Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (7) Issue (5) (2022), (27-35) **online: ISSN 2356–976x**
http://bjas.journals.ekb.eg

The Role of early Use of Corticosteroids (Pulse Steroid Versus Regular dose of Steroid) In Patients of Severe Illness of Covid 19

A.G.El Gazzar[1], T.S.Essawy[1], A.H.Abd el Rahman[2]and R.R.Ahmed[2]
[1]Chest Diseases, Dept., Faculty of Medicine, Benha Univ., Benha, Egypt
[2]Critical care medicine Dept., Faculty of Medicine, Benha Univ., Benha, Egypt
E-mail: randaahmed1000000@gmail.com

Abstract

Background: Coronaviruses are ribonucleic acid viruses, in humans the viruses may infect the respiratory, gastrointestinal, hepatic, and central nervous systems. Infection with four of the most common coronaviruses strains. usually lead to mild, self-limiting upper respiratory tract infections However, other corona viruses, are associated with severe acute respiratory syndrome (SARS-CoV) and the Middle East respiratory syndrome (MERS-CoV). **Aim:** to assess the use of systemic steroid either pulse steroid or regular dose of steroid in patient with severe form of covid 19 as regard hospital stay, need for mechanical ventilation. **Methods:** a cross sectional study, carried out on ٥0 patients who were suspected with covid 19 by history, laboratory investigation, chest imaging and confirmed with PCR selected from the critical care unit and isolation critical care unit at Benha university Hospital. And were classified into two groups, Group1: 25 patients were received dexamethasone (8 mg per day) and Group 2: 25 patients were received solumedrol (2mg per Kg). All data will be tabulated and statistically analyzed. **Results**: the mean ICU length of stay in critically ill patients who received Dexamethasone was 12.5±4.286 versus 14.68±7.851 in critically ill patients who received Methylprednisolone (p-value=0.08). Patients in Dexamethasone group, by the 10th day, had a significantly better D dimer (1153.04±725.34 vs 1633.12±1244.8, p=0.020), ferritin, (899.14±344.22 vs 1523.8±994.44, p<0.001), NLR (3.108±0.430 vs 3.506±0.536, p<0.001), however, Methyl prednisolone group had lower mortality rate (p0.001). **Conclusion** Covid 19 is global pandemic with worldwide mortality rate that need urgent interventions from all world to face this catastrophe. However, ICU stay, d dimer, ferritin, NLR among patients who treated with Dexamethasone lower than among patients who treated with Methylprednisolone, those treated with Methylprednisolone had better mortality rates.

Key words: Covid 19, pandemics, SARS viruses, ARDS, Corticosteroids**.**

1. Introduction

Coronavirus disease 2019 (COVID-19), a highly contagious viral illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in more than 3.8 million deaths worldwide **[1]** (CoVs) have been associated with significant disease outbreaks in East Asia and the Middle East. The severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) began to emerge in 2002 and 2012 with mortality rates up to 10% and 35%, respectively. A novel coronavirus, (SARS-CoV-2), causing COVID-19, emerged in late March 2019 **[2].** CoVs are positive-stranded RNA (+ssRNA) viruses that have an extensive range of natural hosts and affect multiple systems **[3].** CoVs with a crown-like appearance under an electron microscope. Members of Covs can cause respiratory, enteric, hepatic, and neurological diseases in different animal species, in humans, illness ranging from the common cold to more severe diseases such as MERS and SARS **[4].**

