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Clinical Epidemiology and Global Health 15 (2022) 101059

Contents lists available at ScienceDirect

Clinical Epidemiology and Global Health

journal homepage: www.elsevier.com/locate/cegh

Original article

# Differences in inflammatory markers between coronavirus disease 2019 and sepsis in hospitalised patients

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ARTICLE INFO

*Keywords:*
Biomarkers
Pneumonia
SARS-CoV-2 infection
Sepsis
Viral

ABSTRACT

*Background:* Inflammatory markers are pivotal for the diagnosis of coronavirus disease 2019 (COVID-19) and sepsis. This study compared markers between hospitalised patients with COVID-19 and those with bacterial sepsis.

*Methods:* This retrospective single-centre cohort study included 50 patients with COVID-19 clinical stages II and III and 24 patients with bacterial sepsis. Both groups were treated according to the country's official standards. Leukocytes, C-reactive protein (CRP), ferritin, and D-dimer were registered at the time of patient's admission and 24, 48, and 72 h after initiating intrahospital treatment.

*Results:* Upon admission, marker levels were high, with a significant decrease at 72 h after antibiotic therapy in the sepsis group. The leukocyte count was higher in deceased patients with sepsis. The mean ferritin levels were 1105 mcg/dl for COVID-19 and 525 mcg/dL for sepsis. Higher ferritin levels in COVID-19 ($P = 0.001$) seemed to be a predictor of higher mortality. Upon admission, the median D-dimer level was 0.68 mg/L for COVID-19 and 3 mg/L for patients with sepsis, whether recovered or deceased. As D-dimer, procalcitonin levels were higher in patients with sepsis ($P = 0.001$). CRP levels were equally elevated in both entities but higher in deceased patients with COVID-19.

*Conclusion:* Ferritin was the main inflammatory marker for COVID-19, and leukocytes, procalcitonin, and D-dimer were the main markers of sepsis. Markers that were most affected in deceased patients were CRP for COVID-19 and leukocyte for sepsis. The therapeutic implications of these differences require further study.

## 1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and bacterial sepsis are infectious diseases that continue to be life-threatening medical conditions that challenge daily medical practice. Both show inflammation markers that can have prognostic value.[1–3] Three stages characterise the clinical presentations of coronavirus disease 2019 (COVID-19).[3] Stage I presents with fever, malaise, and cough. Stage II (pulmonary) presents with ground glass opacities in computed tomography (CT) scan, oxygen desaturation <94%, and biomarkers indicating inflammation (C-reactive protein [CRP], ferritin, and D-dimer), while stage III shows higher levels of inflammation with cytokine cascade, interleukin, and multiorgan failure.[4] The main markers of inflammatory responses are leukocytes, CRP, ferritin, interleukin-6, and D-dimer.[5,6] In the case of ferritin, values of 1000 mg/dL and above are associated with a poorer prognosis.[7]

On the other hand, sepsis syndrome stages are characterised by high temperature (>38.3 °C), hypothermia (T < 35.6 °C), tachycardia (>90 bpm), tachypnea (respiratory rate >20 rpm), and at least one of the following: mental disturbance, hypoxemia, lactate elevation, and oliguria (<30 mL or 0.4 mL/kg/h). Haemodynamic collapse occurred during this critical stage. This definition, which has been used since 1987 and was described by Bones in 1987,[8] has undergone modifications over time. The Third International Consensus Definitions Task

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https://doi.org/10.1016/j.cegh.2022.101059
Received 11 January 2022; Received in revised form 24 April 2022; Accepted 1 May 2022
Available online 8 May 2022

Force defined sepsis as 'life-threatening organ dysfunction due to a dysregulated host response to infection'.[9] However, there is no consensus on the operational definition.

Sepsis can be caused by bacteria, viruses, fungi, rickettsia, parasites, or protozoa. Likewise, the inflammatory cascade is significant and progressive unless treated. Biomarkers include elevated leukocytes, erythrocyte sedimentation rate (ESR), CRP, ferritin, D-dimer, procalcitonin, and interleukins (IL).[10] Such elevation depends on the severity of the infection and the host's immune response. For example, less than 20% of patients with sepsis present with disseminated intravascular

