial resistance. In our study all patients had taken empirical antibiotics. All blood stream bacterial pathogens were multidrug resistant. Infections were detected among old aged diabetic, hypertensive and mechanically ventilated patients. High CT score, decreased O2 saturation and presence of blood stream bacterial infection are independent predictors for need of mechanical ventilation among severe & critical COVID 19 cases. Prescribing antibiotics in COVID patients should be guided by careful clinical and laboratory assessment to improve their management and outcomes.

There was no funding for this study.

Conflict of interest

The authors declare that there are no conflicts of interest.

Ethical approval

Prior to sample collection, written approval agreed by the Human Rights Committee in Research at Menoufia University was obtained from all studied cases and controls.

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