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Endothelial injury in COVID-19 and septic patients

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ABSTRACT

Systemic inflammatory response, as observed in sepsis and severe COVID-19, may lead to endothelial damage. Therefore, we aim to compare the extent of endothelial injury and its relationship to inflammation in both diseases.

We included patients diagnosed with sepsis (SEPSIS group, n = 21), mild COVID-19 (MILD group, n = 31), and severe COVID-19 (SEVERE group, n = 24). Clinical and routine laboratory data were obtained, circulating cytokines (INF-γ, TNF-α, and IL-10) and endothelial injury markers (E-Selectin, Tissue Factor (TF) and von Willebrand factor (vWF)) were measured.

Compared to the SEPSIS group, patients with severe COVID-19 present similar clinical and laboratory data, except for lower circulating IL-10 and E-Selectin levels. Compared to the MILD group, patients in the SEVERE group showed higher levels of TNF-α, IL-10, and TF. There was no clear relationship between cytokines and endothelial injury markers among the three studied groups; however, in SEVERE COVID-19 patients, there is a positive relationship between INF-γ with TF and a negative relationship between IL-10 and vWF.

In conclusion, COVID-19 and septic patients have a similar pattern of cytokines and endothelial dysfunction markers. These findings highlight the importance of endothelium dysfunction in COVID-19 and suggest that endothelium should be better evaluated as a therapeutic target for the disease.

1. Introduction

Since the early descriptions of COVID-19 (Zhou et al., 2020), it became clear that the disease could affect the vasculature (Nicosia et al., 2021). Patients who developed severe forms of the disease present with thrombotic phenomena (Leentjens et al., 2021) and systemic

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inflammation (Del Valle et al., 2020), suggesting the participation of the endothelium in the disease pathogenesis (Nicosia et al., 2021). Moreover, increased endothelial injury markers have been found in COVID-19 patients and are correlated to the disease severity (Andrianto et al., 2021).

Later, this hypothesis was confirmed when data from autopsies showed the presence of viral elements within the endothelial cell, leading to apoptosis and infiltration of inflammatory cells, characterizing diffuse endothelitis (Varga et al., 2020). Thus, these findings in deceased patients could suggest previous endothelial activation during COVID-19 evolution.

The vascular endothelium is responsible for maintaining the homeostasis in the organism. It controls vascular relaxation and constriction, participates in fibrinolysis and coagulation, and it is also essential to regulate immune responses (Krüger-Genge et al., 2019). Under pathological conditions, endothelial cells assume an activated state, leading to a proinflammatory and procoagulant state (Anderson, 1999).

As observed in sepsis and COVID-19, systemic inflammation is one of the most potent inductors of endothelial activation (Pober and Sessa, 2007). Both diseases, in their more severe forms, present with a high mortality rate (Seymour et al., 2017; Ranzani et al., 2021) and are characterized by intense activation of immune mediators ("cytokine storm") (Del Valle et al., 2020; van der Poll et al., 2017) and prothrombotic and antifibrinolytic state (Ince et al., 2016).

However, the extension of endothelial activation and its relationship with mortality is unclear, both in sepsis and COVID-19. Moreover, doubts persist about the causative effect of endothelial dysfunction in COVID-19. In this study, we aim to determine the presence of circulating markers of endothelial dysfunction (E-Selectin, Tissue Factor (TF) and von Willebrand factor (vWF)) (Abebe and Mozaffari, 2010) and cytokines in patients with COVID-19 or sepsis. We show here that both diseases present with endothelial injury related to the degree of inflammation.

2. Methods

2.1. Study design and ethics statement

This is a retrospective cohort study, with patients enrolled at the Emergency Department of the Hospital das da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil. It is a tertiary hospital designated to assist only patients with severe acute respiratory syndromes (SARS) during the COVID-19 pandemic.

The protocol was approved by the institutional Ethics Committee, under number CAAE: 30417520.0.0000.0068. All patients, or their legal representatives, signed the informed consent.

