Clinical Outcomes of Hemoperfusion Among COVID-19 Severe Patients at the Divine Word Hospital

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ABSTRACT

TITLE
Clinical Outcomes of Hemoperfusion Among COVID-19 Severe Patients in a tertiary hospital

INTRODUCTION/ BACKGROUND OF THE STUDY
Higher levels of inflammatory markers were found in COVID-19 severe patients. Early detection and appropriate management of this cytokine storm can be an important intervention in decreasing the mortality of critically ill COVID-19 patients. Hemoperfusion is a technique developed to clear the blood from a number of cytokines that are candidate culprits for COVID-19 induced inflammation.

OBJECTIVES
The study aims to determine the clinical outcomes of patients with severe COVID-19 infection admitted in a tertiary hospital who underwent hemoperfusion (HP) from June 2021 to November 2021.

METHODS
This retrospective-study utilized quantitative research methods in order to look into the clinical outcomes of patients with severe to critical COVID-19 who underwent hemoperfusion. A total of n=32 participants were randomly selected from the list of COVID-19 severe patients.16 participants each were assigned to the Hemoperfusion group (HP Group) and Non-hemoperfusion group.

RESULTS AND ANALYSIS
Sixteen patients with COVID 19 severe underwent hemoperfusion and was comprised mostly of males. The mean age was approximately 68.75 years old. Hypertension was the most common comorbidity identified. The average length of hospital stay was 20.31 days, wherein most patients survived (68.8%). The immediate cause of death of those who died were COVID related. In terms of COVID markers, there is a non-significant relationship between LDH levels before and after hemoperfusion. When compared to the non-hemoperfusion group, there was also no significant difference between the mean scores of both groups.

CONCLUSION
Hemoperfusion as an intervention did not produce statistically significant improvements or have outcome differences on the patients with severe COVID-19 who underwent hemoperfusion from those who chose to forego the treatment.

CHAPTER I

INTRODUCTION

Background of the Study

In December 2019 a cluster of pneumonia cases with an unknown cause emerged in Wuhan City, Hubei Province, China. The causative agent was identified to be a novel coronavirus, which was initially named 2019 novel coronavirus (2019-nCoV) (Huang et al., 2020). The disease rapidly disseminated across the world in a short span of time, compelling the World Health Organization to declare it as a global pandemic. As of November 13, 2022, there have been 630, 832, 131 confirmed cases of COVID 19 and has resulted in over 6,584,104 deaths globally (WHO, 2021). The disease was later named coronavirus disease 2019 (COVID-19).

The exaggerated cytokine release in response to a viral infection called the cytokine release storm or cytokine storm is emerging as one of the mechanisms leading to acute respiratory distress syndrome and multiple organ failure in COVID-19 (Iannacone et al., 2020).

In a study by Huang et al. (2020) they noted that high concentrations of cytokines were recorded in plasma of critically ill patients with COVID-19 implying that the cytokine storm could be associated with disease severity. Meta-analysis studies show that patients in the COVID-19 severe group had significantly higher inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-2R (IL-2R), ferritin, Serum amyloid A (SAA) and neutrophil-to-lymphocyte ratio (NLR) (Mahat et al, 2021). High levels of lactate dehydrogenase (LDH) and D-dimer are also powerful predictive factors for early recognition of thrombosis and organ injury hence may predict severity of COVID-19 (Shekhanawar, M., Sarala, H. and Shaik, R., 2021).

Early detection and appropriate management of this storm can be an important intervention in decreasing the mortality of critically ill COVID-19 patients. Currently there is no particular cure for COVID-19 but efforts have been made to study potential therapeutic strategies and vaccines against COVID 19. Supportive measures such as oxygen supplementation, anti-viral, and anti-coagulant agents have been used however approximately 5% of patients still worsen and develop severe acute respiratory distress syndrome (ARDS) and multiple organ failure that require intensive-care support and often yield a poor prognosis (Iannaccone et al., 2020).

Investigational therapies for the treatment of COVID-19 pneumonia are still being studied. It is considered after a review of the benefits and safety considerations are discussed with the patient. For severe hospitalized patients, remdesivir 200mg/IV loading dose followed by 100mg/IV for 5-10 days is given. Other anti-virals include favipiravir, lopinavir-ritonavir. Immunomodulating agents as adjunctive treatment for COVID-19 are still being studied which includes corticosteroids, interferon, tocilizumab and other IL-6 inhibitors, convalescent plasma and hemoperfusion (PSMID, 2020).

Hemoperfusion (HP) is a technique developed to adsorb molecules in the middle molecular weight range (up to 55kDa). Studies in vitro and in vivo have shown that hemoperfusion is highly effective in clearing blood from a number of cytokines that are candidate culprits for COVID-19 induced inflammation. It also improved respiratory function and had lower mortality in the treated patients (Rampino et al, 2020). In a study by Shadvar et al (2020), hemoperfusion was done and showed decrease in the level of inflammation and organ dysfunction in critically ill patients with COVID-19. However there is insufficient evidence on the use of hemoperfusion hence it is not yet recommended in the current guidelines. Further

research is needed to clarify the clinical benefits of hemoperfusion. Issues such as cost, patient values and preferences, feasibility, acceptability and affordability have been raised (PSMID, 2020). In the Divine Word Hospital, hemoperfusion is available and have been used in some patients with severe COVID 19 infection. In this study, the clinical outcomes of hemoperfusion will be evaluated which can help physicians in the management of COVID 19 patients.