**Table 1**
**Demographic and clinical characteristics of patients with COVID-19.**

| Variable | COVID-19 (n = 50) | | Sepsis (n = 24) | | OR | 95% CI | *P*-value |
|---|---|---|---|---|---|---|---|
| | N | % | n | % | | | |
| **Age (years)** | | | | | | | |
| <30 | 2 | 4 | 2 | 8.3 | | | |
| 31–40 | 11 | 22 | 3 | 12.5 | | | |
| 41–50 | 7 | 14 | 4 | 16.7 | | | |
| 51–60 | 10 | 20 | 5 | 20.8 | | | |
| 61–70 | 14 | 28 | 3 | 12.5 | | | |
| 71–80 | 2 | 4 | 5 | 20.8 | | | |
| >81 | 4 | 8 | 2 | 8.3 | | | |
| Mean | 54.7 | | 56.4 | | | | 0.7 |
| **Sex** | | | | | | | |
| Male | 30 | 60 | 4 | 16.7 | 7.5 | 2.2–25.2 | 0 |
| Female | 20 | 40 | 20 | 83.3 | | | |
| **Days from onset of symptoms** | | | | | | | |
| 1–3 | 9 | 18 | 9 | 37.5 | | | |
| 4–6 | 16 | 32 | 14 | 58.3 | | | |
| 7–9 | 15 | 30 | 1 | 4.2 | | | |
| 10–12 | 7 | 14 | 0 | 0 | | | |
| >12 | 3 | 6 | 0 | 0 | | | |
| Mean | 6.25 | | 4.29 | | | | 0.001 |
| **Comorbidities** | | | | | | | |
| Diabetes mellitus | 14 | 28 | 16 | 66.7 | 0.19 | 0.06–0.55 | 0.002 |
| High blood pressure | 10 | 20 | 7 | 29.2 | 0.6 | 0.19–1.86 | 0.38 |
| Obesity | 7 | 14 | 0 | 0 | 5.94 | 0.6–181.9 | 0.13* |
| **Oxygen saturation at admission (%)** | | | | | | | |
| <50 | 1 | 2 | 0 | 0 | | | |
| 61–70 | 2 | 4 | 0 | 0 | | | |
| 71–80 | 3 | 6 | 0 | 0 | | | |
| 81–92 | 31 | 62 | 0 | 0 | | | |
| >93 | 3 | 6 | 24 | 100 | | | |
| Mean | 85.75 | | 96.17 | | | | 0 |
| **Chest X-ray** | | | | | | | |
| Normal | 5 | 10 | 9 | 37.5 | | | 0.000* |
| Pneumonia | 20 | 40 | 5 | 20.8 | | | |
| Not done | 25 | 50 | 10 | 41.7 | | | |
| **Chest CT score (%)** | | | | | | | |
| <25 | 2 | 4 | | | | | |
| 26–50 | 14 | 28 | | | | | |
| 51–75 | 10 | 20 | | | | | |
| >75 | 6 | 12 | | | | | |
| Mean | 51.75 | | | | | | |
| **Chest CT score (maximum 25 points)** | | | | | | | |
| <5 | 2 | 4 | | | | | |
| 6–10 | 7 | 14 | | | | | |
| 11–15 | 17 | 34 | | | | | |
| 16–20 | 6 | 12 | | | | | |
| 21–25 | 1 | 2 | | | | | |
| Mean | 13 | | | | | | |
| **Severity of disease** | | | | | | | |
| Mild | 1 | 2 | | | | | |
| Moderate | 33 | 66 | | | | | |
| Severe | 16 | 32 | | | | | |
| **CURB-65*** ** | | | | | | | |
| 0 | 14 | 28 | 13 | 54.2 | | | |
| 1 | 20 | 40 | 7 | 29.2 | | | |
| 2 | 13 | 26 | 3 | 12.5 | | | |
| 3 | 2 | 4 | 0 | 0 | | | |
| 4 | 1 | 2 | 0 | 0 | | | |
| Mean | 1.12 | | 0.57 | | | | 0.014 |
| **Outcome** | | | | | | | |
| Recovered | 39 | | 23 | | | | |
| Deceased | 11 | 22 | 1 (4.3%) | | 6.36** | 0.82–291.1 | 0.107* |
| | 28 | 56 | 22 | 91.7 | 0.11 | 0.02–0.54 | 0.002 |

*Yates correction, **Fisher's exact test.

***CURB-65 mortality risk prediction: 0 or 1 points (1.5%), 2 points (9.2%), and ≥3 points (22%). According to this score 68% of patients with COVID-19 and 83.4% patients with sepsis had a mortality risk of 1.5%; 26% patients with COVID-19 and 12.5% patients with sepsis had a mortality risk of 9.2%, while 6% of patients with COVID-19 had 22% risk of mortality. No patient with sepsis had this high risk.

coagulation (DIC), and almost all have high D-dimer levels.

