# CytoSorb® therapy: a new approach to treat critically ill patients with COVID-19 – a retrospective study

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***ABSTRACT — OBJECTIVE:*** **The Coronavirus 2019 (COVID-19) pandemic has resulted in significant mortality and morbidity. Patients with severe COVID-19 infection experience cytokine storm that makes the treatment approach more challenging. The aim of the present study was to evaluate the effects of CytoSorb® therapy in COVID-19 patients admitted in ICU.**

***PATIENTS AND METHODS:*** **This was a single-center, retrospective study conducted at Sunshine Hospital, Hyderabad, India from January 2020 to November 2020. Patients diagnosed with COVID-19 along with signs of sepsis and with a minimum of one organ dysfunction were enrolled in the study. All the patients were treated with CytoSorb® therapy. Clinical and laboratory parameters such as procalcitonin (PCT), serum lactate, interleukin-6 (IL-6), mean arterial pressure (MAP), C-Reactive Protein and the patients' length of stay in intensive care were measured.**

***RESULTS:*** **A total of 20 patients were enrolled in this study; of these 13 patients (65%) survived. One patient left against medical advice and was thus excluded from the analysis. Post CytoSorb® therapy, a reduction in the levels of PCT, total leucocyte count (TLC), and platelet count in the survivor group was reported. The dosage of norepinephrine decreased by 46% in the survivor group but decreased by 0.8% in the non-survivor group ($p$= 0.0424 for survivor vs. non survivors). The average number of days spent by all patients in ICU was 9±5.25.**

***CONCLUSIONS:*** **The use of CytoSorb® therapy for patients with COVID-19 is a safe and effective treatment option when initiated in a timely manner.**

***KEYWORDS***
***Cytokines, COVID-19, Sepsis, Hemoadsorption, Acute Respiratory Distress Syndrome, Coronavirus, CytoSorb®.***

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## INTRODUCTION

The Coronavirus 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has affected millions of people worldwide. According to recent data from the World Health Organization (WHO), more than 326 M cases and 5.53 M deaths have been reported[1]. India has had over 37 M confirmed cases, with 0.48 M deaths attributed to COVID-19 as of January 17, 2022[2]. Although the majority of patients with COVID-19 develop mild or moderate illness, few (5%) require organ support in the Intensive Care Unit (ICU)[3]. In a subgroup of critically ill COVID-19 patients, the SARS-CoV-2 virus caused immune dysregulation leading to cytokine storm and organ damage[4]. The cytokine profile in COVID-19 is defined as an increase in interleukin (IL)-2, IL-6, IL-7, granulocyte colony-stimulating factor (GCS-F), interferon-γ (INF-γ) inducible protein 10, and tumor necrosis factor-α (TNF-α)[5]. Cytokine storm in patients with COVID-19 seems to be associated with disease severity and mortality[6]. An artificial-liver blood-purification (ALBP) system[7], continuous renal replacement therapy (CRRT) and high-volume hemofiltration have, therefore, been used for cytokine clearance in severely ill patients with COVID-19[8]. CytoSorb® is an extracorporeal hemoadsorption device for blood purification and has the targeted approach for overcoming the cytokine storm mainly in critically ill patients with septic shock[9, 10]. Recently, CytoSorb® therapy (M/s CytoSorbents, Inc., Seven Deer Park Drive, Suite K, Monmouth Junction, NJ 08852, USA) was granted Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA, United States) and was approved by Drugs Controller General of India (DCGI) for emergency use in COVID-19 patients, respectively. It is also used in COVID-19 patients in China, Germany, Italy, and other countries resulting in thousands of CytoSorb® treatments worldwide in this setting[11]. The aim of the present study was to evaluate the effects of CytoSorb® therapy in COVID-19 positive patients admitted in ICU.

## PATIENTS AND METHODS

### Study Design

This single center retrospective study was conducted at the Sunshine Hospital, Gachibowli, Hyderabad, India from January 2020 to November 2020. All the medical records of patients treated during this period with CytoSorb® therapy were obtained.