Review of Related Literature

COVID 19 INFECTION

In a study by Huang et al. (2020) they reported a cohort of patients who presented with fever, dry cough, dyspnea and had serious, sometimes fatal, pneumonia. They had a shared history of exposure to Huanan seafood market in Wuhan, China around December 2019. Local centers for disease control and prevention collected respiratory, blood, and fecal specimens to detect the pathogen. The presence of SARS-CoV-2 in respiratory specimens was detected by next generation sequencing or real time Polymerase Chain Reaction (RT-PCR) methods. A novel coronavirus was isolated from lower respiratory tract specimens and the disease was named 2019-nCoV. Later on, it was named as COVID-19 infection.

The pathophysiology of COVID-19 is not completely understood. What is now known is that SARS-CoV-2 binds to the nasal epithelial cells in the upper respiratory tract via the angiotensin-converting enzyme II (ACE-2). The virus undergoes local replication and propagation with a limited immune response. There is involvement of the conducting airways, upper respiratory tract and migration into the lower respiratory tract. About one fifth of all infected patients progress to this stage and develop severe symptoms. The virus invades and enters the type II pulmonary alveolar epithelial cells via ACE-2. The virus-laden pneumocytes

now release many different cytokines and inflammatory markers such as interleukins, tumor necrosis factor, interferons and macrophage inflammatory protein (Prasher, A., 2020).

Cytokine release syndrome (CRS) can cause severe symptoms of systemic inflammation. It can create hematological complications and affect different parts of the coagulation pathway, including the endothelial cells, platelets, coagulation cascade, and fibrinolytic system. Various underlying causes of CRS like primary hemophagocytic lymphohistocytosis, chimeric antigen receptor T-cell therapy, and COVID-19, have different cytokine profiles and coagulopathy presentations. Microvascular thrombosis and superficial microcoagulation are the most common pathologies (Mousavi-Roknabadi et al., 2022).

CO-MORBIDITIES AND COVID-19 INFECTION

Patients who are aged ≥65 years are at a higher risk of progressing to severe COVID-19. Other underlying conditions associated with a higher risk of severe COVID-19 include asthma, cancer, cardiovascular disease, chronic kidney disease, chronic liver disease, chronic lung disease, diabetes, advanced or untreated HIV infection, obesity, pregnancy, cigarette smoking, and being a recipient of immunosuppressive therapy or a transplant (NIH).

The presence of comorbidities is associated with worse outcome in COVID-19 infection. In a study by Honardoost et al. (2021) they noted that Cerebrovascular disease was the most strongly predictive comorbidity for severe disease, followed by cardiovascular disease, chronic lung disease, cancer, diabetes, and hypertension.

COVID-19 MARKERS

LACTATE DEHYDROGENASE

Lactate dehydrogenase (LDH) is an enzyme implicated in the conversion of lactate to pyruvate in the cells of most body tissues and increased following tissue breakdown. It is

elevated in numerous clinical conditions such as hemolysis, cancer, severe infection and sepsis, liver diseases, hematologic malignancies, and many others. Serum LDH was validated for its potential usefulness as markers for evaluating clinical severity and monitoring treatment response in COVID-19 pneumonia (Wu et al., 2020). LDH elevation in patients with COVID-19 indicates lung and tissue injuries. COVID 19 may lead to inadequate tissue perfusion and multiple organ failure due to various mechanisms including thrombosis. LDH was found to be elevated in COVID-19 severe cases with >16 fold increase in odds of mortality (Henry et al., 2020).

In a study by Zhou et al they found that LDH level was independently associated with Acute Respiratory Distress Syndrome (ARDS) and could strongly predict the incidence of ARDS. Inflammation and cell damage play an important role in the pathological processes of pulmonary tissues. Research has shown that SARS-CoV-2 as a positive-sense RNA virus may activate inflammasomes, leading to cellular pyroptosis and aggressive symptoms. They found that the best threshold for predicting ARDS was 273 U/L.

FERRITIN

Ferritin concentration is a promising predictor of mortality, though, it cannot reliably predict severity. The optimal cut-off for prediction of mortality was 574.5 ng/mL with a sensitivity of 82%. Whereas, for the prediction of severity the optimal cut-off identified was 354 ng/mL with a sensitivity of 80%. It is a useful marker of risk stratification in COVID-19 and can be considered in combination with clinical details and other laboratory tests while designing the patient centered treatment plans (Ahmed et al., 2021).

COVID-19 patients with severe to critical disease had higher ferritin level compared to patients with mild to moderate disease. Non-survivors had higher serum ferritin level compared to survivors. Patients requiring intensive care unit (ICU) and mechanical ventilation had higher serum ferritin levels compared to those who didn't require ICU and did not require mechanical ventilation (Kaushal et al., 2022)

D-DIMER

D-dimer level is one of the measures used to detect thrombosis. Elevated d-dimer levels and thrombocytopenia which suggest a hypercoagulable state may be contributing to severity of illness and mortality in COVID- 19 (Rostami, M. and Mansouritorghabeh, H., 2020).

