

Title page

THE ROLE OF IMMUNOMODULATORY THERAPY WITH OXIRIS IN COVID 19 WITH RENAL FAILURE AND IMMUNE DYSFUNCTION. IMPACT ON RESPIRATORY OUTCOME AND MORTALITY.

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ABSTRACT

"PURPOSE: The main objective of this study is to evaluate the impact of hemoadsorption on the elimination of inflammatory mediators.

METHODS: A prospective, multicenter, pragmatic clinical trial was conducted between March 2020 and February 2022 to explore the immunomodulatory response, demographic and clinical characteristics of individuals with COVID-19 admitted to the ICU with severe acute respiratory failure and in need of CRRT with Oxiris® with or without AKI.

RESULTS: A total of 64 patients were analyzed. Statistically significant differences were found between pre- and post-CRRT in the levels of inflammatory markers: CRP, fibrinogen, D-dimers 6000(1984,5-27.750) vs 2700(2119,5-6145), interleukin-6 317,5(98,5-593,25) vs 180(16-300), and clinical parameters: PEEP, heart rate, temperature with an improvement in organ failure according to the SOFA and APACHE II scales. The decrease in D-dimers was significant (55%). The effect of immunomodulatory therapy was indicated by a statistically significant difference between cases and controls in the clearance of D-dimer, and PAFI.

CONCLUSION: The results suggest that CRRT combined with hemoadsorption is a useful and safe technique in the management of AKI in COVID-19 patients. The therapy is associated with a decrease in biochemical and clinical inflammatory parameters.

KEYWORDS: Hemoadsorption, continuous renal replacement therapy, respiratory failure, acute kidney injury, COVID 19, Oxiris®.

Abbreviations

- CRRT: Continuous renal replace treatment;
- AKI: Acute kidney injury
- CRP: C-reactive protein
- CRRT: continuous renal replacement therapy.
- ARF: acute respiratory failure
- RRT: renal replacement therapy
- CVVHDF: continuous venovenous hemodiafiltration
- SCUF: Slow continuous ultrafiltration
- PaFi : PaO₂/FiO₂ index
- ARDS: Acute Respiratory Distress Syndrome
- ICU: Intensive care unit
- PEEP Positive end-expiratory pressure
- APACHE: Acute Physiology And Chronic Health Evaluation
- SOFA: Sequential Organ Failure Assessment

Main body

INTRODUCTION

On March 11th 2020, the World Health Organization (WHO) declare COVID-19 disease a pandemic. The immune dysfunction triggered by inflammatory cascades and immunosuppressive pathways is similar to that of other respiratory viruses like SARS and MERS(1)(2). This leads to an aberrant adaptive immune response and multi-organ dysfunction, being related to the severity and prognosis of the disease.

The inflammatory cascade of COVID-19 disease affects multiple systems, with the renal clearance system being the most affected (3)(4). Patients with respiratory failure have a prevalence of ARDS of up to 41.8%. The incidence of acute renal failure in ICU patients ranges from 5% to 20% . For ICU patient with COVID-19, the incidence of AKI is between 4.5% and 7% (5). The pathophysiology of COVID-19 and its proinflammatory state (1) justifies the use of immunomodulatory therapies, such us corticosteroids (6) and Tocilizumab (7). However, these therapies can also lead to serious and long-lasting side effects, such as infections or treatment reversal.

In light of this, extracorporeal immunomodulation, such as hemoadsorption and endotoxin removal, is being considered as a potential short-acting and effective therapy for life-threatening diseases (8)(9)(10). Hemoadsorption has previously been used in several other medical conditions, including sepsis (11,12), cardiac surgery (13) and in CRS after oncohematological therapies (CAR-T)(14). Endotoxins and proinflammatory mediators will be released in the COVID-19 infection. The Oxiris® hemoadsorptive cartridge is one such device that has been shown to effectively adsorb cytokines and endotoxins (15).

The main hypothesis is that COVID-19 patients who receive Oxiris® therapy will have a higher clearance of inflammatory parameters compared to those who do not receive the therapy(16). This is a crucial aspect of the study, as understanding the ability to modify the systemic inflammatory response in COVID-19 patients is key to developing more effective treatments for the disease.