### Inclusion/exclusion criteria

ICU patients diagnosed with COVID-19 along with septic shock with minimum one organ involvement were included in this study. Patients <18 years old, pregnant, or lactating women, patients with IL-6 levels <7 pg/ml, were not included.

### Evaluation of Laboratory Parameters

At the time of admission, demographic details, vital parameters, and clinical diagnosis of the patients were recorded in the case report form. The clinical and laboratory parameters were evaluated in all the patients for both pre (baseline) and post (after last device) CytoSorb® therapy. Biomarkers such as mean arterial pressure (MAP), C-Reactive Protein (CRP), serum creatinine, serum lactate, procalcitonin (PCT), and leukocytes were compared among survivors and non-survivors (pre and post CytoSorb® therapy). Change in norepinephrine (NE) dosage and inflammatory parameters such as IL-6 and other biochemical parameters were also evaluated.

### Outcomes

Glasgow Coma Scale (GCS) scores and sequential organ failure assessment (SOFA) scores were recorded at baseline and post treatment[12-14].

### Statistical Analysis

Descriptive statistics was used for statistical analysis of patient characteristics, clinical data, and outcome measures. To test for significance, *t*-test was applied to compare pre-and post- therapy parameters in the group and between survivors and non-survivors. A $p$ <0.05 was considered as statistically significant.

## RESULTS

### Study Population

A total of 20 patients were included in the study. The mean age of the patients was 56.46 ± 11.67 yrs. Majority of the patients were male (n=15/20, 75%). Of the 20 patients, 13 (65%) patients survived (survivor group), 1 patient left against medical advice and 6 (30%) patients did not survive (non-survivor group). The baseline characteristics of all patients are presented in Table 1. Majority of the patients in survivor group were on standalone CytoSorb® therapy (n = 11) while 2 patients were given Sustained Low Effica-

**Table 1.** Comparison of baseline characteristics of survivors and non-survivors before initiating the therapy.

| Parameter | Survivors (n=13) | Non- Survivors (n=6) | *p* |
|---|---|---|---|
| **Hemoglobin (g/dL)** | 12.80 | 11.65 | 0.2136 |
| **Leucocytes ($10^3$/µL)** | 15344.48 | 15319.87 | 0.9966 |
| **Platelet Count ($10^3$/microliter)** | 2.42 | 1.88 | 0.2817 |
| **Serum Creatinine (µmol/L)** | 1.30 | 2.22 | 0.1466 |
| **BUN (mmol/L)** | 60.84 | 116.98 | 0.0038* |
| **Serum Lactate (mmol/L)** | 6.27 | 12.73 | 0.1112 |
| **Bilirubin (µmol/L)** | 1.12 | 1.18 | 0.8846 |
| **SGOT (units per litre)** | 79.31 | 81.67 | 0.9357 |
| **SGPT (units per litre)** | 65.31 | 81.83 | 0.6063 |
| **CRP (mg/L)** | 182.18 | 237.64 | 0.5411 |
| **PCT** | 9.54 | 20.53 | 0.2263 |
| **Interleukin 6** | 440.58 | 908.28 | 0.2286 |
| **MAP (mm Hg)** | 70.33 | 67.33 | 0.5297 |
| **GCS Score** | 13.23 | 7.50 | 0.0008* |
| **Norepinephrine Dose (mcg/kg/hr)** | 8.94 | 12.50 | 0.2746 |

**p* is significant.
*Abbreviations:* MAP: Mean Arterial Pressure; GCS: Glasgow Coma Scale; BUN: Blood Urea Nitrogen; SGOT: Serum Glutamic Oxaloacetic Transaminase; SGPT: Serum Glutamic Pyruvic Transaminase.

cy Dialysis (SLED) along with CytoSorb® therapy. Among the non-survivors, 3 patients were on standalone CytoSorb® therapy whereas 4 patients were treated with SLED along with CytoSorb® therapy. The number of CytoSorb® devices used per patient varied between 1-2. Duration of each CytoSorb® session varied between 12-18 hr. At baseline, the mean GCS score of non-survivors was significantly lower than survivors (<8 *vs.* 13.2, $p$= 0.0008, respectively).