As its etiological agents are different, the response of the white blood cell count and inflammatory markers in both groups of patients differ in their behaviour. Therefore, this study aimed to compare biomarker levels and outcomes between a group of patients with sepsis and COVID-19 at the time of admission and during the first 72 h of in-hospital treatment.

## 2. Patients and methods

### 2.1. Sample collection

A comparative analytical study was carried out at the Hospital General del Sur in the city of Choluteca, Honduras. Patients older than 18 years were recruited between 26 January and 2 March 2021.

The first group consisted of 50 patients with COVID-19, 62% of whom (n = 31) were diagnosed by real-time polymerase chain reaction (RT–PCR) using nasopharyngeal swabs, and 38% (n = 19) were diagnosed by combining clinical, imaging, and inflammatory marker criteria and antigen for SARS-CoV-2 using nasopharyngeal swabs or IgM antibodies. The presence of a positive test for COVID-19 was the inclusion criterion for this group.

The second group consisted of 24 patients with sepsis with negative COVID-19 test results and standard evidence for sepsis of any aetiology. Eleven (46%) patients had cultures that supported the diagnosis of bacterial sepsis. In the other 13 cases, bacterial sepsis was diagnosed by combining clinical, imaging, and laboratory criteria (positive Gram tests and inflammatory markers).

Demographic, clinical, and laboratory data were also collected at the same intervals. Pneumonia was documented using chest radiography or CT tomography, as available. Data were extracted from the clinical files and were anonymised.

### 2.2. Laboratory data

For both groups, inflammatory markers were registered at the time of patient's admission and 24, 48, and 72 h after initiating intrahospital treatment (Table 1). The inflammatory markers included leukocytes, CRP, ferritin, and D-dimer. Owing to resource shortages, there was no access to IL-6 testing.

### 2.3. Severity score and inflammatory markers

The CURB-65 pneumonia severity score calculator[11] was used to classify mortality risk upon admission in both groups.[12] The CURB-65 stands for confusion, blood urea nitrogen (BUN) > 7 mmol/L, respiratory rate ≥30, systolic blood pressure (SBP) < 90 mmHg, diastolic BP (DBP) ≤ 60 mmHg, and age ≥65. This score was previously used as risk stratification and prediction tool for community-acquired pneumonia. The total score was 5, and each risk factor contributed to 1 point and could be used to predict mortality as follows: 0 or 1 point (1.5% mortality), 2 points (9.2% mortality), and 3–5 points (22% mortality).

### 2.4. Statistical analysis

Data were analysed using Statistical Package for the Social Sciences (SPSS) version 2 statistical software,[13] and categorical or binary data were reported as frequencies and percentages. Continuous variables were described as mean ± standard deviation or median (interquartile range [IQR], as appropriate). Differences between study groups were evaluated using the Mann–Whitney *U* test, Yates correction, and Fisher's exact test. Odds ratios (ORs) and 95% confidence intervals were calculated, and a *P*-value of less than 0.05 was considered statistically significant.

## 3. Results

In 50 patients with COVID-19, diagnosis was made by RT-PCR (n = 31, 62%), rapid IgM (n = 10, 20%), and rapid antigen tests using swab (n = 9, 18%). Most patients in this group were men (OR = 7.5), with an average age of 54.7 years, and 56% had comorbidities, especially diabetes (OR, 0.19; *P* = 0.002) and obesity (OR 5.94, *P* 0.38). Sixty-six percent of patients had a moderate clinical presentation of the disease according to the CURB-65 score (Table 1).

In patients with sepsis, 13 (54%) had urinary tract infections, and 9 (21%) had criteria for bacterial pneumonia. In the other cases, there was previous treatment with antibiotics or logistic limitations in performing the test on time (Table 1). The mean number of days of symptoms from onset until admission was 6.25 days in the COVID-19 group and 4.29 days in the sepsis group (*P* 0.001). Oxygen saturation was lower in patients with COVID-19. Comorbidities were more frequent in patients with sepsis (Table 1).

Differences in inflammatory markers were found in the blood counts (Table 2). There was a higher total leukocyte count upon admission in patients with sepsis than in patients with severe COVID-19, but at 72 h of hospitalisation, the count was levelled in both groups, with a marked decrease in the count in the sepsis group after antibiotic treatment was initiated. In the COVID-19 group, the lymphocyte count was lower upon admission and at 72 h, while the mean number of neutrophils was higher in the sepsis group upon admission and at 72 h.