The WHO's current estimate of the global case fatality rate for COVID-19 is 2.2%**.** All ages are at risk of contracting this infection and severe disease. However, patients aged ≥60 years and patients with underlying medical comorbidities have an increased risk of developing severe COVID-19 infection **[5].** It is estimated that 17.9% to 33.3% of infected patients will remain asymptomatic. While most symptomatic patients commonly present with fever, cough, and shortness of breath and less commonly with a sore throat, anosmia, dysgeusia, anorexia, nausea, malaise, myalgias, and diarrhea. laboratory abnormalities that included lymphopenia (47.6%), elevated C-reactive protein levels (65.9%), elevated cardiac enzymes (49.4%), and abnormal liver function tests (26.4%) **[6].** Other laboratory abnormalities included leukopenia (23.5%), elevated D-dimer (20.4%), elevated erythrocyte sedimentation rate (20.4%), leukocytosis (9.9%), elevated procalcitonin (16.7%), and abnormal renal function (10.9%) **[7].** the elevated neutrophil-to-lymphocyte ratio (NLR), derived NLR ratio (d-NLR) and the platelet-to-lymphocyte ratio is indicative of a cytokine-induced inflammatory storm **[8].** RNA tests can confirm the diagnosis of SARS-CoV-2 (COVID-19) cases with real-time RT-PCR or next-generation sequencing, an effective method for confirming the diagnosis in clinical cases of COVID-19**[9].** Nucleic acids of SARS-CoV-2 can be detected from samples such as bronchoalveolar lavage fluid, sputum, nasal swabs, fiber bronchoscope brush biopsy specimen, pharyngeal swabs, feces, blood, and urine, with different levels of diagnostic performance**.** The sensitivity of PCR testing is dependent on multiple factors that include the adequacy of the specimen, technical specimen collection, time from exposure, and specimen source **[10].** The viral loads of SARS-CoV-2 were measured using N-gene-specific quantitative RT-PCR in throat swab and sputum samples collected from COVID-19-infected individuals. Chest Computed Tomography (CT), The American College of Radiology recommends against Chest CT's routine use as an initial imaging study or screening. The sensitivity of chest CT is far

superior to that of X-ray screening **[11]**. The chest CT findings associated with COVID-19-infected patients include characteristic patchy infiltration that later progresses to ground-glass opacities associated with consolidation areas with patchy distribution, mainly peripheral/subpleural, and greater involvement of the posterior regions' lower lobes **[12].**

Remdesivir, a novel nucleotide analog prodrug, and it was also found to inhibit the replication of SARS-CoV and MERS-CoV in primary human airway epithelial cell culture systems**,** it improves pulmonary function and reduced viral loads and lung pathology both in prophylactic and therapeutic regimens compared to lopinavir/ritonavir-IFN-γ treatment in MERS-CoV infection. Remdesivir is also considered the only therapeutic drug that significantly reduces pulmonary pathology **[13].** Chloroquine is an antimalarial drug known to possess antiviral activity due to its ability to block virus-cell fusion**.** The COVID-19 patients received 600 mg of hydroxychloroquine daily along with azithromycin as a single-arm protocol. This protocol was found to be associated with a reduction in viral load. Finally, it resulted in a complete cure **[14].** Another FDA-approved drug, ivermectin, anti-parasitic was reported to inhibit the in vitro replication of SARS-CoV-2. One of the main disadvantages is its potential to cause cytotoxicity. **Corticosteroids,** Severe COVID-19 is associated with inflammation-related lung injury driven by the release of cytokines characterized by an elevation in inflammatory markers. Dexamethasone use resulted in lower 28-day mortality in patients who were on invasive mechanical ventilation or oxygen support but not in patients who were not receiving any respiratory support **[15].** Interferon-β-1, acytokines that are essential in mounting an immune response to a viral infection, and SARS-CoV-2 suppresses its release in vitro **[16].** Conventional Oxygen Therapy, COVID-19 patients with associated respiratory insufficiency should be monitored closely with continuous pulse oximetry. Supplemental oxygen supplementation via nasal cannula or Venturi mask must be administered to maintain oxygen saturation between 92 to 96% (< 88-90% if COPD). If there is improvement in clinical and oxygen saturation, supplemental oxygen should be continued with periodic reassessment. If there is no clinical improvement or worsening of symptoms and/or oxygen saturation, non-invasive treatments such as High-Flow Nasal Cannula (HFNC) or Noninvasive Positive Pressure Ventilation (NIPPV) are recommended **[17].** Personal protective equipment (PPE), like face masks, will help to prevent the spread of respiratory infections like COVID-19 Medical staff are most at risk of getting COVID-19 infection, to protect themselves and others from this deadly disease, they should use PPE such as face masks (N95 or FFP3), eye protection (goggles), gowns, and gloves to nullify the risk of infection **[18].**