## Study Outcomes

### *Effect of CytoSorb® Therapy on Biochemical Parameters*

Post CytoSorb®therapy, the survivor group had a decrease of 54.9% ($p$ = 0.048) in PCT levels from 9.54±13.82 ng/mL to 4.30±6.35 ng/mL. However, PCT levels increased from 20.53±21.87 ng/mL to 79.59±128.69 ng/mL ($p$ = 0.4005) in the non-survivor group.

In the survivor group, a reduction was noted in the total leucocyte count (TLC) and platelet count by 47% and 19.4%, respectively. Before starting CytoSorb® therapy, the TLC and platelet count were 15,334.48±10896.22 cells/$mm^3$ and 2.42±1.09 cells/$mm^3$, respectively which decreased to 8,105.06±8,048.37 cells/$mm^3$and 1.95±0.52 cells/$mm^3$, respectively, post CytoSorb® therapy. In the non-survivor group, a decrease of 11% in platelet count was reported (1.67±0.85 cells/$mm^3$ from 1.88±0.74 cells/$mm^3$, $p$ = 0.1125). A slight improvement in other vital parameters such as heart rate, respiratory rate, blood pressure (BP) and body temperature in survivor group was also reported. Change in the laboratory and vital parameters for pre and post therapy among survivors and non survivors is shown in Tables 2 and 3. The mean number of days spent in ICU was 9±5.25. The average time to start CytoSorb® after admission to ICU in survivors was 5 ± 3.67 days and in non-survivors was 8.8 ± 9.8 days ($p$= 0.1953).

## Evaluation of Norepinephrine Dosage

Post therapy in the survivor group, there was a significant reduction in the NE dose. The change in NE dose from pre to post CytoSorb® therapy was 8.94±5.77 to 4.81±5.56 mcg/kg/hr (46.19%, $p$= 0.0036). In the non-survivor group, NE dose decreased by 0.8% (pre *vs.* post: 12.5±2.88 and 12.4±6.19 mcg/kg/hr, $p$ = 0.1170). In the survivor group, an improvement of 8.66% was recorded in MAP from pre (70.33±7.94mm Hg) to post CytoSorb® therapy (76.42±9.22mmHg, $p$=0.0644) in comparison to the non-survivor group (67.33±11.86 *vs.* 66.5±11.78 mmHg, 1.24%). The change in serum lactate and IL- 6 in both the groups is shown in Figure 1 and 2.

## Outcomes

Overall, 65% (13/20) patients survived. In both groups, a change was observed in the SOFA scores that varied from 10.33±2.42 to 7±1.47 ($p$ = 0.179) in the survivor group, and from 13.84± 0.89 to 14.67±

