

# Sepsis and septic shock in COVID-19: a scoping review of the research data

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## Research

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# Abstract

## Background

Sepsis is a major contributor to global mortality with an estimated 700,000 sepsis-related deaths annually. As sepsis is an acute complication of COVID-19, the ongoing pandemic can increase its global burden. Despite this, there is still limited research evidence on COVID-19 and sepsis. In this scoping review, we described the research data on sepsis and septic shock among patients with COVID-19.

## Methods

We adapted Arksey and O'Malley framework by reviewing relevant studies published on medRxiv, PubMed, and Google Scholar between January 01, 2020, and April 16, 2020, on sepsis and septic shock with the publication language restriction to English. The findings included the prevalence and outcome of COVID-19 patients with sepsis or septic shock, sepsis criteria, laboratory data, and the treatment given to COVID patients.

## Results

Of the 16 eligible articles included in this review, 13 (81.2%) were conducted in China. With the exception of one article, the research work for all the articles was conducted in adult patients. The articles were retrospective studies (12, 75%), case reports (3, 18.8%) and prospective observational studies (1, 6.2%). The estimated prevalence of sepsis and septic shock range from 6.8–100% and 4–28.9%, respectively. Serum lactate, platelets, C-reactive protein, white cell counts, and procalcitonin were elevated in 24.5%, 6.2%, 31.2%, 62.5%, 43.8% and 37.5% of the articles, respectively. Bacterial cultures were documented in 4 (25%) of the eligible articles. 12 (75%) and 11 (68.8%) articles documented the use of antivirals and antibiotics, respectively. Other antimicrobials used among COVID-19 patients were hydroxychloroquine (1, 6.3%), chloroquine (1, 6.3%), and unspecified antifungal drugs (2, 12.5%). Supportive therapies like oxygen therapy, mechanical ventilation, and fluid therapy were documented in 12 (75%), 13 (81.3%), and 2 (12.5%) articles, respectively. The highest and lowest mortality among the study participants is 29.8% (134) and 5.4% (12), respectively.

## Conclusion

There is a paucity of data in the literature on sepsis in COVID-19 despite its high burden among the COVID-19 patient population resulting in a high rate of antimicrobial use that is not backed by clearly documented microbiology laboratory support. Research is needed to understand the burden of sepsis in COVID-19.

# Background

In December 2019, China alerted the World Health Organization (WHO) of a cluster of several flu-like cases of unexplained aetiology in Wuhan City, Hubei Province of China(1). A series of investigations confirmed a previously unknown Coronavirus, now named Severe Acute Respiratory Syndrome 2 (SARS-COV 2) belonging to the *Betacoronavirus* genus as the aetiology of this unexplained community-acquired viral pneumonia on January 7, 2020(2). In February 2020, WHO assigned the name Coronavirus disease 2019 (COVID-19) to the illness caused by this virus. Subsequently, the epidemic caused by SARS-COV 2 spread within China. After establishing a further spread to other parts of the world, WHO declared COVID-19 as a global pandemic in February 2020(3).

Similar to what was previously described for the Severe Acute Respiratory Syndrome Coronavirus (SARS COV), droplets, personal contacts, and indirect transmission via contaminated surfaces are the most likely modes of human-to-human transmission of the SARS-COV 2(1)(4)(5). Aerosol transmission is not believed to be a major driver of transmission, but it should be envisaged in aerosol-generating procedures in health facilities(4). This similarity in transmission mode may not be unconnected with the observed genetic sequence homology between SARS-COV2 and SARS-COV(3)(6).

After its transmission, cellular attachment, and fusion to the functional surface enzyme receptor angiotensin-converting enzyme 2 molecule are initiated with the use of the S protein in the viral envelope (7). This host-viral interaction may have a profound stimulatory effect on the human body's innate and adaptive immune systems with attendant systemic inflammatory response syndrome(7). Cellular death is mediated by apoptosis, autophagy, endoplasmic reticulum stress response, and activation of several other subcellular pathways(7)(8). Symptoms range from a mild respiratory illness characterized by fever, cough, and myalgia to severe disease(9)(10).