Corticosteroids (Cs) are hormone mediators produced by adrenal glands cortex that are categorized into glucocorticoids, mineralocorticoids, and androgenic sex hormone. Glucocorticoids (GCs) are a group of drugs structurally and pharmacologically like the endogenous hormone cortisol with various**.** While mineralocorticoids regulate electrolytes and water balance.They have both endocrine and nonendocrine indications with potent anti-inflammatory and immunosuppressive effects **[19].** Glucocorticoids (cortisol in man) are released in a circadian manner, in response to physiological stress. The circadian profile is regulated by the hypothalamic-pituitary-adrenal (HPA) axis to release corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP), that activate corticotrophin cells to secrete (ACTH) into the general circulation. Subsequently, ACTH acts on the adrenal cortex to stimulate the synthesis and release of glucocorticoids **[20].** Serum cortisol concentrations peak in the mornings and are lowest at night. Dexamethasone and betamethasone are long acting with the highest glucocorticoid efficacy with a biological half-life of 36 to 54 hours. Cortisone and cortisol are short acting with a biological half-life of under 12 hours and are not frequently used. Prednisone, prednisolone, methylprednisolone, and triamcinolone are intermediate acting with a biological half-life of 18 to 36 hours [**21].** The most common GC-associated adverse effects noted in adults includes Osteoporosis, fractures, and osteonecrosis, Adrenal suppression, Cushingoid features, Hyperglycemia and diabetes, Myopathy, Infections, Glaucoma and cataracts, Gastrointestinal, Cardiovascular events, and Neuropsychiatric Adverse Effects, **[22]**. Acute respiratory distress syndrome happened in COVID-19 not just because of uncontrolled viral replication but also because of an uncontrolled immune reaction from the host. That's why antiviral and anti-inflammatory treatments have become an increasing concern for clinicians **[23**]**.** The use of corticosteroids in covid 19 to reduce inflammation is still controversial **[24].** Systemic corticosteroids are used to treat people with COVID-19 because they counter hyper-inflammation. Existing evidence suggest a slight benefit on mortality. It is one of the few treatment options for COVID-19. Severe patients present with respiratory distress associated with systemic hyperinflammatory syndrome, the so-called "cytokine storm". Patients showing this are at higher risk to the most advanced stage of the disease, requiring ICU admission or invasive mechanical ventilation (IMV). Consequently, immunosuppressive agents are presently the cornerstone of treatment regimens for severe COVID-19, reduce inflammatory responses, treatment failure, and the time to clinical stability in community-acquired pneumonia without major adverse effects **[25].** Also, early administration of dexamethasone shortened mechanical ventilation time and overall mortality for patients with moderate-to-severe ARDS. Corticosteroid therapy was associated with improved clinical outcomes in patients with severe COVID-19. It reduced hospital length of stay and intensive care unit (ICU) stay. Chinese experts considered it prudent to administer short courses of corticosteroids at low-to-moderate doses for critically ill patients with COVID-19 as well as treatment with

methylprednisolone decreased the risk of death for individuals with COVID-19 with ARDS **(26).** In addition, the United Kingdom, indicated that the use of low-dose dexamethasone in ventilated COVID-19 patients, and to a lesser degree in patients in need of supplemental oxygen, reduced the mortality **[27].** However, evidence for methylprednisolone, has been limited to date in most RCTs, this agent has been the primary corticosteroids used in the intensive care unit (ICU) management of ARDS**.** Also, previous studies have shown the effectiveness of methylprednisolone on treating SARS disease than other corticosteroids, particularly dexamethasone **[28].**