2.2. Enrollment criteria

We enrolled consecutive patients admitted to the Emergency Department with a diagnosis of severe COVID-19 or sepsis.

COVID-19 was diagnosed by a positive SARS-CoV-2 RT-PCR test in nasopharyngeal and throat swabs and by typical chest CT-scan findings. All enrolled patients had hypoxemia (as defined by peripheral oxygen saturation less than 92%) and were using supplemental oxygen. All of them were classified as severe cases by WHO guidelines (WHO, World Health Organization, 2021).

Sepsis was diagnosed using the Sepsis-3 criteria (Singer et al., 2016). We selected only patients who died from sepsis to compare with the patients who died from COVID-19. All of the septic patients had a negative result for the SARS-Cov-2 RT-PCR test.

Patients under 18 years old, pregnant women, and patients in end-of-life protocols were not included.

2.3. Initial assessment

All patients were evaluated and treated according to the Institution's protocol. After emergency department assessment, they were transferred to hospital yards or intensive care units according to each severe state.

On the first day of hospitalization, patients were submitted to chest tomography, routine laboratory tests, and an additional 20-ml blood sample was collected in a tube with trisodium citrate that was immediately sent to the laboratory. The whole blood was separated by centrifugation, and small aliquots of leukocytes and plasma were stored at -80oC until the measurements.

2.4. Clinical outcomes and study groups

Clinical, radiological, and routine laboratory tests were obtained from electronic medical records.

Initially, we classified patients into two groups: SEPSIS ($n = 21$) comprised the patients diagnosed and died with sepsis and bacterial infection; the SEVERE ($n = 24$) group comprised patients with COVID-19 diagnosis who were intubated and died during hospitalization. In addition, there was a third group, called MILD ($n = 31$), formed by COVID-19 patients who used supplementary oxygen but not mechanical ventilation and survived.

2.5. Cytokines measurement

On the day of the experiments, plasma samples were thawed, and inflammatory mediators (INF-γ, TNF-α, and IL-10) were measured by Human Cytokine/Chemokine Magnetic Bead Panel protocol from the Milliplex® (Catalog No: HCYTOMAG-60K), according to the manufacturer's instructions. In addition, TF, vWF, and E-Selectin were measured by ELISA protocol from the MyBioSource® (Catalog No: MBS033519 for TF, MBS773983 for vWF, MBS762424 for E-Selectin), according to the manufacturer's instructions.

2.6. Statistics

Continuous variables were submitted to the Shapiro-Wilkins test for normality. When distribution was normal, Student's *t*-test was used to compare the means, and results were presented as mean ± standard error of the mean (SEM). The Kruskal Wallis test with Dunn's correction was used when data were not normally distributed and presented as median and interquartile range. For categorical variables, the chi-square test was performed.

The relationship between cytokines and endothelial injury markers was performed by Spearman correlation.

The significance level was set at 0.05.

All statistical analyses were performed with R software (version 4.0.3 for MacOS).

3. Results

3.1. SEVERE COVID-19 and sepsis

We initially compared patients who died from SEVERE COVID-19 or sepsis.

There was no difference between the septic and COVID-19 patients regarding age, previous diseases, and laboratory markers (Table 1).

We further evaluated the inflammatory cytokines in these two groups.

As observed in Fig. 1, there was no difference in circulating INF-γ and TNF-α levels between these two groups. On the other hand, serum levels of IL-10 were higher in septic patients when compared to the COVID-19 patients.

Regarding the markers of endothelial injury, we could observe

Table 1
Clinical and demographic characteristics of SEVERE COVID-19 and Sepsis patients.