SARS-CoV-2 infection affects the whole body even if predominant are respiratory symptoms. Coagulation abnormalities such as hypercoagulation, thrombocytopenia, venous thrombosis (TV) and disseminated intravascular coagulation (DIC) have been observed in approximately 60–70% of hospitalized patients. In the current practice the D-dimers value proves to be useful in the diagnosis and prediction of deep vein thrombosis recurrence; it is also an early marker for disseminated intravascular coagulation. Given the endothelial aggression and prothrombotic mechanisms triggered by SARS-CoV-2, and the statistical results obtained, the increased value of the D-dimers may be predictive for abnormal liver functional parameters and for a severe evolution. (Baroiu et al., 2022).

The most common reason cited in the literature for the elevation of D-dimer includes viremia and the cytokine storm syndrome, wherein the rise in pro-inflammatory cytokines (IL-2, IL-6, IL-8, IL-17, TNF-α) are inadequately controlled by the anti-inflammatory factors which overwhelm the coagulation cascade. Hypoxia itself leads to activation of hypoxia-inducible transcription factor-dependent signaling pathway, predisposing to thrombosis (Poudel et al.,

2021).

C- REACTIVE PROTEIN

C-reactive protein (CRP) is a non-specific acute phase reactant elevated in infection or inflammation. A significant increase in CRP was linked to the overproduction of inflammatory cytokines in severe patients with COVID-19. It predicts probability of disease progression in non-severe patients with COVID-19 (Ali, N., 2020).

In a study by Soleimani et al. (2021) analysis of the results showed that hemoperfusion had resulted in a more significant increase in the SpO2 of patients compared to those that received only conventional treatment. In addition, the CRP is more significantly decreased through performing hemoperfusion in comparison with the use of conventional treatment.

The distributional characteristics of CRP indicated an optimal cut-off of 40mg/L was associated with mortality. This threshold may assist clinicians in using CRP as an early trigger for enhanced observation, treatment decisions and advanced care planning (Stringer et al., 2021).

MANAGEMENT OF COVID 19

The core management recommendations for COVID-19 remain to be supportive care and intensive respiratory management. It includes giving supplemental oxygen therapy to patients with severe pneumonia and/or respiratory distress, hypoxemia, or shock and target SpO2 >92%. Appropriate empiric antimicrobials should be given within 1 hour of identification of sepsis. Intravenous systemic corticosteroids, particularly Dexamethasone is given for patients requiring oxygen support. Based from the Randomised Evaluation of COVID-19 therapy (RECOVERY) trial, Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation, by one-fifth in patients receiving oxygen without invasive mechanical ventilation. Anticoagulation therapy in the form of heparin and low molecular weight heparin for patients

with D-dimer level of >1000. For severe hospitalized patients, remdesivir 200mg/IV loading dose followed by 100mg/IV for 5-10days is given. Other anti-virals include favipiravir, lopinavir-ritonavir (PSMID, 2020).

Current strategies for coronavirus disease 2019 (COVID 19) include extracorporeal membrane oxygenation (ECMO) in the most severe cases of acute respiratory distress syndrome (ARDS), as well as high-flow nasal oxygen (HFNO) and mechanical ventilation for intubated patients. Although these measures are effective in most cases, several COVID-19 patients may present a fatal outcome (Vardanjani et al., 2020).

Extracorporeal blood purification (EBP) therapies are proposed as promising adjunctive treatments, designed for elimination of toxins and removal of inflammatory mediators. It has been previously recommended as complimentary treatment methods for a serious overdose from a number of toxins, including salicylates, lithium, ethylene glycol, methanol and theophylline. The general mechanism of EBPs relies on the removal of various solutes, substances, and excessive fluid from blood through diffusion, convection or adsorption. The common EBP techniques include hemodialysis, hemofiltration and hemodiafiltration, therapeutic plasma exchange, continuous renal replacement therapy, peritoneal dialysis and albumin dialysis (Safari et al., 2022).

HEMOPERFUSION

The major mechanism of hemoperfusion is elimination of circulating inflammatory mediators and endotoxins, when large volumes of the patient's blood are passed over its adsorbent substance. Circulating endotoxin or inflammatory mediators are attached to the highly adsorptive membrane through hydrophobic, ionic, and van der Waals interaction; thus, being

eliminated from circulation. The sorbent system is made up of a biocompatible fixed bed, or cartridge, which contains the adsorbent particles.

There are two major types of adsorbent materials, including activated charcoal and resins (e.g. hydrocarbon polymer, polystyrene). Charcoal has greater affinity for water-soluble molecules, whereas resins have higher affinity toward lipid-soluble molecules (e.g., glutethimide and methaqualone). Particular characteristics of solutes such as molecular size, chemical affinity, and their distribution volume in the body determine the efficacy of the hemoperfusion (Safari, et al., 2020). HA 330 and HA 380 cartridges are two types of hemoperfusion cartridges which are used in inflammatory conditions. These cartridges have the capability of inflammatory cytokine absorption (Darazam et al., 2021).