Other inflammatory markers were also different between the groups (Table 3). Ferritin levels were higher upon admission and at 72 h in the COVID-19 group. D-dimer levels were higher in the sepsis group upon admission and at 72 h, while CRP levels showed a similar reduction in both groups after 72 h of treatment. In contrast, procalcitonin levels

**Table 2**
Comparison of blood counts between patients with COVID-19 and sepsis.

| Blood counts | COVID-19 | | Sepsis | | *P*-value |
|---|---|---|---|---|---|
| | N | % | n | % | |
| Leukocytes ($10^9$ μ/mL) | | | | | |
| *Upon admission* | | | | | |
| <4500 | 7 | 14.0 | 1 | | |
| >11000 | 17 | 34.0 | 19 | | |
| Mean | 9811 | | 15,976 | | 0.000 |
| *72 h* | | | | | |
| <4500 | 1 | 28 | 1 | 4.2 | |
| >11000 | 16 | 16 | 9 | 37.5 | |
| Mean | 10,943 | | 10,724 | | 0.860 |
| **Neutrophils' ($10^9$ μ/mL)** | | | | | |
| *Upon admission* | | | | | |
| <2000 | 2 | 4 | | | |
| >7500 | 24 | 48 | 20 | | |
| Mean | 8120 | | 12,872 | | 0.000 |
| *72 h* | | | | | |
| <2000 | | | | | |
| >7500 | 19 | 38.0 | 9 | 37.5 | |
| Mean (Q25%, 75%) | 7480 (5,200, 10,701) | | 6835 (5,225, 9010) | | 0.263* |
| Range (IQR) | 2349–21,250 (5501) | | 2250–20,350 (18,100) | | |
| **Lymphocytes ($10^9$ μ/mL)** | | | | | |
| *Upon admission* | | | | | |
| <1000 | 28 | 56.0 | 7 | 29.2 | |
| >4500 | 3 | 6.0 | 17 | 70.8 | |
| Median (Q25%, 75%) | 849 (517, 1367) | | 1346 (925, 1935) | | 0.001* |
| Range (IQR) | 146–8191 (850) | | 650–4140 (1010) | | |
| *72 h* | | | | | |
| <1000 | 20 | 40.0 | 2 | 8.3 | |
| >4500 | 0 | | 0 | | |
| Mean | 1154 | | 1877 | | 0.000 |

*Mann–Whitney U.

**Table 3**
Comparison of other inflammatory markers between patients with COVID-19 and sepsis.

| | COVID-19 | | Sepsis | | *P* |
|---|---|---|---|---|---|
| | N | % | n | % | |
| CRP (mg/L) | | | | | |
| *Upon admission* | | | | | |
| <6 | 6 | 12.0 | 2 | | |
| >150 | 10 | 20.0 | 6 | | |
| Median (Q25%, 75%) | 48 (12, 96) | | 48 (12, 196) | | 0.956* |
| Range (IQR) | 0–34(84) | | 0–196 (154) | | |
| *72 h* | | | | | |
| <6 | 14 | 28.0 | 5 | 20.8 | |
| >150 | 1 | 2.0 | 1 | 4.2 | |
| Median (Q25%, 75%) | 12 (6, 24) | | 22 (8.5, 49.5) | | 0.109* |
| Range (IQR) | 0–192 (18) | | 0–192 (41) | | |
| **Ferritin (mcg/L)** | | | | | |
| *Upon admission* | | | | | |
| <338 | 10 | 20.01 | 50 | | |
| >2000 | 7 | 14 | 1 | | |
| Mean | 1105 | | 525 | | 0.001* |
| *72 h* | | | | | |
| <336 | 4 | 8.0 | 11 | | |
| 20,000 | 3 | 6.0 | | | |
| Mean | 1088 | | 464 | | 0.000* |
| **D-dimer (mg/L)** | | | | | |
| *Upon admission* | | | | | |
| 0.5 | 18 | 36.0 | 3 | | |
| >3 | 10 | 20.0 | 11 | | |
| Median (Q25%, 75%) | 0.68 (0.28, 2.62) | | 3 (1.89, 7.13) | | 0.000* |
| Range (IQR) | 0.0–10.0 (2.34) | | 0.36–10.0 (5.24 | | |
| *72 h* | | | | | |
| <0.5 | 12 | 24.0 | 3 | 12.5 | |
| >3 | 8 | 16.0 | 10 | 41.7 | |
| Median (Q25%, 75%) | 0.78 (0.44, 2.03) | | 1.0 (0.72, 4) | | 0.86* |
| Range (IQR) | 0.0–10.0 (1.59) | | 0–10 (3.28) | | |
| **Procalcitonin (ng/mL)** | | | | | |
| *Upon admission* | | | | | |
| <0.5 | 31 | 62.0 | 7 | 29.2 | |
| >5 | 2 | 4.0 | 6 | 25.0 | |
| Median (Q25%, 75%) | 0.20 (0.19, 0.66) | | 1.51 (0.37, 8.0) | | 0.003* |
| Range (IQR) | 0.0–92.0 (0.47) | | 0.0–100 (3.37) | | |
| *72 h* | | | | | |
| <0.5 | 26 | 52.0 | 8 | 33.3 | |
| >5 | 1 | 2.0 | 4 | 16.7 | |
| Median (Q25%, 75%) | 0.26 (0.18, 0.46) | | 1.0 (0.35, 3.75) | | 0.004* |
| Range (IQR) | 0.0–59 | | 0.0–100 (2.48) | | |