**Table 2.** Change in laboratory and vital parameters (Survivors) (n=13).

| Parameter | Pre CytoSorb® (Mean ± SD) | Post CytoSorb® (Mean ± SD) | *p* |
|---|---|---|---|
| **Hemoglobin (g/dL)** | 12.80±2.02 | 12.38±1.34 | 0.2014 |
| **TLC ($10^3$/µL)** | 15,344.48±10,896.22 | 8,105.06±8,048.37 | 0.0338* |
| **Platelet Count ($10^3$/microliter)** | 2.42±1.09 | 1.95±0.52 | 0.0261* |
| **Serum Creatinine (µmol/L)** | 1.30±1.19 | 1.12±1.05 | 0.0269* |
| **BUN (mmol/L)** | 60.84±28.27 | 125.05±286.33 | 0.4104 |
| **Serum Lactate (mmol/L)** | 6.27±2.13 | 3.51±3.53 | 0.0010* |
| **Bilirubin (µmol/L)** | 1.12±0.75 | 1.24±1.55 | 0.8045 |
| **SGOT (units per litre)** | 79.31±48.15 | 46.77±19.54 | 0.0198* |
| **SGPT (units per litre)** | 65.31±44.54 | 45.08±16.43 | 0.0753 |
| **CRP (mg/L)** | 182.18±155.39 | 119.03±195.88 | 0.2920 |
| **Sodium (mEq/L)** | 137.97±5.54 | 221.43±347.59 | 0.4012 |
| **Potassium (mEq/L)** | 4.40±0.72 | 3.97±0.69 | 0.0246* |
| **Albumin (g/dL)** | 3.38±0.53 | 2.76±0.51 | 0.0017* |
| **Arterial pH** | 7.43±0.06 | 7.41±0.06 | 0.3440 |
| **Bicarbonates (mEq/L)** | 42.38±50.68 | 25.88±3.18 | 0.2881 |
| **$PaO_2$ (kPa)** | 81.70±22.67 | 78.07±20.89 | 0.6919 |
| **$PaCo_2$ (kPa)** | 45.15±23.13 | 42.90±17.60 | 0.3583 |
| **$FiO_2$** | 61.52±18.60 | 62.88±24.53 | 0.6622 |
| **$PaO_2/FiO_2$** | 135.43±56.72 | 164.90±88.77 | 0.0345* |
| **Norepinephrine** | 8.9±5.7 | 4.8±5.6 | 0.0036* |
| **IL- 6** | 440.58±720.99 | 233.39±417.81 | 0.0365* |
| **PCT** | 9.54±13.82 | 4.30±6.35 | 0.0480* |
| **MAP (mm Hg)** | 70.33±7.94 | 76.42±9.22 | 0.0644 |
| **GCS Score** | 13.23±2.05 | 15.00±0.00 | 0.0089* |

**p* is significant.
*Abbreviations:* CRP: C-Reactive Protein, MAP: Mean Arterial Pressure, TLC: Total Leucocyte Count, SGOT: Serum Glutamic Oxaloacetic Transaminase, SGPT: Serum Glutamic-Pyruvic Transaminase, BUN: Blood Urea Nitrogen, PCT: Procalcitonin, IL6: Interleukin-6, GCS: Glasgow Coma Scale.

0.74 ($p$ = 0.356) in the non-survivor group (Table 4). There was a statistically significant improvement in GCS post CytoSorb® therapy in survivor group (13.23±2.05 *vs.* 15.00±0.00; $p$ = 0.0089*) and non-survivor group (7.50±4.18 *vs.* 5.17±4.83; $p$ = 0.0395) compared to baseline.

## DISCUSSION

In this study of critically ill patients with COVID-19, the use of CytoSorb®therapy was evaluated in respect to clinical outcomes. CytoSorb® is a hemoadsorption device which can be effectively used for patients with severe COVID-19 or septic shock resulting in large and meaningful reductions in inflammatory mediators and a reduced dosage requirement for NE. This therapy may potentially prevent progression to ventilator requirement and effectively improves the patient's hemodynamic condition when initiated in a timely manner. The use of CytoSorb®therapy was found to be safe and feasible.

A common cause of death in 28% of patients with COVID-19 is cytokine storm and sepsis[15]. Other manifestations in relation to the SARS- CoV-2 infection are organ dysfunction including acute respiratory distress syndrome (ARDS), shock, and acute cardiac and renal injury. An excessive cytokine release in response to the viral infection can result in a cytokine storm, which can lead to ARDS and multiple-organ failure (MOF) in patients with COVID-19. The elevated levels of pro-inflammatory mediators such as IL-6, IL-8, and TNF might indicate severity of the disease[16]. The process of hemoadsorption is intended to reduce the high levels of several inflammatory mediators including CRP and IL6 which requires close daily monitoring or alternatively aiming to control the cytokine storm. Previously published observational and randomized controlled studies reported that CytoSorb® reduced excess levels of inflammatory mediators in patients with septic shock. CytoSorb® has also shown promising results for various other conditions such as hemophagocytic lymphohistiocytosis (HLH)[17,18] and intoxication[19].