Hemoperfusion should be planned when the patient with COVID-19 is in the cytokine storm phase, which means the presence of high levels of ferritin, CRP, and IL-6 in the bloodstream, as well as severe hypoxic condition (P/E < 100) (Mousavi-Roknabadi et al., 2022).

HEMOPERFUSION IN COVID-19

Infectious and noninfectious triggers can result in a cytokine storm, progressing to vasoplegic shock and finally multi-organ dysfunction syndrome (MODS). Early detection and appropriate management of this storm can be an important intervention in decreasing the mortality of critically ill COVID-19 patients. The mechanism is nonspecific removal of the peaks of the circulating cytokines in both the pro-and anti-inflammatory sides, which results in the reduction of circulating levels of cytokines and may allow the immune system of the patient to redirect the immunocompetent cells to the source or site of inflammation . Hemoperfusion was performed after the diagnosis of cytokine storm during the first 48 hours of ICU admission. After

the first application of hemoperfusion, the patients showed an improvement in pulmonary markers, dynamic indices, and LDH level was decreased. A decrease in CRP, ferritin, procalcitonin, cardiac index and extravascular lung water levels was evident following the second application. Ferritin level and extravascular lung water declined after the third application. Overall, improved levels of inflammatory, respiratory, and perfusion parameters were evident after hemoperfusion 6-8 hours daily for 3 consecutive days; however no effect was evident on the prognosis (Shadvar et al., 2020).

RELATIONSHIP OF CYTOKINE STORM AND HEMOPERFUSION

The profile of cytokine and inflammation in SARS-CoV-2 infection suggests that a severe dysregulated inflammatory response is a fundamental problem in quite some critically ill COVID-19 patients. Therefore, the rationale of using extracorporeal organ support therapies including hemoperfusion, with efficient sorbent cartridges for removal of cytokines and other inflammatory circulating mediators, should be considered in critically-ill COVID-19 patients (Safari et al, 2020).

OUTCOMES OF HEMOPERFUSION IN COVID-19

Results of multiple studies have demonstrated that application of HA 330 cartridge to eliminate circulating and alveolar levels of pro-inflammatory cytokines in severe sepsis, septic shock, or acute lung injury patients significantly improved patients' hemodynamics, reduced the length of intensive care unit stay, and intensive care unit mortality (Safari et al, 2022). Three sessions of hemoperfusion improved the partial pressure of oxygen and oxygen saturation in patients with severe COVID 19 (Amirsavadkouhi et al, 2021).

Patients who received at least 3 sessions of HA-330 hemoperfusion (hemoperfusion group) exhibited lower organ failure severity (decreased SOFA score), improvement of chest X-ray infiltration, decreased hyperinflammatory marker (CRP) compared to control group. Interesting findings were lower 28-day mortality and higher mechanical ventilator-free day that were observed among the patients in hemoperfusion group. Furthermore, it was observed that intubation rate might be reduced significantly after performing hemoperfusion in COVID-19 patients using high flow nasal cannula or noninvasive ventilation (Surasit, K. and Nattachai, S., 2021).

The limited sample size and retrospective design preclude a definitive statement about the potential effectiveness of this treatment in COVID-19 patients and these observations require evaluation in a randomized clinical trial (Rampino et al, 2020). However, the high cost of HA-330 hemoperfusion was also another barrier of conducting randomized control trial design especially in a limited resource setting (Surasit, K. and Nattachai, S., 2021).

Significance of the Study

The results of the present investigation can be of benefit to the following stakeholders:

Hospital administration and Department of Internal Medicine: This would help in formulating COVID-19 management protocols in the hospital. This would also support the administration's choice to acquire the machines and cartridges for hemoperfusion and to carry out the ncesessary personnel training.

Internists: This would aid and guide the choice to propose hemoperfusion regardless of the expense.

Patients: This would serve as adjunctive treatment in order to prevent death from COVID 19 infection.

Future researchers: As a pilot study, this one may be expanded upon by residents, who may also look into the advantages of hemoperfusion in treating various illnesses.

Healthcare Policy Makers: The dentification of the mortality rate and the cause of death would necessitate healthcare interventions to limit the spread of COVID 19

Objectives of the Study

General Objective:

The study aims to determine the clinical outcomes of patients with severe COVID-19 infection admitted at the Divine Word Hospital (DWH) who underwent hemoperfusion (HP) from June 2021 to November 2021.

Specific Objectives:

To unravel this, the study shall:

1. Know the demographic profile of the severe COVID-19 patients at DWH from June 2021 to November 2021 in terms of:
    a. Age
    b. Sex
2. Determine the comorbidities present among the severe COVID-19 patients who underwent Hemoperfusion.
3. Find out the clinical outcomes of the severe COVID-19 patients who underwent Hemoperfusion in terms of:
    a. Survival / Death
    b. Length of Total Hospital Stay, Length of Stay prior to Hemoperfusion, Length of Stay after Hemoperfusion

4. Compare the LDH levels of severe COVID-19 in terms of Baseline LDH and Post-Hemoperfusion LDH Levels of the HP Group.
5. Compare the Outcome Scores of the HP Group and Non-HP group.