AN69 Oxiris® cartridge is more effective in removing endotoxins than the conventional AN69 ST membrane, improving quality of the filtered solution (17). The increased adsorptive capacity is achieved through the use of two additional layers in the membrane: a layer of polyethylenimine and a layer of heparin. Polyethylenimine and heparin are biologically active materials that selectively bind to endotoxins, allowing for more efficient removal of these toxic substances.

MATERIAL AND METHODS:

We conducted a prospective, multicenter, pragmatic clinical trial involving individuals with COVID-19 who were admitted to the ICU due to severe acute respiratory failure caused by the

virus. The study's inclusion criteria consisted of patients aged 18 years and above, with confirmed microbiological diagnosis of COVID-19 and presenting severe acute respiratory failure requiring invasive mechanical ventilation and showing a hyperinflammatory state (as defined by persistent fever and C-reactive protein, CRP >15). Patients under 18 years of age, those unable to undergo therapy, those receiving less than 24 hours of therapy, or those not meeting the aforementioned conditions were excluded from the study (*Figure 1*).

The study's patient selection method was based on convenience, with the treating professional's decision and therapy availability determining the assignment of patients to either the "exposed" or "unexposed" group. Acute kidney injury was classified based on the AKI category (*Table 1. Supplementary*). "Exposed" and "unexposed" patients were matched in a 1:1 ratio through pairwise matching, considering baseline characteristics and the degree of acute renal injury they presented, AKI I-II, or AKI III, with no significant differences between the two groups (*Figure 1*). "Exposed" patients received both conventional immunomodulatory therapy (such as corticosteroids or tocilizumab) and hemoadsorptive therapy (Oxiris®), for a duration of 24 hours per session. On the other hand, "unexposed" patients received only conventional immunomodulatory therapy. For both "exposed" and "unexposed" patients who required RRT (renal replacement therapy), the procedure was carried out following the unit's protocol (*Supplementary material, RRT protocol*).

The study was conducted in the intensive care units of two tertiary hospitals: the Regional Hospital of Malaga and the 12 de Octubre University Hospital in Madrid. The study covered a two-year follow-up period, from March 2020 to February 2022, during which several COVID-19 variants were reported, including the alpha, delta, and omicron variants, as well as sub-variants BA.1.1, BA.2, BA.4, and BA.5 (18).

The main hypothesis was that the use of continuous renal replacement therapy (CRRT) combined with hemoadsorption (Oxiris®) in patients with severe acute respiratory failure (ARF) caused by COVID-19 may have an impact on the systemic inflammatory response. The primary objective of the study was to describe the ability to modify the systemic inflammatory response in COVID-19 patients based on the clearance of inflammatory mediators, comparing conventional immunomodulatory treatment versus hemoadsorptive therapy (10)(19). As secondary objectives, the study aimed to collect clinical-analytical data on the hyperinflammatory state of these patients, investigating the effects of therapy on associated thrombotic phenomena, renal failure, clinical evolution, ICU and hospital length of stay, mortality, and demographic and epidemiological characteristics of the patients (*Table 1*). Overall, the study aimed to make a significant contribution to the understanding of the treatment of COVID-19 patients with severe acute respiratory failure and a hyperinflammatory state.

Variables were collected within the first 96 hours of patient recruitment, during which acute respiratory failure and a hyperinflammatory state were assessed. For the "exposed" group, the highest value within the first 48 hours before the start of therapy ("pre-therapy") was recorded and compared with the highest value within the 48 hours following the therapy ("post-therapy"). In contrast, for the "unexposed" group, which did not undergo intervention, the

highest value within the first 96 hours from recruitment was considered (*Table 1. Supplementary material*). Patients were classified based on the presence or absence of renal failure, using the AKI-KDIGO criteria. In patients with severe AKI (AKI III), the primary goal of the RRT (renal replacement therapy) was to maintain homeostasis. For patients with AKI I-II who underwent RRT, the primary purpose was immunomodulation or achieving a target ultrafiltration by slow continuous ultrafiltration (SCUF). All RRT procedures were initiated using continuous venovenous hemodiafiltration (CVVHDF) and were managed following a protocol with a citrate anticoagulation system (20).