*Mann–Whitney U.

were higher in patients with sepsis upon admission and at 72 h.

In patients with COVID-19 treated with tocilizumab when available or indicated, the mean ferritin level was 1105 mcg/L upon admission and 1089 mcg/L at 72 h. In patients not treated with tocilizumab, the mean levels were 1725 and 1074 mcg/L upon admission and at 72 h, respectively. Remdesivir was prescribed more often in patients with mild-to-moderate clinical presentations (n = 18), and tocilizumab was mostly prescribed in critical patients (n = 30). No significant differences were seen between the two subgroups at 72 h.

The mean ferritin levels in COVID-19 survivors were 983 mcg/L upon admission and 1427 mcg/L in the deceased. Upon admission, D-dimer mean levels did not vary significantly in COVID-19 survivors compared with the deceased (3.8 mg/L vs. 2.59 mg/L). A total of 11/50 patients died in the COVID-19 group and 1/24 in the sepsis group (OR 6.36, 95% CI 0.82–291.1, $P = 0.107$). According to the CURB-65 score, the mortality risk was higher in COVID-19 (Table 1): 26% patients with COVID-19 and 12.5% patients with sepsis had a mortality risk of 9.2%, while 6% of patients with COVID-19 had 22% risk of mortality. No patient with sepsis had this high risk.

Table 4 shows differences in inflammatory markers between recovered and deceased patients in both groups. White cell counts were higher in deceased patients with sepsis, whereas CRP and ferritin levels were higher in deceased patients with COVID-19. D-dimer was higher in patients with sepsis, whether recovered or diseased. Procalcitonin levels were higher in patients with sepsis. Only one patient with sepsis died, but his procalcitonin levels were normal.

## 4. Discussion

Upon admission, the leukocyte count, procalcitonin, and D-dimer levels were higher in the sepsis group than in the COVID-19 group, with leukocytes decreasing at 72 h after antibiotic treatment in the sepsis group. Ferritin levels were higher at 72 h in patients with COVID-19. CRP levels were high in both groups and decreased after treatment. Upon admission and at 72 h, lymphocytes were lower in the COVID-19 group, and neutrophils were higher in the sepsis group.

Upon admission, higher leukocyte counts in patients with sepsis than in patients with severe COVID-19 have already been reported in the medical literature.[14,15] The use of pulmonary tomography has improved the diagnosis of pneumonia in COVID-19. In our study, an average lung involvement of 52% was found. It is recommended to perform a tomographic study in patients with sepsis and suspected pneumonia with a