CytoSorb® is already in use for patients with COVID-19 associated cytokine storm syndrome throughout the world. There is a paucity of data from clinical studies using the CytoSorb® device

**Table 3.** Change in Laboratory and Vital Parameters (Non survivor) (n=6).

| Parameter | Pre CytoSorb® (Mean ± SD) | Post CytoSorb® (Mean ± SD) | *p* |
|---|---|---|---|
| **Hemoglobin (g/dL)** | 11.65±1.14 | 11.75±1.32 | 0.7884 |
| **TLC ($10^3$/µL)** | 15319.87±12810.50 | 11400.62±6865.79 | 0.5180 |
| **Platelet Count ($10^3$/microliter)** | 1.88±0.74 | 1.67±0.85 | 0.1125 |
| **Serum Creatinine (µmol/L)** | 2.22±1.29 | 2.20±1.54 | 0.9781 |
| **BUN (mmol/L)** | 116.98±30.31 | 110.83±49.08 | 0.5897 |
| **Serum Lactate (mmol/L)** | 12.73±13.98 | 24.45±16.41 | 0.2125 |
| **Bilirubin (µmol/L)** | 1.18±1.28 | 0.85±0.74 | 0.2545 |
| **SGOT (units per litre)** | 81.67±77.50 | 52.50±25.11 | 0.4269 |
| **SGPT (units per litre)** | 81.83±95.20 | 41.17±21.64 | 0.3050 |
| **CRP (mg/L)** | 237.64±203.61 | 152.66±79.01 | 0.2899 |
| **Sodium (mEq/L)** | 144.70±7.62 | 143.30±6.82 | 0.9608 |
| **Potassium (mEq/L)** | 4.8±15.99 | 3.66±0.24 | 0.2873 |
| **Albumin (g/dL)** | 3.13±0.56 | 2.60±0.30 | 0.0282* |
| **Arterial pH** | 7.1±0.10 | 7.38±0.06 | 0.0877 |
| **Bicarbonates (mEq/L)** | 20.53±5.29 | 22.35±4.90 | 0.4066 |
| **$PaO_2$ (kPa)** | 73.28±27.75 | 72.63±30.72 | 0.8263 |
| **$PaCo_2$ (kPa)** | 67.50±50.79 | 58.25±33.06 | 0.2970 |
| **$FiO_2$** | 79.33±23.04 | 82.17±17.44 | 0.5107 |
| **$PaO_2/FiO_2$** | 112.12±52.55 | 99.74±36.65 | 0.2006 |
| **Norepinephrine** | 12.5±2.88 | 12.4±6.19 | 0.1170 |
| **IL- 6** | 908.28±675.79 | 474.90±595.64 | 0.0684 |
| **PCT** | 20.528±21.869 | 79.59±128.69 | 0.4005 |
| **MAP (mm Hg)** | 67.33±11.86 | 66.5±11.777 | 0.1412 |
| **GCS Score** | 7.50±4.18 | 5.17±4.83 | 0.0395 |

*$p$ is significant.
*Abbreviations:* CRP: C-Reactive Protein, MAP: Mean Arterial Pressure, TLC: Total Leucocyte Count, SGOT: Serum Glutamic Oxaloacetic Transaminase, SGPT: Serum Glutamic-Pyruvic Transaminase, BUN: Blood Urea Nitrogen, PCT: Procalcitonin, IL6: Interleukin-6, GCS: Glasgow Coma Scale.

in COVID-19 patients; however, a few case studies and case reports have been published recently. In a case series of 26 patients with COVID-19, CytoSorb®therapy resulted in a reduction in inflammatory mediator plasma levels, and hemodynamic stabilization that was accompanied by a rapid decrease in vasopressor requirements and an improvement in SOFA scores. The authors found an improvement in lung function/oxygenation and hypothesized that CytoSorb®therapy might result in a positive effect on pulmonary integrity. In another case series of 13 patients with COVID-19 induced ARDS, CytoSor-