Patients also received supportive treatment, antimicrobial therapy if necessary, corticosteroids, and antiviral therapy following established recommendations. The presence of infection was coded as "yes" when compatible isolates were identified within the 96 hours before or after the initiation of therapy for the "exposed" group, or within the first 96 hours of ICU admission for the "unexposed" group.

A comprehensive statistical analysis was performed using SPSS® version 26.0 and Epidat 3.0 software. To assess the normality of quantitative data, both histogram analysis and the Kolmogorov-Smirnov test were applied. Continuous variables that followed a normal distribution were expressed as mean and standard deviation, while non-normally distributed variables were described using the median and interquartile range. Categorical variables were presented as absolute and relative frequencies. The significance of differences between categorical variables was assessed using either the Chi-square test or Fisher's exact test, with a bilateral significance level set at 5%. For comparing means, appropriate tests such as Student's t-test or its nonparametric equivalent, the Mann Whitney U and Wilcoxon test, were applied. P-values < 0,05 or $p < 0,003$, if multiple testing was adjusted ($p < 0,05/15$), were considered statistically significant. The degree of association of quantitative variables was evaluated using Spearman correlation and binary logistic regression methods. The guidelines CONSORT and TREND were followed for the preparation of the manuscript (21).

The ethics committees of both hospitals approved the use of extracorporeal deputation therapies in critically ill patients (CEI 25/07/2019), as documented in the Dialyreg registry(22). Informed consent was obtained from all patients included in the study.

RESULTS:

64 patients were analyzed, with 32 patients in the "exposed" and 32 patients in the "unexposed" group; Within each group, 22 patients presented with AKI III, and 10 patients had AKI I-II. (*Figure 1*). The sample had a mean age of 64 years (10,07). The majority of the patients were male (73%), and the most commonly reported comorbidities were arterial hypertension (56,3% and 49%), obesity (mean body mass index of 28,9 (4,4)), diabetes (34,4% and 37%), and immunosuppression (22%). However, no statistically significant differences were found between the baseline characteristics of the sample (*Table 1*). The average length of stay in the ICU was 12 days (IQR 6-18), and the overall hospital stay was 23 days (IQR 6-30). The median number of days from symptom onset to hospital admission was 7 days (IQR 5-8) and to ICU admission 10 days (IQR 7-13). Mechanical ventilation was initiated on the same day of admission to the ICU, and renal replacement therapy was started 3 days (IQR 1-7) after admission.

PRIMARY OBJECTIVE: IMMUNOMODULATION

Regarding the immunomodulatory impact of Oxiris therapy, the study analyzed clinical and biochemical data along with severity scales before and after therapy (*Table 2*). A statistically significant two-tailed difference ($p < 0,003$ adjusted for multiple testing) was observed in the analysis before and after therapy, indicating changes in various inflammatory parameters such as C-reactive protein ($p = 0,001$), fibrinogen ($p = 0,001$), D-dimers ($p = 0,001$), ferritin ($p = 0,021$), and Interleukin-6 ($p = 0,002$). Additionally, clinical parameters including the evolution of PEEP ($p = 0,001$), heart rate ($p = 0,001$), temperature ($p = 0,000$), and severity scales such as APACHE II ($p = 0,001$) and SOFA ($p = 0,002$) also showed significant differences before and after therapy. However, no significant difference was found in the reduction of vasoactive support after therapy with previous doses of noradrenaline of 0.1 mcg/kg/min (0-0,3) and subsequent doses of 0.1 mcg/kg/min (0-0,1).

The immunomodulatory therapy's effectiveness was supported by the discovery of a statistically significant difference in the "exposed" group compared to their matched "unexposed" counterparts regarding the clearance of inflammatory parameters (*Table 3*). Notably, D-dimer ($p = 0,001$), and PAFI ($p = 0,001$) showed substantial differences between the two groups. Specifically, the study revealed that the median D-dimer level before therapy was 6.000 (1.984,5-27.750), and after treatment, it decreased to 2.700 (2.119,5-6.145), representing an impressive 55% reduction from the pre-therapy value. Regarding the analysis of qualitative variables and their degrees of association, a strong positive correlation was observed between the pre and post-therapy PCR variable with ferritin (Rho 0,65 $p < 0,007$), and heart rate (Rho 0,49 $p < 0,006$) variables. Additionally, a strong negative correlation was found between the PCR variable and lymphocytes (Rho -0,5 $p < 0,005$).