**Table 4**
Inflammatory markers upon admission and outcome of patients.

| Inflammatory markers admission | Outcome | | | |
|---|---|---|---|---|
| | Recovered (n = 62) | | Deceased (n = 12) | |
| | COVID-19 (n = 39) | Sepsis (n = 23) | COVID-19 (n = 11) | Sepsis (n = 1) |
| Leukocytes ($10^9$ μ/ml) | | | | |
| Mean | 9391 | 14,869 | 11,836 | 31,200 |
| Median | 8750 | 14,700 | 12,500 | 31,200 |
| Standard deviation | 4693 | 7667 | 6034 | 0 |
| Distribution | Normal | Normal | Normal | Normal |
| Neutrophils ($10^9$ μ/mL) | | | | |
| Mean | 7664 | 11,703 | 10,325 | 25,272 |
| Median | 6963 | 12,070 | 10,625 | 25,272 |
| Standard deviation | 4315 | 6238 | 5577 | 0 |
| Distribution | Normal | Normal | Normal | Normal |
| Lymphocytes ($10^9$ μ/mL) | | | | |
| Mean | 1317 | 1448 | 1138 | 3774 |
| Median | 892 | 1420 | 648 | 3774 |
| Standard deviation | 1610 | 675 | 1573 | 0 |
| Distribution | Not normal | Normal | Not normal | Normal |
| CRP (C-reactive protein) mg/mL | | | | |
| Mean | 78.5 | 71.54 | 92.27 | 24 |
| Median | 48 | 48.0 | 54 | 24 |
| Standard deviation | 94.9 | 75.35 | 65.9 | 0 |
| Distribution | Not normal | Not normal | Not normal | Normal |
| Ferritin (**mcg/L**) | | | | |
| Mean | 1022 | 336.4 | 1427 | 401 |
| Median | 954 | 265.0 | 1713 | 401 |
| Standard Deviation | 653 | 218.75 | 814 | 0 |
| Distribution | Normal | Normal | Normal | Normal |
| D-dimer (mg/L) | | | | |
| Mean | 2.02 | 4.40 | 2.59 | 3.5 |
| Median | 0.72 | 2.70 | 0.65 | 3.5 |
| Standard deviation | 2.96 | 3.82 | 3.77 | 0 |
| Normal distribution | Not normal | Normal | Not normal | Normal |
| Procalcitonin (ng/mL) | | | | |
| Mean | 2.94 | 18.96 | 1.51 | 0.25 |
| Median | 0.30 | 0.77 | 0.39 | 0.25 |
| Standard deviation | 14.85 | 36.48 | 2.88 | 0 |
| Distribution | Not normal | Not normal | Not normal | Normal |

normal chest X-ray.[16]

COVID-19 in its advanced stages and bacterial sepsis both cause changes in the white blood cell count. In patients with severe COVID-19 disease, the white cell count is slightly elevated at the expense of neutrophils with a marked decrease in the cluster of differentiation (CD)4 and CD8 lymphocytes because they express angiotensin-converting enzyme-2 (ACE2) receptors on their surface, which converts them into SARS-CoV-2 target cells.[14,15] On the other hand, cytokine storms in COVID-19 can lead to lymphocyte apoptosis and lymphoid organ atrophy.[4] Unlike COVID-19, leukocytosis in sepsis is more frequent due to neutrophilia; however, neutropenia may occasionally be observed, especially in the paediatric population.[17]

CRP was a biomarker that showed a reduction in both groups after treatment initiation. This marker is an acute phase reactant secreted by the liver during inflammation and favours the phagocytosis of microorganisms, with high levels correlating with severe bacterial pneumonia or COVID-19.[18] Elevated CRP is considered sensitive but not specific for the diagnosis of sepsis;[19] however, a CRP level >100 mg/L on the third day of intensive care unit (ICU) admission is associated with higher mortality.[20]

As explained, ferritin levels were higher in the COVID-19 group. Ferritin is an acute-phase reactant nonspecifically elevated in acute and chronic inflammatory processes, such as chronic kidney disease, rheumatoid arthritis, and autoimmune diseases. Ferritin is elevated during the COVID-19 cytokine storm and may be a predictor of mortality in these cases.[21] Although it is less used to make the diagnosis and estimate the prognosis of mortality in sepsis. A study showed an association between low levels of iron and transferrin and high levels of serum ferritin in patients with sepsis. The much higher serum ferritin levels in patients with COVID-19 in our study reinforce the hypothesis that this disease can be considered a hyperferritinemic syndrome.[22,23] In inflammation, serum ferritin rises in the blood by at least 25% and values greater than 3000 ng/L have exponentially higher mortality.[23]

D-dimer levels were higher in the sepsis group than in the control group at 72 h. This marker is a fibrin degradation product during thrombotic diseases; however, it can also be elevated in malignant diseases, chronic liver diseases, inflammatory processes, and infections. A study found elevated D-dimer levels in patients with COVID-19 pneumonia and community-acquired bacterial pneumonia, with the highest levels in COVID-19 pneumonia.[24] This elevation was associated with critical viral disease and was even higher in deceased patients.[25]

Another study, including multivariate analysis to determine whether several biomarkers, such as CRP, procalcitonin, and D-dimer, were markers of mortality in patients with sepsis, showed that the only biomarker with a linear relationship with mortality was D-dimer.[26] COVID-19 can produce a coagulopathy similar to that of sepsis. However, unlike the DIC seen in sepsis, prolonged prothrombin and partial thromboplastin times, decreased antithrombin activity, and thrombocytopenia are less common in COVID-19.[27] This could explain why D-dimer values were higher in patients with sepsis upon admission and at 72 h.