Scope and Limitations of the Study

Scope

The study is single-centered and will be conducted in the Divine Word Hospital, a tertiary level hospital in Tacloban City. Admitted patients from June 2021 until November 2021 who tested positive for SARS-COV-2 by RT-PCR and underwent hemoperfusion aside from the standard treatment of COVID 19 infection will be included in the study. There is no protocol yet for the recommendation of hemoperfusion among COVID-19 patients of the Divine Word Hospital, however patients who underwent hemoperfusion were all in the severe-critical disease severity classification by the World Health Organization Interim Clinical Guidance May 2020.

Limitation

Since this is a retrospective study design, not all COVID markers were requested before and after hemoperfusion. The most compared marker which was LDH was the one compared in this study. Hence, all COVID 19 patients who underwent hemoperfusion but did not have serum LDH before and after hemoperfusion were excluded in the study.

Conceptual Framework

Cytokine storms and high levels of inflammatory factors play a role in the pathogenesis of COVID-19. Current studies evaluate the role of hemoperfusion in the removal of circulatory cytokines in critically-ill patients with COVID-19. However it is not yet recommended as the standard treatment of care for COVID-19 patients by the World Health Organization.

The study shall address this concern with the following null hypothesis:

Ho: There is no significant difference between the LDH scores (dependent variable) of patients before and after hemoperfusion (independent variable).

However, not all the patients have the means or are confident to undergo hemoperfusion. Several studies have also pointed out that hemoperfusion did not seem to help with the survival rates of patients who were diagnosed with Severe to Critical COVID-19.

The study shall address this concern with the following null hypothesis:

Ho: There is no significant difference between the clinical outcome values of patients before and after hemoperfusion.

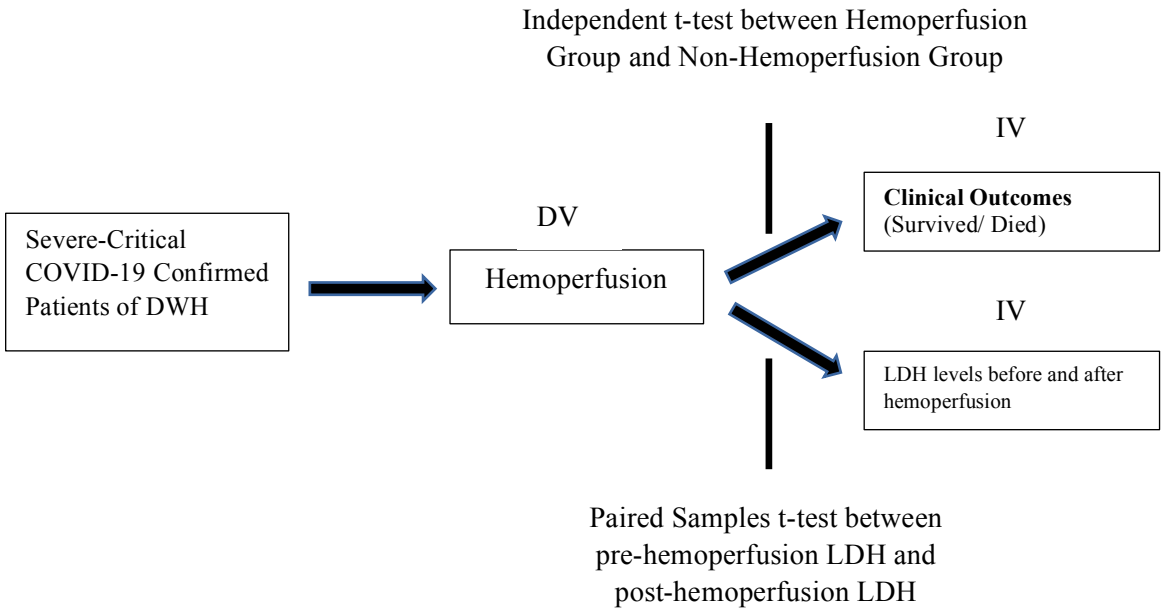


Figure 1. Conceptual Framework of the Study

Definition of Terms

Clinical outcome: Defined as the outcomes of patients in terms of survival or death and decrease of Lactate dehydrogenase (LDH) levels.

Coronavirus Disease 2019 (COVID 19): is an infectious disease caused by the SARS-CoV-2 virus.

COVID-19 real-time reverse transcription polymerase chain reaction (RT-PCR) test: It is the gold standard test for COVID-19 infection. It involves detection of SARS-CoV-2 in upper and lower respiratory specimens.

COVID related death: immediate cause of death is related to COVID-19 infection.

Comorbidity: The simultaneous presence of two or more medical conditions in a patient.

Length of total hospital stay: time from patient admission to the time the patient is discharged or the patient died.

Length of stay prior to hemoperfusion: time from patient admission until initiation of hemoperfusion

Length of stay after hemoperfusion: time after first hemoperfusion until discharge or death

Lactate Dehydrogenase (LDH): It is a blood test that is used as a biomarker in COVID-19 infection since it is a marker of multiple organ injury and decreased oxygenation. Normal range of 125 - 220 U/L (Divine Word Hospital's reference range)

Hemoperfusion (HP): It is an extracorporeal blood purification modality that consists of the passage of anticoagulated whole blood through a device, usually a column, that contains adsorbent particles. It is used for the removal of toxins in poisoning and cytokines from septic and inflamed patients.