SECONDARY OBJECTIVES

As secondary objectives, the characteristics of therapy, respiratory status, associated renal injury and thrombotic phenomena were described. The median effluent dose of Oxiris® therapy was found to be 33ml/kg/h (30-40). The anticoagulation system used in 100% of cases was citrate, and no citrate accumulation was observed. On average, patients required 1.09 (0,29) Oxiris treatments with a mean of 2.9(2) hemofilter sets. No complications were evidenced during therapy, without complications compared to the conventional anticoagulation system. Severe respiratory failure due to COVID-19 was associated with acute kidney injury in 66% of cases based on the AKI classification. The primary indication for CRRT was AKI III (59%), followed by the need for hemoadsorptive treatment (37,5%).

The report indicates that 22% of the patients had some form of infection: 11% pulmonary infections, 5% bacteremia, and 2% urinary tract infections. When examining the case and control groups separately, 25% of the case patients had infections (6% with pulmonary infections), while 20% of the control patients had infections (16% with pulmonary infections). In the study sample, various microorganisms were isolated from both pulmonary and extrapulmonary sites, where antibiotic treatment was adjusted based on isolates or suspected infections. A large majority of patients received immunomodulatory therapies, with 67% receiving Tocilizumab and 76% receiving corticosteroids, showing no differences between the

groups. Other therapeutic options, such as remdesivir, hydroxychloroquine, Interferon, Kaletra, and hyperimmune plasma, were administered alongside standard treatments. These therapies were used alone or in combination to effectively manage the patients.

Thrombosis was detected in 36% of the cases and 27% of the controls, making up 30% of the entire sample, with no significant differences between the two groups (*Table 3. Supplementary material*). The thrombotic events observed included arterial thrombosis (5,4%), deep vein thrombosis (9%), and thromboembolic disease (15,6%) within the entire group. At the onset of the disease, the majority of the sample received thromboprophylaxis at usual or intermediate doses (69%), while 30% were administered anticoagulation. Upon detecting thrombotic phenomena or elevated D-dimers during the critical stages of the disease, therapy was adjusted to anticoagulation in 52% of patients following current recommendations. Hemorrhagic phenomena were reported exclusively in the case group, affecting 15.5% of patients. The analysis of the prothrombotic state in patients with documented thrombosis versus those without did not reveal any significant differences.

All patients developed severe ARDS (Acute Respiratory Distress Syndrome) and required mechanical ventilation, neuromuscular blockade, and prone decubitus positioning, with a median of 2 cycles (2-2,75). The worst PaFi (PaO₂/FiO₂ index) observed in the case group was 85. Before therapy, the mean PAFI in the case group 157,26 (65,30) and control group 124,4 (39) were similar. The overall mortality in the sample was 47%, with no significant differences observed between the "exposed" and "unexposed" groups. Regarding the characteristics of the sample and factors associated with mortality, logistic regression analysis independently associated acute kidney injury as independent factor of mortality (Odds ratio 12,65 CI 95% 2,55-62,65).

DISCUSSION

Hemoadsorptive therapy has emerged as a potentially effective short-acting treatment for life-threatening diseases. This study focused on patients with severe respiratory disease, hyperinflammatory states, and acute kidney injury (24). The results demonstrated a significant decrease in key acute phase reactants, notably Interleukin-6 ($p = 0,002$), C-reactive protein ($p < 0,001$), and especially D-dimers ($p < 0,005$). Additionally, a reduction in the severity scales, APACHE II, and SOFA, was observed. Although these scales may not be perfect for this patient population, the reduction in COVID-19 patients treated with hemoadsorptive therapy aligns with findings from previous studies (23)(24)(25).