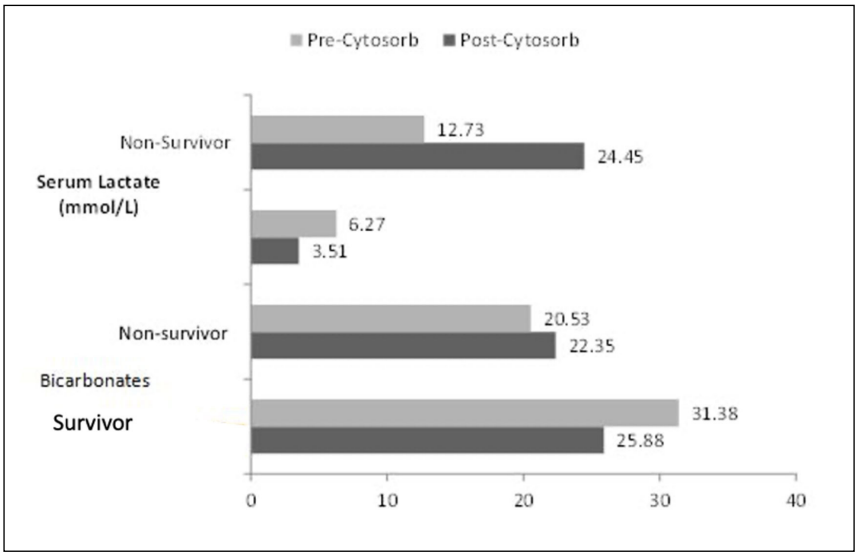


**Figure 1.** Comparison of Serum Lactate and Bicarbonate between Survivor and Non-survivor Groups.

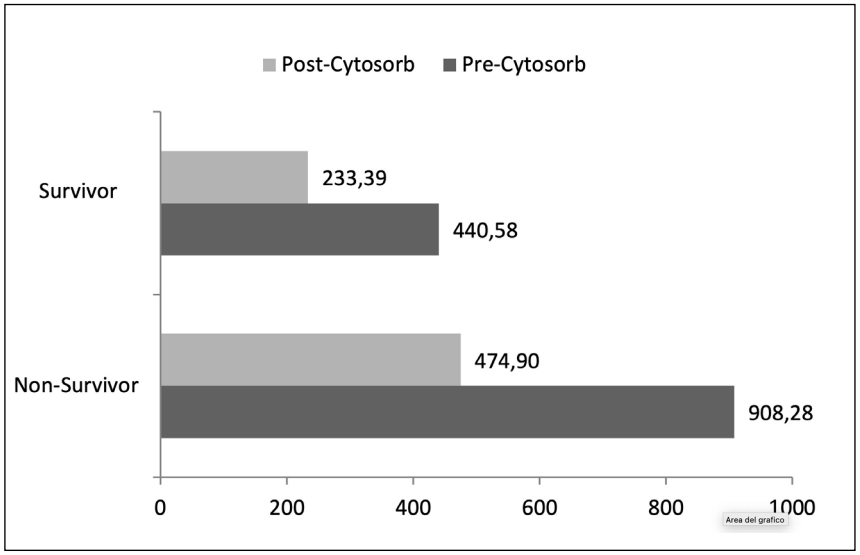


**Figure 2.** Comparison of IL-6 between Survivor and Non-survivor Groups.

b®therapy was associated with a reduction in inflammatory parameters throughout the treatment cycles; a significant decrease was observed in CRP and IL-6 compared with baseline[20]. Mehta et al[21] reported that after CytoSorb® therapy there was a marked reduction in PCT (65%), CRP (27%), bilirubin (43%), and serum lactate (27%) levels in patients with sepsis. Another study reported a significant decrease in PCT and serum lactate levels (33%) after CytoSorb® therapy in patients with sepsis[22]. Several recent studies including a meta-analysis reported elevated PCT levels are positively associated with the severity of COVID-19[23-25]. Hu et al[26] in their study of 95 patients with COVID-19 reported that the patients who were categorized as moderate, severe and critical showed rise in PCT levels according to the disease severity; the mean serum PCT levels were about four times higher in severe patients than in moderate patients and eight times higher in critical patients than in moderate patients. Rizvi et al[27] reported on a case of a 51 year-old man who developed ARDS after infection with COVID-19. He received hemoadsorption (CytoSorb®) and CRRT for 12 days. A total of 8 CytoSorb® devices were used and the adsorber was changed after every 12 hours. The patient showed an improvement after treatment and CytoSorb® therapy helped to prevent his imminent death. Kumar et al[28] reported a case utilizing CytoSorb® intraoperatively for antiplatelet drug removal during a CABG procedure including guidewire retrieval to prevent expected substantial postoperative bleeding. Parikh et al[29] have reported a case of 40-year-old man with viper snake bite induced septic shock and acute kidney injury who further progressed to multi organ failure. The patient was initiated on CytoSorb® along with hemodialysis for 8 hours following which a reduction in noradrenaline dose, procalcitonin levels, SOFA score and normalization of hemoglobin, platelet counts, and leukocyte counts was observed. The patient was eventually weaned off from ventilatory support. SOFA score also reduced significantly to 1, which, at the time of admission, was 14. Another case report by Kumar et al[30] concluded that Cytosorb® along with standard care is a safe and advantageous treatment option in paediatric dengue patients with multi organ failure. In COVID-19, IL-6 and CRP, are related to disease severity[31]. The CytoSorb® device plays a pivotal role for control of an ongoing inflammatory response. A decrease in values of IL-6 and CRP from 1,040 to 415 pg/mL and from 229 to 59 mg/L respectively after a combination treatment with tocilizumab and CytoSorb® was reported in a patient with COVID-19[32]. Overall, our results are in line with recent publications. The present study showed a significant effect on hemodynamic stabilization with reductions in the vasopressor dose, as well as a significant decrease in diagnostic markers such as PCT, CRP, and serum lactate after using CytoSorb® therapy in the survivor group. It is important to note here that non-survivors were more severely ill as compared to survivors at baseline (difference in GCS was statistically significant) and CytoSorb®