Secondary infections which together with the primary Coronavirus infection, may result in sepsis and septic shock. Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection can be complicated by end-organ dysfunction including acute respiratory distress syndrome, acute kidney injury, and severe neurologic sequelae(11)(12). Viral sepsis and cytokine storm are major component in the pathogenesis of COVID-19 (9) and significantly contribute to the COVID-19-related mortality which is documented mostly in elderly patients and those with immunosuppression and comorbidities(13).

Management of patients with mild illness is less complex and in some settings, patients with mild illness are managed in their communities(14)(15). However, the management of patients with COVID-19 complicated by sepsis and septic shock requires supportive therapy including appropriate fluid management and empiric antibiotic therapy. Notwithstanding the availability of this supportive infrastructure in high-income countries, the reported mortality among patients with advanced COVID-19 disease has not been encouraging(13) and may worsen in countries with limited resources and weak health infrastructure.

In this scoping review, we focus on sepsis and septic shock in patients with COVID-19. We aim to summarize and analyze the available research data on sepsis and septic shock and their management as reported in patients with COVID-19. Understanding the evidence on sepsis and septic shock in patients with COVID-19 may have an important policy implication as more cases are being reported in countries with weak health systems and limited microbiology laboratory capacity to support rational antibiotic use.

## Methods

### Study design

A scoping review was conducted using the Arksey and O'Malley framework by a) defining a clear research objective and search strategy b) identifying relevant research articles, c) selection of research articles, d) extraction and charting of data, and e) collating, summarizing, and reporting the results(16).

### Search strategy

We search published articles between January 1, 2020 to April 16, 2020 on Sepsis or septic shock in COVID-19 globally. Studies were identified in multiple databases including medRxiv, PubMed, and Google Scholar. The main search terms used were "COVID-19 AND sepsis" and/or septic shock" and Coronavirus AND sepsis" and/or septic shock". Other search terms were "nCOV AND sepsis", "2019 nCOV and sepsis" and "2019 novel coronavirus and sepsis" in English were included.

### Inclusion criteria

Titles of articles were all reviewed, followed by the abstracts and the full articles. All research articles that indicate a diagnosis of sepsis or septic shock were considered for inclusion. Policy documents on COVID-19 published online with information on sepsis and septic shock and non-scientific articles and news commentaries without researched data were excluded in the analysis.

### Study selection

The literature search was independently conducted by two researchers who aligned the data in two sets both of which were compared by a third researcher. Disagreements on the inclusion or exclusion of articles were resolved by consultation, and where necessary the third researcher makes the final decision. Duplicated articles were eliminated.

Sixteen articles were eligible for inclusion, of which 9 (56.3%) and 7 (43.7%) were retrieved through medRxiv and PubMed, respectively. All articles were published between 11<sup>th</sup> January 2020 and 16<sup>th</sup> April 2020. **Table 1** provides data on characteristics and findings for all studies included.

### Data analysis

Data were extracted and recorded in two separate Microsoft excel sheets after selection. The extracted data were the date of publication, the title of article, the name of journal, the author's country and affiliation, the study design, sample size, study setting, and key findings. The focus of the findings included prevalence and outcome of COVID-19 patients with sepsis or septic shock, sepsis criteria (Sequential Organ Failure Assessment, SOFA, Systemic Inflammatory Response Syndrome, SIRS), levels of white blood cell count, platelet count, lactate, procalcitonin and C-reactive protein, and treatment (antibiotics, antivirals, other antimicrobials, oxygen therapy, and mechanical ventilation).