Acute respiratory distress syndrome (ARDS) is a common condition which is caused by pulmonary and extra-pulmonary pathologies, with hypoxemia and bilateral pulmonary infiltrates **[29].** ARDS is defined as an acute disorder that starts within 7 days of the inciting event and is characterized by bilateral lung infiltrates and severe progressive hypoxemia in the absence of any evidence of cardiogenic pulmonary edema. The definition of ARDS was updated in 2012 and is called the Berlin definition. The underlying etiology of ARDS divides into pulmonary and extra-pulmonary causes. Commonest include bacteremia, sepsis, trauma, burns, reaction to massive transfusion, pneumonia, aspiration, severe pancreatitis, near drowning and fat embolism. Patients with increased severity scores for critical illness, (APACHE) II score) are more prone to develop ARDS manifestations. Risk factors for ARDS include, Advanced age, Female gender, Smoking, Alcohol use, Aortic vascular surgery, Cardiovascular surgery, and Traumatic brain injury **[30].** The incidence of ARDS in the United States range from 64.2 to 78.9 cases/100,000 person-years. 25% of ARDS cases are initially classified as mild and 75% as moderate or severe. However, a third of the mild cases go on to progress to moderate or severe disease **[31].** Mortality rate decreased of 1.1% per year for the period 1994 through 2006. However, the overall pooled mortality rate for all the studies evaluated was 43%. The mortality of ARDS is related to the severity of the disease; it is 27%, 32%, and 45% for mild, moderate, and severe disease, respectively. There are three distinct phases in the development of ARDS: exudative, proliferative and fibrotic phase. The first exudative phase that occurs over the first 7 to 10 days occurred after lung exposure to injury **[32].** In the second proliferative phase, the repair process takes place by restoration of epithelial and endothelial barriers and absorption of the intra-alveolar fluid **[33].** The syndrome is characterized by the development of dyspnea and hypoxemia, which progressively worsens within 6 to 72 hours of inciting event, frequently requiring mechanical ventilation and intensive care unit-level care. ARDS is diagnosed clinically based on the diagnostic Berlin criteria, Development of new-onset respiratory symptoms within one week of known clinical insult, Bilateral opacities are apparent on chest X- ray or CT, Respiratory failure not fully explainable by cardiogenic pulmonary edema or fluid overload, Hypoxemia defined as partial arterial oxygen pressure to a fraction of inspired oxygen (PaO2/FiO2) ratio is less than or equal to 300 mmHg. The severity of ARDS is classified according to the PaO2/FiO2 ratio on a mechanical ventilator with minimum positive end-expiratory pressure (PEEP) into mild, moderate, and severe. Diffuse bilateral opacities and infiltrates classically present on chest radiograph, but these findings could be variable showing lobar or unilateral opacities. CT usually shows widespread patchy airspace opacities more evident in the dependent areas **[34].** Safe mechanical ventilation with avoiding further lung injury is the cornerstone of treatment in ARDS. Current guidelines recommend lung protective ventilation consists of low tidal volumes (4 to 8 ml/kg of ideal body weight) with a target of plateau airway pressure less than 30 cm of water**.** Furthermore, in patients with moderate-to-severe ARDS (PaO2/FiO2 less than or equal to 150 mmHg), the American Thoracic Society and European Respiratory Society (ATS/ERS) recommend the prone position for 12 hours per day especially in patients with resistant hypoxemia **[35].** Conservative fluid strategy is recommended in patients with ARDS to decrease the risk of fluid accumulation in alveolar space as it associated with a reduction of the duration of mechanical ventilation and ICU stay with an improvement of lung function without causing non-pulmonary organ dysfunction. Early use of neuromuscular blockade and deep sedation in patients with moderate-to-severe ARDS correlates with 90-day survival without increasing the risk for muscle weakness. Complications of ARDS include barotrauma from high PEEP, prolonged mechanical ventilation -thus the need for tracheostomy, Post extubating laryngeal edema and subglottic stenosis, nosocomial infections, pneumonia, line sepsis, urinary tract infection, deep venous thrombosis, antibiotic resistance, muscle weakness, renal failure, and post-traumatic stress disorder **[36].** It is common among COVID-19 patients to develop acute respiratory distress syndrome (ARDS), a life-threatening form of respiratory failure, approximately 1/3 (33%) of hospitalized patients with Covid 19 develop ARDS. And nearly 3/4 (75%) of COVID-19 patients admitted to the ICU have ARDS **[37].** Patients with COVID-19 ARDS may have normal or even high lung compliance; this is not the case in patients with classic ARDS. the dependence on mechanical ventilation of COVID-19 ARDS is longer than that of non-COVID-19 ARDS. Due to the anti-inflammatory effects of corticosteroids, they are considered a possible treatment for ARDS and WHO strongly recommended systemic corticosteroid therapy for patients with severe and critical COVID-19 and recommended against corticosteroid therapy for patients with non-severe COVID-19 **[38].** Cytokine storm, a serious condition caused by sustained viral replication, occurs in some patients and it has been shown to be the main cause of COVID-19 related ARDS Some of the cytokines and chemokines overexpressed during the cytokine storm **[39].** In COVID-19 patients, induced

moderate to severe ARDS the standard treatment plus i.v. dexamethasone led to a statistically significant increase in days alive and free of mechanical ventilation over 28 days compared with standard treatment alone **[63].** In a controlled, open-label trial, it has been determined that dexamethasone use reduced 28-day mortality in hospitalized Covid-19 patients' who received either mechanical ventilation or oxygen, but not those receiving no respiratory support **[40].** Some preliminary trial results suggest methylprednisolone and dexamethasone can be used for the severe form of COVID-19 **[41].** Ranjbar et al. compared to the use of 6 mg/day of dexamethasone in patients admitted to hospital with COVID-19 pneumonia, the administration of 2 mg/kg per day of intravenous methylprednisolone resulted in a shorter hospital stay and less need for mechanical ventilation. Methylprednisolone demonstrated better outcomes in COVID-19 hypoxic patients when compared to dexamethasone **[42].**