Procalcitonin levels were higher in the sepsis group upon admission and at 72 h. It is a precursor to the hormone calcitonin, and elevated levels have been correlated with the severity of COVID-19 or bacterial coinfection in these patients.[28] In bacterial sepsis, procalcitonin levels increase 6–12 h after the onset of infection and fall by 50% at 24 h with adequate antibiotic therapy. In addition, procalcitonin levels are not affected by anti-inflammatory drugs. In our study, procalcitonin levels were higher in patients with sepsis than in patients with COVID-19 with a secondary bacterial infection. Procalcitonin is a useful biomarker for differentiating bacterial infections from viral infections, with high sensitivity and specificity. High levels of this marker predict the severity of sepsis and correlate with the severity of inflammation.[29,30]

According to the CURB-65 score, the mortality risk in this study was higher in COVID-19. To date, this score has served as a predictor of complications in patients with pneumonia. Recently, Elmoheen et al. reported that CURB-65 outperformed pneumonia severity index in predicting 30-day mortality and critical care intervention in a multiethnic population from Qatar (2021).[31] Besides the CURB-65 score, it could be studied if including procalcitonin, D-dimer, and ferritin could help predict sepsis's inflammatory and coagulation states. Additionally, other scores, such as sequential organ failure assessment (SOFA), could be used for further evaluation of patients in the intensive care setting.[32]

Although more studies have been conducted on this approach, ferritin, procalcitonin, and D-dimer should be included in the laboratory panel in sepsis. Ferritin could indicate a hyperinflammatory process, and the D-dimer level in the context of sepsis should be interpreted based on the patient's profile and should be treated with anticoagulants if indicated. Procalcitonin could be considered as a reactant that increases in non-COVID sepsis.

This study was limited by the sample size, but the results obtained in this comparative study between patients with COVID-19 and sepsis suggest that the approach to a patient with sepsis might need a change, pointing to the importance of the role of the hypercoagulable state, a condition that could increase the risk of death in these patients due to thromboembolic complications. More studies are needed to revisit anticoagulation and anti-inflammatory therapies for sepsis.

In this study, patients with COVID-19 presented with higher levels of ferritin, and patients with sepsis presented with higher leukocytes, procalcitonin, and D-dimer levels. At baseline, CRP levels were higher in deceased patients with COVID-19, and leukocytes were higher in deceased patients with sepsis. This should be further evaluated to determine its therapeutic implications.

## Funding

This work was supported by the Hospital General del Sur (Secretary of Health of Honduras) and the Universidad Tecnológica Centroamericana (UNITEC, Honduras).

## Ethical approval

This study was approved by the Research Ethics Committee of Universidad Tecnológica Centroamericana. Patient data were extracted from the files and were anonymised.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

## Acknowledgements

We thank the staff and COVID-19 Committee at the Hospital General del Sur, Choluteca.

## References

1 Marshall JC. Sepsis definitions: a work in progress. *Crit Care Clin*. 2018;34:1–14.
2 Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemostasis*. 2020;18:844–847.
3 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.
4 Asrani P, Hassan MI. SARS-CoV-2 mediated lung inflammatory response in host: targeting the cytokine storm for therapeutic interventions. *Mol Cell Biochem*. 2021;475:675–687. https://dx.doi.org/10.1007/s11010-020-03935-z.
5 Zhang L. Response to uncertainties on the prognostic value of D-dimers in COVID-19 patients. *J Thromb Haemostasis*. 2020;18:2067–2068. https://doi.org/10.1111/jth.14899.
6 Lippi G, Favaloro EJ. D-dimer is associated with severity of Coronavirus Disease 2019: a pooled Analysis. *Tromb Haemost*. 2020;120:876–878. https://doi.org/10.1055/s-0040-1709650.

7 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(102229):1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3.

8 Bone RC, Fisher Jr CJ, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med*. 1987;317(11):653–658.

9 Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):762–774. https://doi.org/10.1001/jama.2016.0288.

10 Carrillo Esper R, Peña Pérez C, Zepeda Mendoza AD, et al. Ferritina y síndrome hiperferritinémico. Su impacto en el enfermo grave; conceptos actuales. *Rev Asoc Mex Med Crít Ter Intensiva*. 2015;29:157–166.

11 Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58:377–382. https://doi.org/10.1136/thorax.58.5.377.

12 Carriel J, Muñoz-Jaramillo R, Bolaños-Ladinez O, Heredia-Villacreses F, Menéndez-Sanchón J, Martin-Delgado J. CURB 65 as a predictor of 30 days mortality in patients hospitalized with COVID-19 in Ecuador: COVID-19-EC study. *Rev Clin Esp*. 2021;222(1):37–41. https://doi.org/10.1016/j.rceng.2020.10.006.