## Results

### General research characteristics

Of the 16 eligible articles included in this review, 13 (81.2%) were conducted in China. The research work for an article of 24 participants was conducted in the Netherlands. The United States and Iran, each reported a case of COVID-19 complicated by sepsis. None of the research work was conducted specifically on sepsis. With the exception of one article, the research work for all the articles was conducted in adult patients. The articles were retrospective studies (12, 75%), case reports (3, 18.8%) and prospective observational studies (1, 6.2%). The sample size varies from one patient for the case reports to 449 for observational studies. Table 1 highlighted the additional characteristics of the eligible articles.

### Sepsis, septic shock, and mortality among study participants with COVID-19

The prevalence of sepsis reported in the various research articles is variable. Estimates of the prevalence of sepsis range from 6.8% (15) to 100% (24). On the other hand, the prevalence of septic shock reported among the researched articles varied from 4% (4) to 28.9% (13). Table 1.

The quick Sequential Organ Failure Assessment (qSOFA) was the criteria used to make a diagnosis of sepsis but it is documented in only 38% of the articles. Figure 3.

Mortality among the study participants is varied with the highest and lowest mortality of 29.8% (134) and 5.4%(12), respectively. Although the outcome in one of the case report was not stated, there was no reported mortality in all the reported cases. In two of the articles, the study was conducted in COVID-19 non-survivors. Table 1.

### Laboratory parameters

Of the 50% of the articles with documented serum lactate, levels are high in 24.5%. Platelet count is either high in 6.2% of the articles or low in 12.5%. C-reactive protein, procalcitonin, lactate dehydrogenase, and white cell count are all elevated in 31.2%, 62.5%, 43.8%, and 37.5% of the articles, respectively. Figure 2.

Bacterial cultures were documented in 4(25%) of the eligible articles. Figure 3.

## Antimicrobials and supportive treatment

Of the 16 articles, 12 (75%) documented use of antiviral drugs. The antivirals used in these articles included oseltamivir (4, 25%), and lopinavir/ritonavir (2, 12.5%). The use of remdesivir, arbidol, and ganciclovir use is each documented in 1 (6.3%) article. Use of antivirals without specific names is documented in 6 (37.5%) of the articles. **Table 2**

Antibiotic use was documented in 11 (68.8%) of the articles. Of these, azithromycin, quinolones and cephalosporins is documented in 3 (18.8%) of the articles. Less commonly, the use of piperacillin-tazobactam, carbapenem, tigecycline, amikacin, and vancomycin is each documented in 1(6.3%) article. There is no specification on the type of antibiotic used in 5 (31.3%) of the articles.

Other antimicrobial used among COVID-19 patients were hydroxychloroquine (1,6.3%), chloroquine (1, 6.3%), and unspecified antifungal drugs (2, 12.5%). **Table 2.**

Supportive therapy like oxygen therapy, mechanical ventilation, and fluid therapy is documented in 12(75%), 13 (81.3%), and 2 (12.5%), respectively. **Table 3**

## Discussion

This scoping review assessed the researched literature on sepsis and septic shock among patients with COVID-19. Although data in the literature on sepsis in COVID-19 is limited, this paper highlighted the available evidence on sepsis and COVID-19.

COVID-19 has a well-established association with sepsis and septic shock(17). This fact further adds to the burden of a highly incident condition as reported in the analysis for the global burden of disease study where an estimated 48.9 million global sepsis incident cases and 11.0 million sepsis-related mortality are reported in 2017(18). In this review, a substantial proportion of COVID-19 patients had a documented diagnosis of sepsis with prevalence ranging from 6.8–100%(19)(20). Even a case report of COVID-19 patients in relatively low sepsis incidence countries (18) had documented clinical features of sepsis(21). Supporting the diagnosis of sepsis or septic shock are the elevated levels of serum procalcitonin, lactate, C-reactive protein, and the white cell counts documented by several of the reviewed articles(13)(19–25). Elevated serum procalcitonin(26) and lactate level > 2 mmol/l(27) are promising markers of sepsis and septic shock, respectively.