2. Subjects and methods

This study is across sectional study that was conducted on ٥0 patients who were highly suspected with covid 19 by history, laboratory investigation, chest imaging and confirmed with PCR. The cases were selected from the critical care unit and isolation critical care unit at Benha university Hospital. Written consent forms approved by local ethical research committee were obtained from every patient subject They were classified into two groups; Group **1**: 25 patients received dexamethasone (8 mg per day) and **Group 2**: 25 patients received Solumedrol (2mg per Kg). **Inclusion criteria were,** history of contact to patients with Covid 19 Laboratory investigation (CBC – normal or low leucocytes with lymphopenia, Chest imaging (ground glass opacities) and PCR +ve for Covid 19. The **exclusion criteria were,** age less than 21 years, Respiratory failure rather than covid 19 and Mild cases of covid 19. All patients will applied for laboratory investigation (CBC, CRP, kidney function test, ABG , liver function test , PCR) and chest imaging at ten day from admission and days of stay in ICU. The mean age of cases in group Dexa was 0.57.28±8.811 years while in group Sol it was 56.28±11.69 years. As regards patient weight the mean weight of cases in group Dex was 87.58±12.95 while in group Sol it was 85.48±13.32.

2.1. Statistical Analysis

The collected data was analysed using Statistical package for Social Science. (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Student T Test was used to assess the statistical significance of the difference between two study group means.A p value is considered significant if <0.05 at confidence interval 95%.

3. Results

Table 1 shows comparison of PH, PaCO2 and PaO2 at different follow up points among studied groups. PaO2 showed significant increase at 10th day in DEX when compared to SOL group (p=0.005). Otherwise, no significant differences were found between both groups regarding pH, PaCO2 and PaO2 at different follow up point (p>0.05) (table1).

Table (1) Comparison of PH, $PaCO_{2\ and}$ PaO_2 at different follow up points among studied groups.

		Group DEX	Group SOL	*p*-value
pH	**On admission**	7.28±0.101	7.30±0.114	*0.50*
	1st day	7.31±0.076	7.33±0.086	0.27
	3rd day	7.34±0.085	7.32±0.125	0.30
	5th day	7.29±0.086	6.30±0.101	0.86
	7th day	7.28±0.086	7.29±0.095	0.73
	10th day	7.30±0.0100	7.16±1.0045	0.33
$PaCO_2$	**On admission**	39.48±8.144	38.08±9.378	0.42
	1ST day	47.58±13.63	49.1±14.45	0.58
	3rd day	45.48±11.79	45.64±12.84	0.94
	5th day	43.3±9.685	43.58±11.923	0.89
	7th day	45.02±10.07	46.98±11.282	0.36
	10th day	49.12±10.839	47.44±13.17	0.89
PaO_2	**On admission**	48.64±8.515	50.98±8.175	0.16
	1ST day	54.58±8.487	53.78±7.980	0.62
	3rd day	50.74±7.831	50.74±7.526	1.00
	5th day	54.14±5.7888	55.78±6.946	0.20
	7th day	59.42±5.540	58.16±7.519	0.34
	10th day	64.16±5.508	60.6±6.860	0.005

Table 2 shows comparison of laboratory and radiologic parameters on admission and 10th day among studied groups. DEX group showed significantly higher AST on 10th day, significantly lower AST on admission, D dimer, ferritin on admission and 10th day, NLR on 10th day when compared to SOL group. Otherwise, no significant differences were found between both groups regarding laboratory parameters (**Table 2, figure 1).**

Table (2) Comparison of laboratory and radiologic parameters on admission and 10th day among studied groups.