13 IBM Corp. Released. *IBM SPSS Statistics for Windows, Version 27.0*. Armonk, NY: IBM Corp; 2020.

14 Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. *Am J Hematol*. 2020;95:834–847. https://doi.org/10.1002/ajh.25829.

15 Aird WC. The hematologic system as a marker of organ dysfunction in sepsis. *Mayo Clin Proc*. 2003;78:869–881. https://doi.org/10.4065/78.7.869.

16 Castillo AF, Basaes ND, Huete GA. Radiology in the COVID-19 Pandemic: current role, recommendations for structured reporting and experience of our Department. *Rev Chil Radiol*. 2020;26(3):88–89. https://doi.org/10.4067/S0717-93082020000300088.

17 Lee JA, Sauer B, Tuminski W, et al. Best pharmaceuticals for children act—pediatric trials network steering committee. Effectiveness of granulocyte colony-stimulating factor in hospitalized infants with neutropenia. *Am J Perinatol*. 2017;34:458–464. https://doi.org/10.1055/s-0036-1593349.

18 Wang L. C-reactive protein levels in the early stage of COVID-19. *Med Maladies Infect*. 2020;50:332–334. https://doi.org/10.1016/j.medmal.2020.03.007.

19 Pradhan S, Ghimire A, Bhattarai B, et al. The role of C-reactive protein as a diagnostic predictor of sepsis in a multidisciplinary Intensive Care Unit of a tertiary care center in Nepal. *Indian J Crit Care Med*. 2016;20:417–420. https://doi.org/10.4103/0972-5229.186226.

20 Devran Ö, Karakurt Z, Adıgüzel N, et al. C-reactive protein as a predictor of mortality in patients affected with severe sepsis in intensive care unit. *Multidiscip Respir Med*. 2012;7(47). https://doi.org/10.1186/2049-6958-7-47.

21 Carubbi F, Salvati L, Alunno A, et al. Ferritin is associated with the severity of lung involvement but not with worse prognosis in patients with COVID-19: data from two Italian COVID-19 units. *Sci Rep*. 2021;11(4863). https://doi.org/10.1038/s41598-021-83831-8.

22 Missano Florido M, Assunção M, Mazza B, et al. Evaluation of iron, transferrin and ferritin serum levels in patients with severe sepsis and septic shock. *Crit Care*. 2012;16(Suppl 1):424. https://doi.org/10.1186/cc11031.

23 Carrillo ER, Peña PC, Zepeda MA, Meza MJ, Maldonado RN, et al. Ferritina y síndrome hiperferritinémico: su impacto en el enfermo grave; conceptos actuales. *Rev Asoc Mex Med Crít Ter Intensiv*. 2015;29(3):157–166.

24 Yu B, Li X, Chen J, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. *J Thromb Thrombolysis*. 2020;50:548–557. https://doi.org/10.1007/s11239-020-02171-y.

25 He X, Yao F, Chen J, et al. The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients. *Sci Rep*. 2021:11. https://doi.org/10.1038/s41598-021-81300-w, 1830.

26 Rodelo JR, De la Rosa G, Valencia ML, et al. D-dimer is a significant prognostic factor in patients with suspected infection and sepsis. *Am J Emerg Med*. 2012;30:1991–1999. https://doi.org/10.1016/j.ajem.2012.04.033.

27 Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. *J Thromb Haemostasis*. 2020;18:2103–2109. https://doi.org/10.1111/jth.14975.

28 Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. *Int J Antimicrob Agents*. 2020;56:106051. https://doi.org/10.1016/j.ijantimicag.2020.106051.

29 Han J, Gatheral T, Williams C. Procalcitonin for patient stratification and identification of bacterial co-infection in COVID-19. *Clin Med*. 2020;20(3):e47. https://doi.org/10.7861/clinmed.let.20.3.3.

30 Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13:426–435. https://doi.org/10.1016/s1473-3099(12)70323-7.

31 Elmoheen A, Abdelhafez I, Awad W, et al. External validation and recalibration of the CURB-65 and PSI for predicting 30-day mortality and critical care intervention in multiethnic patients with COVID-19. S1201-9712 *Int J Infect Dis*. 2021:660–663. https://doi.org/10.1016/j.ijid.2021.08.027, 21.

32 Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286(14):1754–1758. https://doi.org/10.1001/jama.286.14.1754, 10.