Substantial mortality among COVID-19 patients was reported in most of the studied participants even though the documented mortality was not specific to sepsis. This is not unique to the COVID-19 situation as sepsis is related to high mortality especially with increasing age (28). Reducing this mortality warrants early detection, timely commencement of appropriate antibiotics, conservative fluid management, and implementation of infection prevention and control practices(29).

Thus existing guidelines on COVID-19 management recommends the early detection and prompt management of sepsis in patients with COVID-19(17). Appropriate fluid therapy using conservative rather

than liberal fluid administration is a recommended intervention with improved outcomes in the management of sepsis or septic shock in COVID-19(29).

Early administration of empiric antibiotics therapy can prevent sepsis-related mortality and is strongly recommended in the management of critically ill patients with sepsis(30). However, rational antibiotic use backed up by local evidence on resistance pattern is warranted. This may be a challenge in the setting of a highly infectious pandemic especially in many developing countries where there are weaknesses in the microbiology laboratory infrastructure. Supporting this fact, a recent study on antibiotic use in a low resource setting with high prevalence of extended spectrum beta lactamase-producing organisms reported antibiotic use without culture data in 81.8% of 753 patients(31)(32). Of the 16 articles included in this review, only 4(25%) documented incomplete culture data with no resistance profile(22)(33)(19)(34).

Notwithstanding, the lack of microbiology diagnostic support does not preclude the use of antimicrobials in COVID-19 management as a high proportion of the articles documented antimicrobial use in this review.

Complicating matters is the increasing global interest in repurposing antimicrobial agents like hydroxychloroquine(35), remdesivir(36), and lopinavir/ritonavir(37) for the treatment of COVID-19 as documented in some of the eligible articles summarized in this paper(13)(20)(21).

This practice of empiric antimicrobial use without support for escalation or de-escalation in response to the rapidly evolving COVID-19 pandemic are growing concerns and have the possibility of breeding a slowly growing antimicrobial resistance (AMR) pandemic. Without intervention to address the indiscriminate antimicrobial use in epidemics of emerging infectious diseases, the global annual AMR-related deaths may surpass the estimated 10 million in 2050 (38).

Like any group of patients with critical illness, a large proportion of articles documented the use of oxygen therapy and mechanical ventilation. This is a major concern for the health service delivery in sub-Saharan Africa especially with the increasing burden of COVID-19 in the region where these resources are largely unavailable to support COVID-19 critical care(39).

Notwithstanding the public health and clinical relevance of the evidence on sepsis provided by our article, it has some limitations including the lack of data specific to sepsis-related mortality and the unavailability of a wider global scope of the research work.

## **Conclusion**

In summary, there is a paucity of data in the literature on sepsis in COVID-19 despite its huge burden among the COVID-19 patient population resulting in a high rate of antimicrobial use that is not backed by clearly documented microbiology laboratory support. Research is needed to understand the actual burden of sepsis in COVID-19.

Again, empiric antimicrobial prescriptions in COVID-19 should be supported by both existing evidence on antimicrobial resistance patterns and ongoing culture data to allow rational antibiotic use.

## Declarations

### Ethics approval and consent to participate

Not applicable

### Consent for publication

Not applicable

### Availability of data and materials

The data set generated during the current study are available at the repository of the University of Sierra Leone and will be made available on request.

### Competing interests

Not applicable

### Funding

Not applicable

### Authors' contributions

Conceptualization: SL, DFJ, MB

Search for articles: SL, DFJ, MB, AOV

Writing of the draft: SL., GAY., SS., FS.