		Group DEX	Group SOL	*p*-value
Hemoglobin	**On admission**	10.94±1.67	10.97±1.60	0.93
	On 10th day	10.15±1.50	10.212±1.58	0.85
Platelets	**On admission**	291.1±71.39	290.4±83.08	0.96
	On 10th day	243.5±85.53	219.1±88.124	0.16
TLC	**On admission**	14.94±6.37	17.13±6.77	0.98
	On 10th day	14.048±5.56	15.206±4.71	0.26
Urea	**On admission**	84.72±57.55	81.7±47.70	0.77
	On 10th day	35.08±10.94	37.66±12.35	0.27
Create.	**On admission**	2.34±1.393	2.61±1.38	0.33
	On 10th day	2.32±1.69	2.12±1.218	0.49
Alb.	**On admission**	3.29±0.543	3.26±0.635	0.76
	On 10th day	3.30±0.504	3.19±0.537	0.60
ALT	**On admission**	35.58±9.926	36.14±10.33	0.78
	On 10th day	32.72±6.49	32.04±6.518	0.60
AST	**On admission**	27.72±7.717	32.92±11.98	0.011
	On 10th day	30.46±10.057	25.46±9.060	0.010
D-dimer	**On admission**	1391.76±752.64	1823.64±1156.98	0.029
	On 10th day	1153.04±725.34	1633.12±1244.8	0.020
Ferritin	**On admission**	1699.56±852.006	2453.72±1583.41	0.003
	On 10th day	899.14±344.22	1523.8±994.44	<0.001
LDH	**On admission**	695.14±187.80	741.98±189.96	0.21
	On 10th day	556.46±213.06	565.72±184.96	0.81
NLR	**On admission**	3.544±0.652	3.726±0.527	0.12
	On 10th day	3.108±0.430	3.506±0.536	<0.001
CT	**On admission**	4.26±0.750	4.38±0.666	0.40
	On 10th day	3.5±1.054	3.54±0.994	0.84

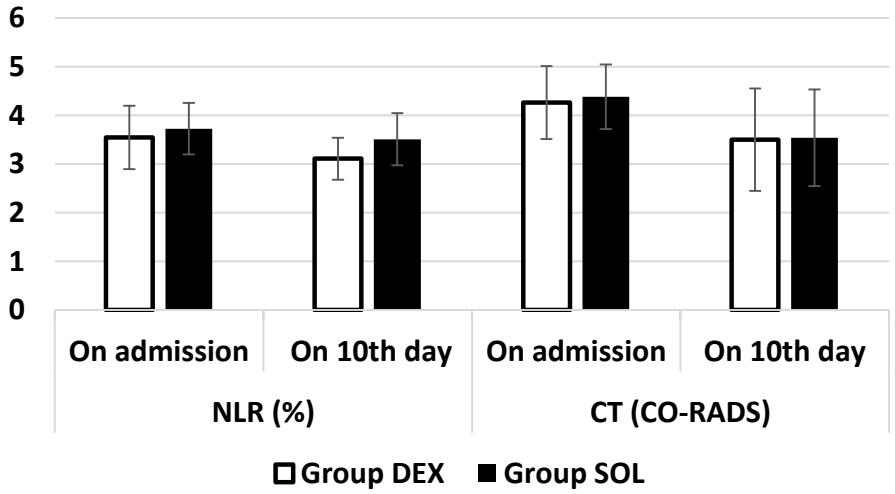

Fig. (1) NLR and CT among studied cases.

Table 3 shows comparison of ICU stay and mortality among studied groups. DEX group showed significantly higher mortality when compared to SOL group. ICU stay did not differ significantly between both groups (**Table 3, figure 2).**

Table (3) Comparison of ICU stay and mortality among studied groups.

	Group DEX	Group SOL	p-value
ICU stay (day)	12.5±4.286	14.68±7.851	0.08
mortality	0.498569	0.35051	<0.001

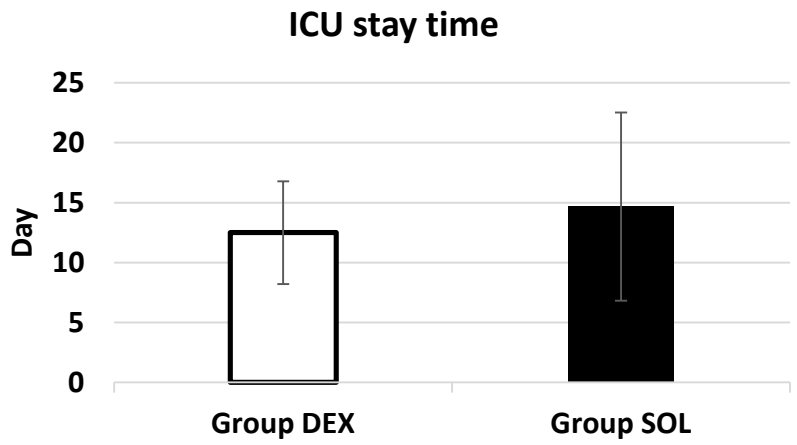

Fig. (2) ICU stays among studied cases.