Initially studied for cytokine elimination in proinflammatory states and septic patients (11)(26)(27)(12,28) hemoadsorptive therapy has garnered increasing interest. While the results should be interpreted cautiously, evidence from clinical trials and multicenter registries (29), consistently indicates reductions in inflammatory markers. As Villa and colleagues demonstrated in their study (30), the use of extracorporeal blood purification therapies may attenuate systemic inflammation, preventing or mitigating multiple organ dysfunction. They found a significant reduction in IL-6 levels, which was associated with an improvement in hemodynamic and respiratory function. This therapy was found to be feasible and not associated with adverse events.

The strong correlation between elevated C-reactive protein and leukopenia, hyperferritinemia, and tachycardia reflected the proinflammatory state of the patients, which was consistent with what has been previously described in the disease's pathophysiology. This study demonstrated an immunomodulatory effect with statistically significant improvements in clinical inflammatory parameters, such as temperature and heart rate, aligning with previous research and supporting the therapy's immunomodulatory effect compared to pre-therapy values and between the "exposed" and "unexposed" groups.

Additionally, these improvements were also observed in respiratory function, as evidenced by the post-therapy values of PAFI and compliance. It is important to note that these improvements may not solely be attributed to the therapy, but rather the result of a combination of interventions. Furthermore, the study revealed significant differences in the improvement of respiratory function and clinical inflammatory parameters between the groups (2,9,23,31)

The impact of therapy on inflammatory markers was particularly notable, with a significant decrease of 55% observed in D-dimer levels before and after the therapy. This study is the first to demonstrate a statistically significant decrease in D-dimer levels, setting it apart from previous studies with Oxiris® and Cytosorb®, which did not find significant effects(32). D-dimers have been described as a crucial marker of the prothrombotic state, especially in the context of COVID-19. Elevated D-dimer levels, reaching 3 to 4 times the upper limit in the early stages of the disease, have been associated with a worse prognosis and increased activation in patients with underlying comorbidities (33)(34). In fact, elevated D-dimer levels have been identified as an independent factor for mortality (35).

Regarding therapy and the presence of renal failure, the prevalence of renal failure in critically ill patients in the ICU, both in general and specifically in COVID cases, is not clearly described and varies from 5% to 20% (4). In this study, a prevalence of 66% was reported, consistent with some series (30). Significant differences were observed in the therapy's recommendation depending on whether patients had AKI III or AKI I-II (*Table 4*). These differences may partially explain the mortality associated with the sample. In this study, the overall mortality rate was 47%, which is consistent with findings from other studies. The presence of renal injury was identified as an independent factor for mortality (OR 12.65 CI of 2.55-62.65). Notably, patients with AKI III had a substantially higher mortality rate of 62% compared to those with AKI I-II at 18%. This highlights the significant impact of acute renal failure severity on patient outcomes. Similarly, as seen in previously described studies, patients with SARS-CoV-2 and severe respiratory failure had a mortality rate of 30-50%, which increased to 60% when associated with acute renal failure (3,30).

The use of citrate anticoagulation systems offers several advantages, including a significant decrease in set coagulation, longer set half-life, and reduced unnecessary patient contact time. In this study, no complications were observed with the use of citrate, indicating its effective and safe utilization. Our previous data from the DiallyReg(22) registry demonstrated that set coagulation was 26% with citrate compared to 47% with heparin (p 0,005). The median major set duration was 55 hours (24-72) with citrate, compared to the 23 hours (12-48) with heparin (p < 0,05). Additionally, the use of citrate allowed dynamic and individualized adjustments to

the patient's needs, with a higher proportion of patients receiving personalized treatment (76% with citrate versus 58% with heparin, $p < 0,05$)(22).

Weaknesses Our study includes a heterogeneous sample, comprising patients with different criteria, such as hyperinflammation and renal failure (AKI III). The non-randomized and pair matching model used for sample selection may introduce selection bias, potentially leading to the initiation of therapy in the most severe patients with hyperinflammatory states and renal failure (66%), a factor previously associated with increased mortality in similar series. The therapy's specificity and its use in a specific subpopulation contribute to a limited sample size, despite being the largest reported in this patient subgroup. Consequently, caution is necessary when interpreting the results and drawing conclusions due to the small sample size. Further studies in this direction are warranted.