Severe COVID-19: It encompasses the criteria of severe and critical COVID-19 according to the World Health Organization Disease classification of COVID-19. It includes RT PCR confirmed COVID-19 patient with severe pneumonia or severe acute respiratory infection and present with the following: fever, cough, dyspnea, respiratory rate of ≥30 breaths/minute, severe respiratory distress or oxygen saturation ≤92% on room air. It includes patients who have sepsis or septic shock.

CHAPTER II
METHODOLOGY

Study Design

This retrospective-study utilized quantitative research methods in order to look into the clinical outcomes of patients with severe to critical COVID-19 who underwent hemoperfusion.

Study Population

The target population were COVID-19 RT-PCR positive patients admitted at Divine Word Hospital from June 2021 to November 2021.

Research Subjects

Being archival in nature, the study did not involve contact with any patient. Rather, the participants referred to in this study are patient charts. Therefore, the researcher sent a request letter to the Medical Records Department of the Divine Word Hospital requesting for clinical charts of patients who were diagnosed with severe to critical COVID-19 from June 2021 to November 2021.

A total of n=32 participants were randomly selected from the list of COVID-19 severe patients including those who underwent hemoperfusion. 16 participants were assigned to the Hemoperfusion group (HP Group) according the following criteria:

1. Participants must be COVID-19 RT PCR-test confirmed patients who were admitted at DWH from June 2021 to May 2022,
2. Diagnosed with severe to critical COVID-19,
3. Must have undergone hemoperfusion, and
4. Must have baseline and post-hemoperfusion LDH results.

Meanwhile, 16 participants were randomly selected via non-probability convenience sampling, and were assigned to the non-hemoperfusion group (non-HP Group). These participants were subject to the following criteria:

1. Participants must be COVID 19 RT PCR-test-confirmed patients who were admitted at DWH from June 2021 to May 2022, and
2. Diagnosed with severe to critical COVID-19.
3. Must not have undergone hemoperfusion.

Exclusion criteria

Patients with incomplete information in their medical charts such as values for inflammatory markers were excluded in the study. Patients who transferred to other institution were also excluded since outcome can no longer be monitored.

Research Instruments

To extract relevant data from the patient records, the researcher constructed a structured questionnaire (see Annex A).

Research Procedure and Gathering of Data

A letter of request to conduct the study was given to the Hospital Administrator. After getting approval, the medical charts of the patients who were COVID-19 positive and who met the inclusion and exclusion criteria were reviewed. The data that were extracted included study parameters such as age, sex, comorbidity, LDH values before and after hemoperfusion, and status upon discharge.

Data Analysis

The study utilized both descriptive and inferential statistics to address the research objectives. A paired samples t-test was used to look into significant differences between LDH levels pre-hemoperfusion and post-hemoperfusion. Meanwhile, an independent samples t-test was done to look into significant differences in clinical outcomes of patients who underwent hemoperfusion, and those who did not undergo hemoperfusion.

CHAPTER III
RESULTS AND DISCUSSION

The study included a total of n=32 patients and were divided into the hemoperfusion (n=16) and non-hemoperfusion group (n=16). Table 1 shows the demographic and clinical characteristics of the patients who underwent hemoperfusion and those who did not undergo hemoperfusion. In the hemoperfusion group, 5 people were females while 11 were males. The mean age of the participants was 68.75 years old. In the non-hemoperfusion group, 9 people were females while 7 were males. The mean age of participants was 64.56 years old.

Table 1. Demographic and clinical profile of COVID 19 severe patients who underwent hemoperfusion versus those who did not undergo hemoperfusion

	Hemoperfusion Group	Non-hemoperfusion Group
Sex, n (%)		
Male	11 (68.8)	7 (43.75)
Female	5 (31.3)	9 (56.25)
Age, average years (SD)	68.75 (12.315)	64.56 (13.14)
Comorbidities , n (%)		
Hypertension	9 (56.3)	12 (75.0)
Diabetes	7 (43.8)	10 (62.5)
Chronic Kidney Disease	4 (25.0)	1 (6.3)
Coronary Artery Disease	3 (18.8)	0
Chronic Kidney Disease on Hemodialysis	1 (6.3)	1 (6.3)
Parkinsons	1 (6.3)	0
Benign Prostatic Hyperplasia	1 (6.3)	1 (6.3)
Abdominal Aortic Aneurysm	1 (6.3)	0
Peripheral Arterial Disease	1 (6.3)	0
Bronchial Asthma	0	1 (6.3)
Hypothyroidism	0	1 (6.3)
Osteoarthritis	0	1 (6.3)
Length of Hospital Stay, average days (SD)		
Hospital Stay	20.31(14.44)	10.18 (12.38)
Days Pre-hemoperfusion	3.75 (3.68)	
Days Post-hemoperfusion	16.44 (11.38)	
Outcomes		
Died	5 (31.3)	5
Survived	11 (68.8)	11
Immediate cause of death		
COVID related		**3**
COVID Pneumonia		1
ARDS		2
Non-COVID related		**2**
Cardiogenic shock		2

Through chart reviews, the study has identified diseases associated as comorbid with COVID-19. Hypertension is the most common comorbidity in both groups. 56.3% in the hemoperfusion group and 75% in the non-hemoperfusion group. Diabetes ranked as the second most common 43.8% in the hemoperfusion group and 62.5% in the non-hemoperfusion group.