All authors review the draft manuscript

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Not applicable

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## Tables

**Characteristics of research articles with data on sepsis**

Author	Country	Study population	Design	Sample size	Mortality in the study population	Prevalence of sepsis	Prevalence of septic shock
Li	China	Adult	Retrospective	221	12 (5.4%)	15 (6.8%)	-
9/01/20*	China	Adult	Retrospective	99	11 (11%)	-	4(4%)
	China	Adult	Retrospective	82	82 (100%)	23 (28.1%)	-
Wang	China	Adult	Retrospective	45	1 (2.2%)	-	13 (28.9%)
Li	China	Adult	Retrospective	138	6 (4.3%)	12 (8.7%)	-
1/03/20*	China	Adult	Retrospective	211	54 (25.6%)	124 (59%)	
1/03/20*	China	Adult	Retrospective	191	54 (28.3%)	112 (59%)	38 (20%)
Chen	China	Adult	Retrospective	101	101 (100%)	46 (40.6%)	-
Chen	China	Adult	Retrospective	274	113 (41.2%)	179 (65%)	-
Sun	China	Adult	Retrospective	449	134 (29.8%)	-	-
20*	China	Adult	Retrospective	83	40 (48.2%)	-	16 (19.3%)
J 03/20	USA	Adult	Case report	1	Not stated	1 (100%)	-
4/01/20*	Iran	Child	Case report	1	0 (0%)	1 (100%)	-
Zhang	China	Adult	Case report	1	0 (0%)	1 (100%)	-
3/04/20	China	Adult	Retrospective	101	101 (100%)	41 (40.6%)	-
Kox	Netherlands	Adult	Prospective observational	24	2 (8%)	24 (100%)	-

(-) indicate not documented

2: Antimicrobial use among patients with COVID-19		
Antimicrobial documented	No. of journals (n=16)@	%
Antivirals	12	75.0
Zanamivir	4	25.0
Oseltamivir/ritonavir	2	12.5
Lamivudine	1	6.3
Acyclovir	1	6.3
Ganciclovir	1	6.3
Not documented	6	37.5
Antibiotics	11	68.8
Clindamycin	3	18.8
Clonazepam	3	18.8
Azaloporphins	3	18.8
Ampicillin-tazobactam	1	6.3
Meropenem	1	6.3
Ciprofloxacin	1	6.3
Vancomycin	1	6.3
Not documented	5	31.3
Antimicrobial use	4	25.0
Chloroquine	1	6.3
Hydroxychloroquine	1	6.3
Fungal therapy	2	12.5

@=multiple answers are allowed

3: Supportive care of COVID-19 patients documented by articles with data on sepsis		
of treatment	Frequency	Percentage
Antibiotic therapy	12	75.0
Mechanical ventilation	13	81.3
Other therapy	2	12.5