Strengths This study stands out as a prospective, multicenter pragmatic clinical trial involving a large series of patients undergoing a novel therapy. The use of a 1:1 pair matching "unexposed" group with similar baseline characteristics enhances the internal validity of the study, contributing to its robustness and reliability. Additionally, the study is continuously monitored through a prospective, multicenter registry (DialyReg) facilitated by the RedCap® platform, adding to its methodological rigor and data quality (20)(22) Pragmatic clinical trials play a crucial role in comprehending the immunomodulatory effects of therapies, not only in COVID-19 but also in other conditions like chemotherapy and cytokine release syndrome. The study's emphasis on COVID-19 carries significant implications, providing valuable insights for clinical practice and guiding future research to develop more effective treatments for these patients.

CONCLUSIONS:

Hemoadsorptive therapy with Oxiris in this study shows an immunomodulatory effect, with statistically significant reduction of inflammatory and clinical parameters, improvement in respiratory parameters and prognostic scales of severity. CRRT associated with hemoadsorption is an useful and safe technique in the management of systemic inflammatory response with or without association to acute renal failure in COVID-19 patients.

FIGURES AND TABLES

Figure 1. Participant Flow.

<i>Table 1. Patient baseline characteristics.</i>		
	Exposed (n= 32)	Unexposed (n= 32)
MALE (percentage)	24 (75%)	32 (71,9%)
FEMALE	8 (25%)	9 (28%)
AGE (years old)	59,9 (9,39)	57,06 (10,50)
BODY MASS INDEX (BMI)	30,30 (4,26)	27,88 (4,29)
ARTERIAL HIPERTENSION	18 (56,3%)	16 (50%)

DIABETES MELLITUS	11 (34,4%)	12 (37,5%)
ASTHMA	4 (12,5%)	0 (0%)
STROKE	0 (0%)	1 (3%)
PNEUMOPATHY	1 (3%)	1 (3%)
IMMUNOSUPPRESSION	8 (25%)	8 (25%)
COPD	4 (12,5%)	1 (3%)
NAD>0,3MCG/KG/MIN	14 (43,8%)	12 (37,5%)
DOBUTAMINE	3 (9,5%)	1 (3%)
INFECTION	8 (25%)	6 (20%)
PULMONARY INFECTION	2 (6%)	5 (16%)
RENAL INJURY	22 (69%)	23 (72%)
THROMBOSIS (TVP/TEP/ICTUS)	8 (36%)	8 (27%)
CORTICOSTEROIDS	25 (78%)	23 (72%)
TOCILIZUMAB	23 (72%)	19 (60%)
ECMO	1 (3%)	3 (9,4%)
MORTALITY	15 (47%)	15 (47%)
APACHE II score	18,06 (6,50)	13,64 (4,39)
SOFA score	6,97 (2,62)	6,59 (2,3)

Table 1. Patient baseline characteristics. Comorbidities presented as percentages. Pneumopathy includes pulmonary fibrosis, in addition to COPD and asthma. Immunosuppression includes transplant recipients, patients with oncohematologic disease, HIV, and those with autoimmune diseases on chronic corticosteroid use. COPD stands for chronic obstructive pulmonary disease, and NAD refers to noradrenaline at a dosage of 0,3 micrograms per kilogram per minute.

Table 2. Clinical and biochemical parameters and severity scales before and after therapy in "exposed" patients

	PRE-THERAPY	POST-THERAPY	P
BIOCHEMICAL PARAMETERS			
CRP (C-Reactive Protein, mg/dl)	16,27 (10,99)	10,94 (8,21)	0,001
PCT (Procalcitonin, ng/ml)	0,44 (0,21-0,98)	0,40 (0,10-0,99)	0,327
FIBRINOGEN (mg/dl)	742,17 (259,68)	651,39 (254,43)	0,001
D-dimer (ng/ml)	6.000 (1.984,5-27.750)	2.700 (2.119,5-6.145)	0,001
Ferritin (ng/ml)	2.700 (2.022,5-3.815)	2.050 (1253,5-2743)	0,021
IL-6 (InterleukIN-6, pg/ml)	317,50 (98,5-593,25)	180 (16-300)	0,002
Lymphocytes (l/ μ L)	775 (427,5-1.075)	810 (555-1.500)	0,008
Neutrophils (n/ μ L)	6.379 (4533)	9.217 (5782)	0,080
CLINICAL PARAMETERS			