4. Discussion

Covid 19 is a disease caused by a virus belonging to SARS Co V2 family of viruses. It primarily effects the lungs resulting in inflammation and pneumonia. Based on clinical, biochemical and radiological parameters it is divided into mild, moderate and severe disease. In mild disease there is fever and upper respiratory signs but no documented hypoxia or x-ray infiltrates. In moderate disease, there is tachypnea >30/min, hypoxia (SpO 2 < 94%) and infiltrates > 50% on chest x-ray and CT scan **[43].** Whereas in severe disease patient needs mechanical ventilation and biochemical parameters suggest cytokine storm and patient can develop multi-organ failure. In mild disease patient can be managed at home with symptomatic treatment. In moderate disease patient is admitted in hospital and given supplemental oxygen along with other treatment modalities (44). This work was designed to detect the difference between using either Methylprednisolone versus Dexamethasone in critically ill Covid 19 patients and their effects on outcome morbidity and mortality. The current study was carried out on one hundred adult patients of moderate to severe cases of Covid 19. Patients were divided into two groups. The first group received Dexamethasone with dose of 6mg /kg/day while the second group received Methylprednisolone with dose of 2mg/kg/day. In our study the age of the patients ranged from 35 - 71 years. No statistically significant ICU length of stay difference observed between patient in both groups. In our study the mean ICU length of stay in critically ill patients who received Dexamethasone was 12.5±4.286 versus 14.68±7.851 in critically ill patients who received Methylprednisolone while other found that both groups had similar primary and secondary outcomes and similar ICU length of stay **[45].** A study in Wuhan Chin**a**, had showed that There was significant reduction in morbidity and mortality with methylprednisolone with shorter length of ICU stay **[46].** A study in Michigan, observed significant improvement in outcome and shorter length of stay in hospital in the methylprednisolone group **[47].** This is agreed with our study and detect the effect of methylprednisolone in decreasing the period in which critically ill patient stayed in ICU. Also, another study had showed that both groups had similar primary and secondary outcomes and similar ICU length of stay **[41].** while others found that treatment with methylprednisolone led to significantly greater improvements in clinical status and shortened hospital length of stay than treatment with dexamethasone in hospitalized COVID-19 patients with Hypoxia **[40].** As regarding the laboratory investigation in our study there was statistically significant improvement of serum ferritin level after 10 days of ICU admission, while in other study, The Methylprednisolone group showed more improvement in serum ferritin level after 10 days of ICU admission rather than Dexamethasone group [**48].** In addition, in another trial, there was no statistically significant difference in serum ferritin level between two groups which unlike our study **[49, 50].** In our study, there was statistically significant difference in D-dimer observed between patients in both groups on admission and after 10 days of admission which disagreed with others who found that there was no statistically significant difference in D-dimer between patients in both groups. But agreed with our study in measurement of D-dimer after 10 days of ICU stay **[51].** Serum LDH showed no statistically significant difference between patients in both groups in our study either on admission or after 10 days of ICU stay which in same line with other study **[51].** On the other hand, they found that there was statistically significant difference between patients in both groups 10 days after admission. They found more improvement in LDH in the patients who treated with Methylprednisolone rather than the patients who treated with Dexamethasone **[51].** There was no statistically significant difference between patients in both groups in our study regarding other laboratory finding as ALT, Urea, Creatinine either on admission or after 10 days of ICU admission. Also agreed with other **[51]** As regard patients Mortality Our study showed that the rate of mortality among patients who treated with Methylprednisolone much lower than the mortality among patients who treated with Dexamethasone which

agreed with other report, sufficiently dosed methylprednisolone can lead to a further decreased mortality as compared to dexamethasone **[48].** Our study has some limitations as small sample size and the overall outcome of ARDS in Covid still unclear as well as the outcome of the present protocols. Further studies and research will solve these limitations.

4. Conclusion

Covid 19 is global pandemic with worldwide mortality rate that need urgent interventions from all world to face this catastrophe. However, ICU stay, d dimer, ferritin, NLR among patients who treated with Dexamethasone lower than among patients who treated with Methylprednisolone, those treated with Methylprednisolone had better mortality rates.

References

[1] M. Cascella, M. Rajnik, A. Aleem. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2022 Jan 5]. In: Stat Pearls [Internet].

[2] AJ. Rodriguez-Morales, DK. Bonilla-Aldana, GJ. Balbin-Ramon, AA. Rabaan, R. Sah, Paniz-Mondolfi A, Pagliano P, Esposito S History is repeating itself: Probable zoonotic spillover as the cause of the 2019 novel Coronavirus Epidemic Infez Med. .vol.1; 28(1),pp.3-5,2020.