## Figures

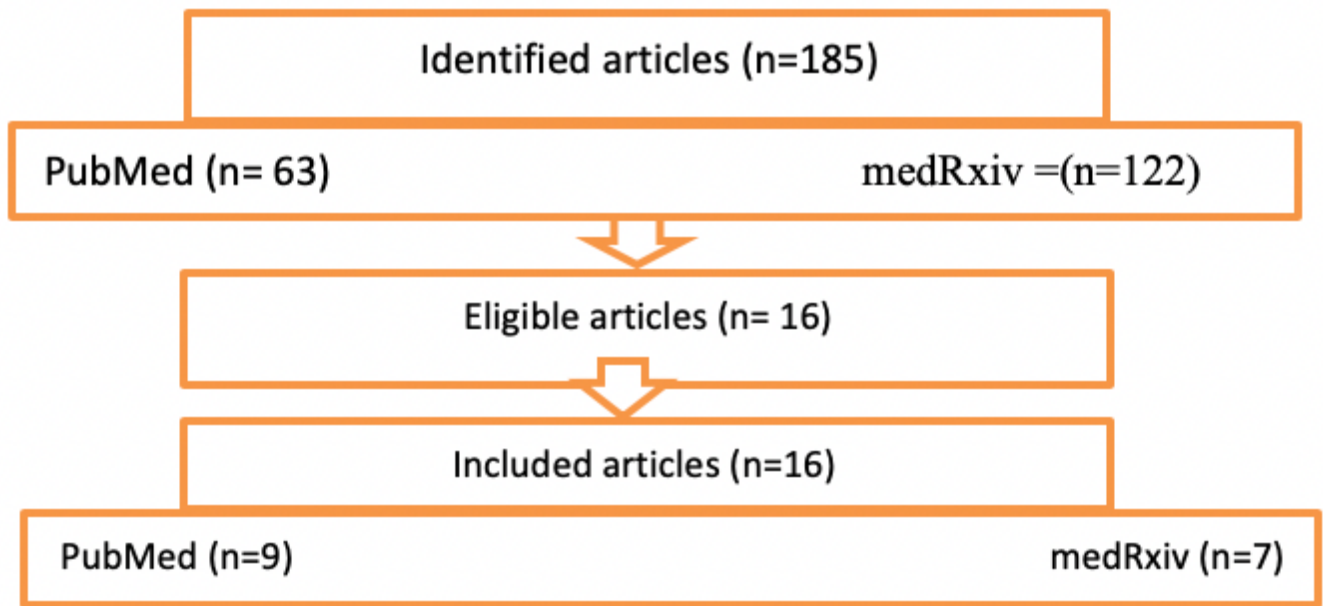


Figure 1

Article retrieval

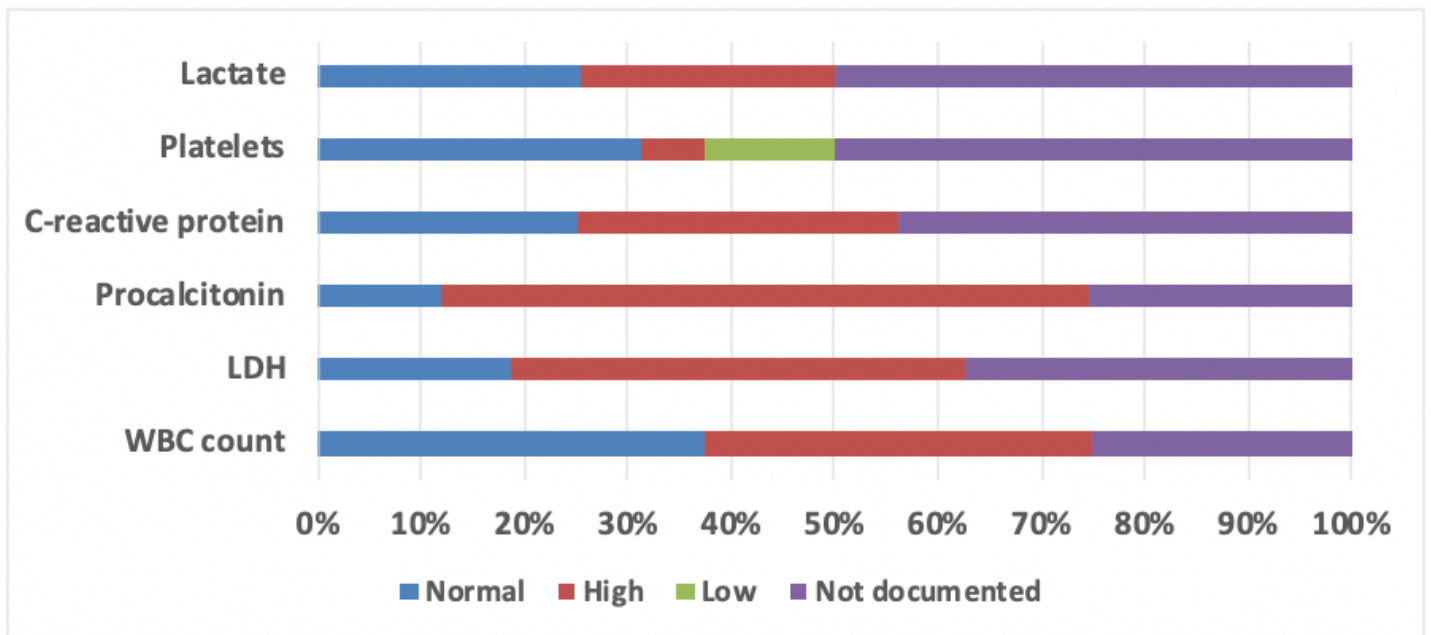
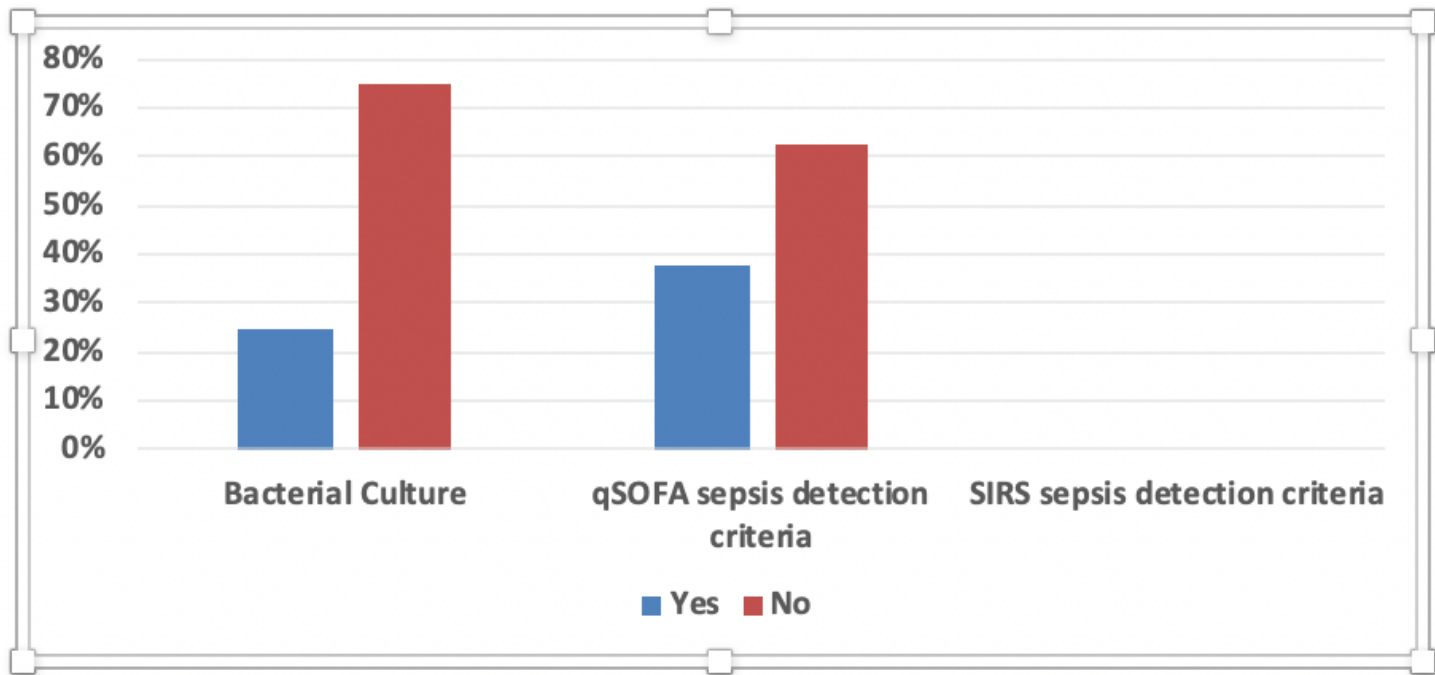


Figure 2

Laboratory parameters of COVID-19 patients



**Figure 3**

Figure 3: Bacterial culture and documented sepsis criteria. qSOFA: quick Sequential Organ Failure Assessment SIRS: Systemic Inflammatory Response Syndrome