	SEVERE COVID-19 n = 24	Sepsis n = 21	*p*-Value
Age	74.0 ± 8.6[b]	75.6 ± 9.6[b]	0.559
Hemoglobin	12.44 ± 2.28[b]	11.56 ± 2.00[b]	0.177
Leukocytes	9.22 ± 4.64[b]	11.84 ± 7.10[b]	0.159
Neutrophils	7.87 ± 4.11[b]	9.85 ± 6.56[b]	0.239
Lymphocytes	0.95 ± 0.50[b]	1.09 ± 0.75[b]	0.485
CRP	179.5 (143.0–264.3)[c]	128.0 (56.0–237.0)[c]	0.169

[a] Statistical test used: chi-square..
[b] Data are presented as mean ± SD; statistical test used: Students' *t*-test.
[c] Data are presented as median and interquartile range; statistical test used: Kruskal-Wallis with Dunn's post-test.

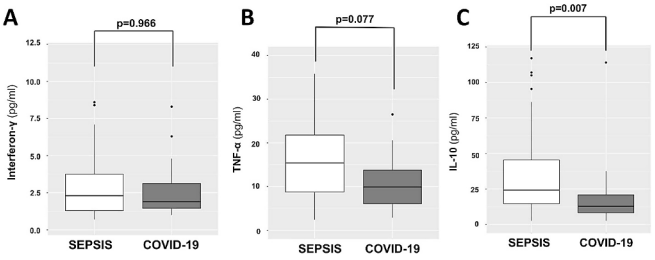

Fig. 1. Cytokines in Sepsis and SEVERE COVID-19. The cytokines profile was similar in patients who died from sepsis or COVID-19. The only exception was IL-10 (Panel C), which was higher in septic patients.

higher levels of E-Selectin in septic patients compared to COVID-19 patients. However, circulating levels of TF and vWF were not different between these two experimental groups (Fig. 2).

3.2. MILD and SEVERE COVID-19

We further evaluated the endothelial dysfunction markers in COVID-19 patients classified as mildly or severely ill.

Initially, we observed that both groups were very similar in demographic and clinical variables. There was no difference in age or previous diseases, although a higher serum level of creatinine and C-reactive protein (CRP) were found in the SEVERE group, compared to MILD. Notwithstanding, except for renal function and the low-grade systematic inflammation marker, no other laboratory test differs between the experimental groups (Table 2).

Higher levels of TNF-α and IL-10 were detected in patients in the

Table 2
Clinical and demographic characteristics of MILD and SEVERE COVID-19 patients.

	SEVERE COVID-19 n = 24	MILD COVID-19 n = 31	*p*-Value
Age	74.0 ± 8.6[b]	70.1 ± 6.6[b]	0.070
Male	14 (58.3%)[a]	17 (54.83%)[a]	0.795
Arterial hypertension	15 (62.5%)[a]	20 (64.51%)[a]	0.877
Diabetes	11 (45.83%)[a]	8 (25.8%)[a]	0.121
CAD	4 (16.66%)[a]	3 (9.67%)[a]	0.440
Obesity	4 (16.66%)[a]	2 (6.45%)[a]	0.228
Tabagism	5 (20.83%)[a]	9 (29.03%)[a]	0.488
Hemoglobin	12.44 ± 2.28[b]	12.90 ± 2.16[b]	0.458
Leukocytes	9.22 ± 4.64[b]	9.08 ± 3.93[b]	0.905
Neutrophils	7.87 ± 4.11[b]	7.15 ± 3.65[b]	0.490
Lymphocytes	0.95 ± 0.50[b]	1.19 ± 0.53[b]	0.087
Creatinine	1.69 ± 1.45[b]	1.04 ± 0.54[b]	0.045
CRP	179.5 (143.0–264.3)[c]	89.7 (42.6–153.8)[c]	<0.001

[a] Statistical test used: chi-square.
[b] Data are presented as mean ± SD; statistical test used: Students' *t*-test.
[c] Data are presented as median and interquartile range; statistical test used: Kruskal-Wallis with Dunn's post-test.