The length of hospital stay was measured in days. The average total length of hospital stay of the patients from admission to discharge or death was 20.31 days (SD=14.44) in the hemoperfusion group. Upon admission, the average number of days it took before hemoperfusion was 3.75 days (SD=3.67), after which, the patients stayed for an additional 16.43 days (SD=11.38) before being discharged or expiring. In the non-hemoperfusion group the average length of hospital stay was 10.18 days.

In this study, the outcomes of the patients who underwent hemoperfusion and did not undergo hemoperfusion were similar. 11 people (68.8%) were discharged/survived while 5 (31.3%) died in both groups. In the non-hemoperfusion group 11 people (68.8%) were discharged/survived while 5 (31.3%) died.

Table 2. Paired Samples Statistics of LDH Levels of Patients Pre and Post Hemoperfusion

	Mean	N	Std. Deviation	Std. Error Mean
LDH_Pre	580.11	16	224.130	56.032
LDH_Post	677.11	16	361.525	90.381

To test the idea that hemoperfusion helps in reducing inflammatory markers, this study looked into the Lactate dehydrogenase (LDH) levels of the patients (HP Group) before and after they underwent hemoperfusion. Table 6 shows that the mean baseline LDH of the HP group was 580.11 U/L (SD=224.13) while the post-hemoperfusion LDH was 677.11 U/L (SD=361.52).

Table 3. Paired Samples Correlations of LDH Levels Pre and Post Hemoperfusion

		N	Correlation	Sig.
Pair 1	LDH_Pre & LDH_Post	16	.029	.914

Table 3 contains the correlation coefficient that shows that there is a non-significant relationship between LDH levels before and after hemoperfusion [r(16) = .029, p = .914].

Table 4. Paired Samples Test of LDH Levels Pre and Post Hemoperfusion

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
LDH_Pre - LDH_Post	-97.001	419.720	104.930	-320.654	126.652	-.924	15	.370

A paired samples t-test was conducted to determine the effect hemoperfusion onthe LDH levels of patients with severe COVID-19. The results indicate no significant difference between baseline LDH levels (M=580.11; SD=224.13) and post-hemoperfusion LDH levels (M=677.11; SD=361.52); [t(16) = -.924, p = .370]. The 95% confidence interval of the difference between the means ranged from [-320.65 to 126.65] and did not indicate a difference between the means of the samples. Therefore, the study fails to reject the null hypothesis that there is no difference between the means and conclude that there is no significant effect of hemoperfusion on reduction of LDH levels.

Table 5. Group Statistics of LDH Levels of HP Group and Non-HP Group

	Group	N	Mean	Std. Deviation	Std. Error Mean
LDH_Pre	Hemoperfusion Group	16	580.11	224.130	56.032
	Non-Hemoperfusion Group	16	487.86	299.886	74.971

To further probe into patient outcomes, the study looked into 16 patients who were diagnosed with severe COVID-19 and did not undergo hemoperfusion, this group shall be referred to as the non-HP group. Table 5 shows that the mean LDH level of the patients who underwent hemoperfusion (M=580.11, SD=224.13) was higher than the mean LDH level of the non-HP group (M=487.66, SD = 74.97).

Table 6. Independent Samples Test Between LDH Levels of HP Group and Non-HP Group

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
LDH_Pre	Equal variances assumed	.938	.340	.986	30	.332	92.254	93.597	-98.896	283.404
	Equal variances not assumed			.986	27.772	.333	92.254	93.597	-99.541	284.049

Although the non-HP group had a lower mean LDH level than the HP group, Table 6 contains an independent t-test that displays that there was no significant difference between their mean scores. [t(32) = -.986, p = .332]. Therefore, the HP group and non-HP group were not statistically different based on LDH levels, which is an important inflammatory marker of COVID -19.

Table 7. Independent Samples Test Between Outcome Scores of HP and Non-HP Group

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Outcome_Score	Equal variances assumed	.582	.452	-.382	30	.705	-.06250	.16378	-.39698	.27198
	Equal variances not assumed			-.382	29.862	.705	-.06250	.16378	-.39704	.27204

Assuming now that the n=32 patients with severe COVID-19 were on the same starting line in terms of LDH levels, the researcher then performed an independent t-test to compare the

outcome scores of the patients from the non-HP group and the HP group. A score of 0 was given to those who died and a score of 1 was assigned to those who survived.

Table 7 shows that there was no significant difference in the outcome scores of the HP Group (M=0.68, SD=0.47) and non-HP Group (M=0.75, SD=0.44); t (32) =-.382, p = 0.45. These results suggest that hemoperfusion did not have a significant effect on patient outcomes.