HEART RATE (bpm)	86,10 (19,66)	76,91 (16,96)	0,001
Temperature (degrees celsius)	38,2 (37,5-38,5)	36,25 (35,67-37)	0,000
RESPIRATORY PARAMETERS			
PAFI (PaO ₂ /FiO ₂)	157,26 (65,30)	193,03 (67,71)	0,070
STATIC COMPLIANCE (ml/cmH ₂ O)	39,76 (10,30)	43,59 (11,23)	0,004
PEEP (Positive end expiratory pressure, cmH ₂ O)	14 (12,50-16)	12 (12-14)	0,001
SEVERITY SCALES			
APACHE II score	18,06 (6,50)	16,00 (6,26)	0,001
SOFA score	6,97 (2,62)	6,53 (3,13)	0,002
<i>Table 2. Clinical and biochemical parameters and severity scales before and after therapy in “exposed” patients. The variables are described according to therapy, expressed as mean (SD) or median (IQR). A p-value of < 0.003 was considered statistically significant, taking into account multiple testing (0.05/15).</i>			

<i>Table 3. Clinical and biochemical parameters and severity scales in exposed versus unexposed group.</i>			
	EXPOSED	UNEXPOSED (POST-THERAPY)	P
BIOCHEMICAL PARAMETERS			
CRP (C-Reactive Protein, mg/dl)	18,65 (12,2)	10,94 (8,21)	0,004
PCT (Procalcitonin, ng/ml)	0,38(0,2-1,25)	0,40 (0,10-0,99)	0,88
FIBRINOGEN (mg/dl)	811,46 (199,3)	651,39 (254,43)	0,006
D-dimer (ng/ml)	6.500 (2.267-22029)	2.700 (2.119,5-6145)	0,001
Ferritin (ng/ml)	1.600 (1.052-2.009)	2.050 (1.253,5-2.743)	0,004
IL-6 (InterleukIN-6, pg/ml)	1.075 (225-1075)	180 (16-300)	1,000
Lymphocytes (l/μL)	700 (275-1.425)	810 (555-1.500)	0,578
Neutrophils (n/μL)	13.215,3 (8.374,9)	9.217 (5.782)	0,02
RESPIRATORY PARAMETERS			
PAFI (PaO ₂ /FiO ₂)	124,4 (39)	193,03 (67,71)	0,001
STATIC COMPLIANCE (ml/cmH ₂ O)	38,29 (8,9)	43,59 (11,23)	0,2
SEVERITY SCALES			
APACHE II score	13,64 (4,39)	16,00 (6,26)	0,3
SOFA score	6,59 (2,3)	6,53 (3,13)	1,4

Table 3. Clinical and biochemical parameters and severity scales in exposed versus unexposed group. Unexposed patients were monitored for el valor máximo de la variables en el intervalo de tiempo de las primeras 96h of ICU admission while the exposed one were monitored for variables 48 hours post-therapy. The variables are described according to therapy, expressed as mean (SD) or median (IQR). A p-value of < 0.003 was considered statistically significant, taking into account multiple testing (0.05/15).

Table 4. Subgroup analysis according to acute kidney injury classification (AKI)		
DIFFERENTIAL ACCORDING TO ASSOCIATION WITH RENAL FUNCTION		
	AKI III (22)	AKI I-II (10)
MORTALITY	13 (62%)	2 (16%)
INDICATION FOR THERAPY		
HOMEOSTASIS	18 (76%)	3 (27%)
HEMOADSORPTION	3 (19%)	7 (73%)
Balance	1 (5%)	-
Table 4. Subgroup Analysis by Acute Kidney Injury (AKI) Classification in the “case” group. Variables are presented as percentages, N(%).		

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