SEVERE group, compared to the MILD one, but there was no difference in serum level of INF-γ (Fig. 3). Circulating TF was also higher in the severely ill patients, while the other endothelial dysfunction markers (vWF and E-Selectin) did not differ between groups (Fig. 4).

3.3. Relationship between cytokines and endothelial injury markers

To better understand the mechanisms of endothelial injury, we sought the relationship between inflammatory and endothelial injury

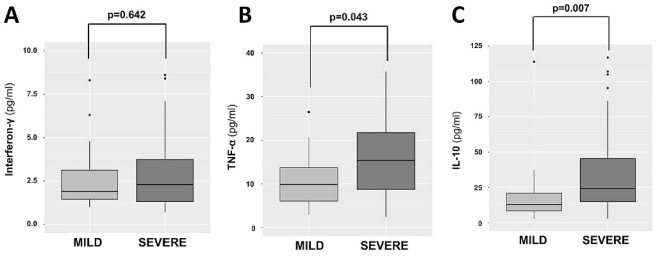

Fig. 3. Cytokines in MILD and SEVERE COVID-19. SEVERE COVID-19 patients present higher plasma levels of TNF-α (Panel B), and IL-10 (Panel C) compared to MILD patients. However, other cytokines were not different between these two groups.

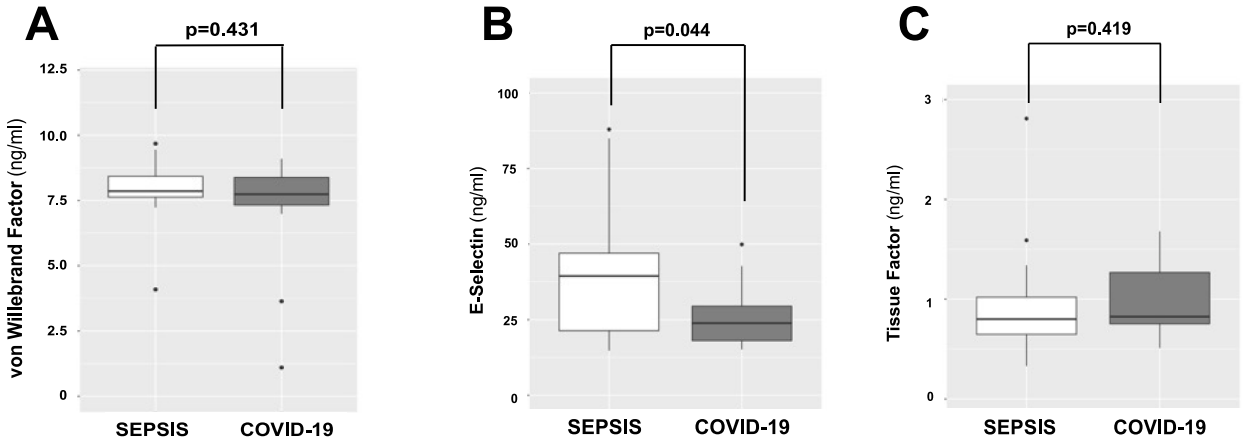

Fig. 2. Endothelial dysfunction markers in Sepsis and SEVERE COVID-19. When compared to septic patients, SEVERE COVID-19 patients present lower plasma levels of E-Selectin (Panel B) and similar levels of vWF and TF (Panels A and C).