**Table 4.** Comparison of Serum Lactate and Bicarbonate between Survivor and Non-survivor Groups.

| Parameter | Pre CytoSorb® (Mean ± SD) | Post CytoSorb® (Mean ± SD) | *p*-value |
|---|---|---|---|
| ***Survivors*** | ***10.33*** **± 2.42** | ***7*** **± 1.47** | **0.179** |
| ***Non-survivors*** | ***13.84*** **± 0.89** | ***14.67*** **± 0.74** | **0.356** |

was used as a rescue therapy for these patients when everything else had failed. It can be used as a rescue therapy when initiated on the right patient at the right time (preferably within 48 hours of admission to the ICU). However, we faced challenges especially in non-survivors where the CytoSorb® therapy was started extremely late after the ICU admission as it was difficult to convince the patient's relatives to initiate this therapy in the crucial window period due to prohibitive cost, lack of randomized controlled studies and proper guidelines to support this therapy. There were infrastructural challenges including limited resources that worsened in the pandemic situation, the key challenge being that the dialysis machine and technician were occupied approximately for 12-24 hours with one patient; thus, leaving the authors with little options for use in a large number of patients simultaneously.

## Limitations

Though our study presents real-world data for cytokine removal, there are certain limitations which should be raised. The study was single-centered and conducted with a small sample size without any control group.

## CONCLUSIONS

The present study gave insights into the effectiveness of the CytoSorb® hemoadsorber in patients with COVID-19. The CytoSorb® hemoadsorption treatment approach proved to be beneficial for patients with COVID-19 with meaningful reductions in inflammatory mediators and hemodynamic stabilization as evidenced by a decrease in requirements for norepinephrine when initiated in a timely manner.

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None

**Ethics approval and consent to participant:**
This retrospective case series de-identified all patient data, and the authors didn't require additional intervention or contact with the patients after their treatment. The intervention (CytoSorb) had already been screened and approved by the hospital authorities at the time of treating the patient. For these reasons, no additional approvals were sought for this case series.

**Availability of data and materials:**
The data that support the findings of this study are available from the corresponding author, [KP], upon reasonable request.

**Conflict of interests:**
The authors declare no conflict of interest

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