DISCUSSION

In this study, there were more males than females. In a study by Jin et al. (2020), similar susceptibility to SARS-COV-2 between males and females was observed among patients who survived COVID-19infection. The number of men is 2.4 times that of women in the deceased patients. While men and women had the same susceptibility, men were prone to dying. The higher incidence of men for most diseases could correlate with a general demographic fact of shorter life expectancy in men compared to women. In a study by Marik et al. (2021), the CRP, ferritin and D-dimer levels were significantly higher in men as compared with women.

The mean age of COVID-19 severe patients who underwent hemoperfusion was 68.75 years old, which is similar to the study by Manalili et al (2021). Patients with age >50 years were at a significantly massive risk of mortality compared to those aged <50 years (Biswas et al., 2020).

Hypertension was the most common comorbidity identified among the COVID-19 severe patients who underwent hemoperfusion. This was similar to other studies conducted in China and even in the Philippines. Higher uncontrolled systolic blood pressure may contribute to more severe disease course, due to its association with hypertension-mediated organ damage, including vascular remodeling, which may worsen endothelial dysfunction, endothelial damage

and endothelitis induced by SARS-CoV-2 infection (Gallo, G., Calvez, V. and Savoia, C., 2022). In a study by Batiha et al. (2021) it was observed that the mortality risk increases steadily in hypertensive patients who are positive for SARS-COV-2 due to underlying coagulopathy. Multiple cardiovascular complications have been associated with SARS-CoV-2 infection including myocarditis, acute cardiac damage, arrhythmias, and thrombotic diseases.

CLINICAL OUTCOMES OF HEMOPERFUSION

This study showed that severe to critical COVID-19 patients who underwent hemoperfusion mostly survived and was discharged (68.8%) while others died (31.2%). This finding was different from the outcomes of patients in the study of Manalili et al. (2020) wherein mortality occurred in 62.1% of patients who underwent hemoperfusion. The average length of hospital stay however was similar, with the average length of hospital stay (20.3 days), duration of admission to first HP(3.75 days), and days from first HP to death or discharge (16.43 days).

In other studies, COVID-19 markers were all elevated and showed decrease following hemoperfusion. However since this is a retrospective study, not all COVID-19 markers were compared from baseline and after-hemoperfusion. Only LDH was the COVID-19 marker compared and the study showed that there is no significant effect of hemoperfusion on reduction of LDH levels. LDH elevation in patients with COVID-19 indicates lung and tissue injuries. COVID 19 may lead to inadequate tissue perfusion and multiple organ failure due to various mechanisms, including thrombosis, which lead to LDH elevation (Martha, J., Wibowo, A., and Pranata, R. (2021). Elevated LDH values were associated with 6 fold increased odds of severe COVID-19 disease and >16 fold increase in odds of mortality (Henry et al., 2020).

CHAPTER IV
CONCLUSION & RECOMMENDATIONS

CONCLUSION

In society's effort to combat the effects of COVID-19, multiple experimental approaches have been utilized, and this study aimed to shed led on the issue of the effectivity of hemoperfusion. From a general perspective, hemoperfusion is known to filter the blood from toxins, but considering its high cost among other things, it is worth looking into its overall practicality and effectivity.

Through a dependent t-test, the study has found out that hemoperfusion as an intervention did not produce statistically significant improvements on the patients of DWH with severe COVID-19. Furthermore, our independent samples t-testing revealed that patients who underwent hemoperfusion did not have statistically significant outcome differences from those who chose to forego the treatment.

Much like the results of a study conducted by Manalili et al. (2022) from the UP-PGH, the findings of this study points to the direction that hemoperfusion does not produce any significant results.

RECOMMENDATIONS

After the analysis of the data gathered from COVID-19 patients admitted at Divine Word Hospital (DWH) the researcher highly recommends the following:

For researchers:

1. Replicate the study with a bigger sample size, and a wider range of inflammatory markers.
2. Cross-examine updated data from other hospitals.
3. Explore if hemoperfusion has improved the subjective quality of life of patients.

For hospitals and medical practitioners:

1. The study recommends that hemoperfusion be given under consideration of the financial capacity and willingness of patients to undergo the "experimental approach".

2. The study recommends practitioners to seek other methods of treatment for inflammatory markers reduction.

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ANNEX A

DATA GATHERING FORM

PATIENT ID _____
PATIENT'S NAME _____ AGE_____
GENDER_____
DATE OF ADMISSION: _____ DATE OF PCR RESULT: _____
DATE OF HEMOPERFUSION: _____ DATE OF DISCHARGE/DEATH: _____

CO-MORBIDITIES	☐ Diabetes mellitus ☐ Hypertension ☐ Chronic Kidney Disease ☐ ESRD on HD ☐ Thyroid disorder ☐ Malignancy ☐ COPD ☐ Bronchial Asthma ☐ Autoimmune Disease Others: _____
STATUS ON DISCHARGE	☐ SURVIVED ☐ DIED
OTHER COVID MANAGEMENT	☐ Dexamethasone ☐ Remdesivir ☐ Tocilizumab ☐ Enoxaparin ☐ Others: _____

	BASELINE	POST HP	POST- HP
LDH			
FERRITIN			
D- DIMER			
CRP- QUANTITATIVE			