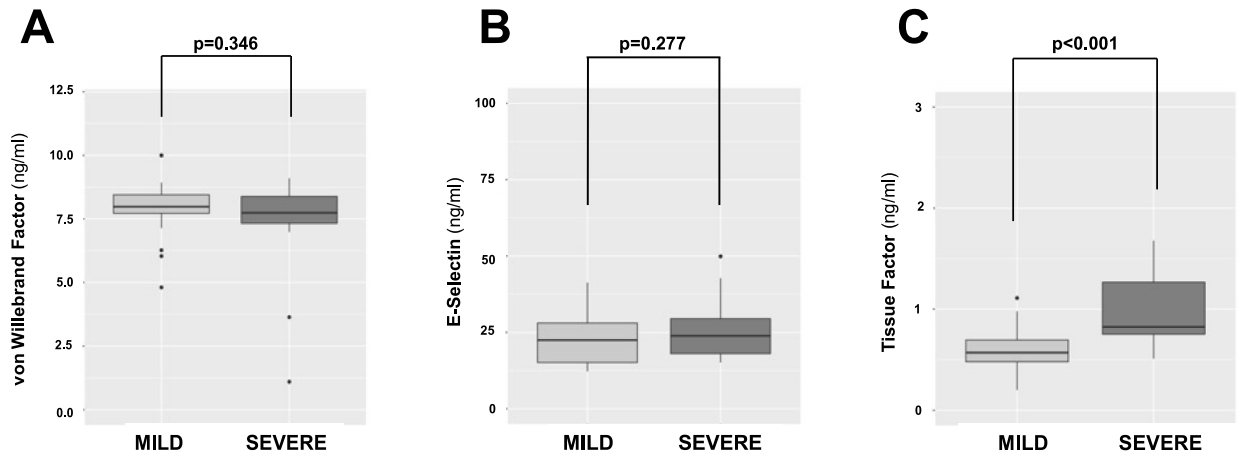

Fig. 4. Endothelial dysfunction markers in MILD and SEVERE COVID-19. Severely ill COVID-19 patients showed higher plasma levels of TF (Panel C) and similar levels of vWF and E-Selectin when compared to MILD COVID-19 patients.

markers.

As observed in Table 3, there was no clear relationship between cytokines and endothelial injury markers among the three studied groups.

Nevertheless, some important correlations were found. Particularly intriguing are the positive relationship between INF-γ with TF in SEVERE COVID-19 patients and the negative relationship between IL-10 and vWF in this same group of patients.

4. Discussion

There is evidence showing that COVID-19 may affect endothelial function. This study shows that COVID-19 and septic patients present a similar profile of inflammatory and endothelial dysfunction markers.

Initially, we compared the inflammatory reaction in septic and COVID-19 patients. There was no difference in circulating white blood cell counts, CRP, and cytokines between these two groups of patients. The only exception was decreased levels of IL-10 in COVID-19 patients.

IL-10 is a cytokine mainly produced by activated TH2 lymphocytes, monocytes, and epithelial cells. It suppresses the interferon synthesis and other TH1 cytokines, such as IL-12 and IL-18; therefore, it is considered an anti-inflammatory cytokine (Moore et al., 1993).

IL-10 plasma levels are elevated in septic patients and correlate with proinflammatory cytokine levels (like TNF-α) and unfavorable outcomes (Marchant et al., 1995). Interestingly, high plasma IL-10 levels have also been reported in COVID-19 patients. In a review that evaluated 27 studies comprising 3939 COVID-19 patients in China, high IL-10 levels were reported in almost half of them (Wang et al., 2020).

Table 3
Relationship between cytokines and endothelial injury markers.

	IFNG		TNF		IL10	
	Rsq	p	Rsq	p	Rsq	p
SEPSIS						
Selectin	**0.508**	**0.022**	0.347	0.133	0.032	0.895
TF	0.337	0.146	**0.460**	**0.041**	−0.239	0.311
vWF	0.116	0.627	0.077	0.748	−0.041	0.862
MILD COVID						
Selectin	0.088	0.639	**0.400**	**0.026**	**0.500**	**0.004**
TF	0.263	0.153	0.148	0.427	0.330	0.070
vWF	0.070	0.707	**0.365**	**0.043**	**0.377**	**0.036**
SEVERE COVID						
Selectin	0.115	0.567	0.162	0.421	0.292	0.140
TF	**0.447**	**0.019**	0.283	0.153	**0.469**	**0.014**
vWF	−0.322	0.102	0.175	0.383	**−0.507**	**0.007**

All values in bold are statistically significant.

Here we report that IL-10 levels are higher in septic patients than in COVID-19 patients. This finding suggests that bacterial infection may lead to a more consistent anti-inflammatory response. However, since we included only patients who died, it is not possible to evaluate the IL-10 role as a modulator of inflammation in these diseases.

We further analyzed the endothelial injury markers in septic and COVID-19 patients.

E-Selectin is a cell adhesion molecule expressed by endothelial cells activated by cytokines. It has an essential role in recruiting leukocytes to the inflammation site, helping to eliminate the potential invading pathogens (Leeuwenberg et al., 1992). E-Selectin blood levels rise early during sepsis, and it is suggested to be used as a severity marker for the disease (Martin-Fernandez et al., 2020). High circulating E-Selectin levels have also been reported in COVID-19 patients and are correlated with the disease severity (Smadja et al., 2020).

In this study, we detected higher E-Selectin levels in septic patients compared to COVID-19 patients. A possible explanation for this finding is the necessity to phagocytize the invading pathogens in septic patients, leading to a more robust chemoattractant response.

Our next step was to compare the mildly and severely ill COVID-19 patients.

Firstly, a higher level of CRP in SEVERE COVID-19 patients compared to the MILD group can be observed. CRP is a sensitive marker for low-grade systematic inflammation, and it is associated with a higher risk of developing ischemic stroke, peripheral arterial disease, myocardial infarction, and coronary heart disease (Ridker et al., 1998). The higher levels in the SEVERE group indicate that these patients have a basal low-grade systematic inflammation, which cannot be observed in the MILD patients.

Furthermore, we found higher TNF-α, IL-10, and TF levels in severely ill COVID-19 patients, compared to the MILD group. This is an interesting finding, and it is in accordance with other authors (Rosell et al., 2021); however, this issue is not consensual and more research should be performed to better understand this signaling pathway.

TF is a protein expressed in the subendothelial tissue and, together with factor VIIa, is responsible for activating the extrinsic pathway of coagulation (Mackman, 1995). TF expression has been reported to be enhanced by inflammatory cytokines, and TF has been reported to be overexpressed in septic patients (Sungurlu et al., 2020). TF has also been found in high levels in COVID-19 patients (Rosell et al., 2021). This finding may, in part, explain the high incidence of thrombotic phenomena in COVID-19 patients (Klok et al., 2020).

Although we could observe increased levels of inflammatory and endothelial injury markers in septic and COVID-19 patients, there was no clear relationship between them.

Nevertheless, some interesting findings need to be discussed. First, there was a positive and significant relationship between INF-γ and TF in severe COVID-19 patients. This finding may suggest that interferon secretion initiated by the antiviral response may also trigger the thrombotic events observed in these patients. Second, in this same group of patients, there was a negative relationship between IL-10 and vWF, suggesting that an anti-inflammatory response may be protective to the endothelium.

This study has some limitations. First, it was conducted in just one center, with few patients. We did not include a control group because our main objective was to compare sepsis and COVID-19 and not determine whether these diseases could affect the endothelium. Moreover, we did not measure a large number of inflammatory markers and cytokines. We opted to limit the number of markers to avoid false-negative correlations. We reasoned that if we measured dozens of cytokines, it would be complicated to interpret the results.

Therefore, despite all these limitations, we report here that COVID-19 and septic patients have a similar pattern of cytokines and endothelial dysfunction markers. These findings highlight the importance of endothelium dysfunction in COVID-19 and suggest that endothelium should be better evaluated as a therapeutic target for the disease.

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CRediT authorship contribution statement

LTH, Formal analysis; ADMV, MCSM and AASP, Data curation; TML, SKKA, HVB, DFB and CLM, Methodology; GS, RAB, JFM, JCA, LOM, Clinical data collection; LMG, Statistical Analysis; HPS, Conceptualization, Writing - review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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