[3] G. Li, Y Fan, Y. Lai, T. Han, Z. Li, P. Zhou, P. Pan, W. Wang, D. Hu, X. Liu, Q. Zhang, J. Wu Coronavirus infections and immune responses. J Med Virol.Vol. 92(4),pp.424-432,2020.

[4] J. Lei, Kusov Y, Hilgenfeld R. Nsp3 of coronaviruses: Structures and functions of a large multi-domain protein. Antiviral Res. 2018 Jan; 149:58-74

[5] Ahmed W, Angel N, Edson J, Bibby K, et al. 2020. First confirmed detection of SARS-CoV-2 in untreated wastewater in Australia: a proof of concept for the wastewater surveillance of COVID-19 in the community. Sci Total Environ **728**:138764.

[6] LA. Teuwen, V. Geldhof, A. Pasut, P. Carmeliet. COVID-19: the vasculature unleashed. Nat Rev Immunol.vol.20(7),pp.389-391,2020.

[7] J. Li, DQ. Huang, B. Zou, H. Yang, WZ. Hui. A systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. J Med Virol. 2021 Mar;93(3):1449-1458.

[8] Yang C Does hand hygiene reduce SARS-CoV-2 transmission? Graefes Arch Clin Exp Ophthalmol. May.vol.258(5),pp.1133-1134,2020.

[9] Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. 2020. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology **158**:1831–1833.

[10] K. Shen, Y. Yang, T. Wang, D. Zhao, Y. Jiang.. Chinese Medical Doctor Association Committee on Respirology Pediatrics., Chinese Research Hospital Association Committee on Pediatrics., Chinese Non-government Medical Institutions Association Committee on Pediatrics., China Association of Traditional Chinese Medicine, Committee on Children's Health and Medicine Research., China News of Drug Information Association, Committee on Children's Safety Medication., Global Pediatric Pulmonology Alliance.World J Pediatr.vol. 16(3),pp.223-231,2020.

[11] WJ. Wiersinga, A. Rhodes, AC. Cheng, SJ. Peacock, HC. Prescott. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA.vol. 25;324(8),pp.782-793,2020.

[12] RT. Gandhi, JB. Lynch, C. Del Rio. Mild or Moderate Covid-19. N Engl J Med.vol.29;383(18),pp.1757-1766,2020.

[13] Y. Pan, D. Zhang, P. Yang, LLM. Poon, Q. Wang. Viral load of SARS-CoV-2 in clinical samples.Lancet Infect Dis. Apr.vol.20(4),pp.411-412,2020.

[14] L. Zou, F. Ruan, M. Huang, L. Liang, H. Huang, Z. Hong, J. Yu, M. Kang, Y. Song, J. Xia, Q. Guo, T. Song, J. He, HL. Yen, M. Peiris, J. Wu SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients.N Engl J Med. Vol.19; 382(12),pp.1177-1179,2020.

[15] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet.vol.395(10223),pp.497–506,2020.

[16] TP. Sheahan, AC. Sims, RL. Graham. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med.vol.28,pp.9 (396),2017.

[17] P. Horby, WS. Lim, JR. Emberson. RECOVERY Collaborative Group Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med.vol. 25;384(8),pp.693-704,2021.

[18] 18- CK. Yuen, JY. Lam, WM. Wong, LF. Mak, X. Wang, H. Chu, JP. Cai, DY. Jin, KK. To, Chan JF, Yuen KY, Kok KH. SARS-CoV-2 nsp13, nsp14, nsp15 and orf6 function as potent interferon antagonists. Emerg Microbes Infect.vol.9(1),pp.1418-1428,2020.

[19] 19- DW. Cain, JA. Cidlowski. Immune regulation by glucocorticoids. Nat Rev Immunol.vol.17(4),pp.233-247,2017.

[20] 20- JP. Herman, JM. McKlveen, S. Ghosal, B. Kopp, A. Wulsin, R. Makinson, J. Scheimann, B. Myers. Regulation of the Hypothalamic-

Pituitary-Adrenocortical Stress Response. Compr Physiol.vol. 15;6(2),pp.603-21,2016.

[21] 21-Ward LM. Glucocorticoid-Induced Osteoporosis: Why Kids Are Different. Front Endocrinol (Lausanne). 2020 Dec 16;11:576.

[22] 22- JJ. Walker, F. Spiga, R. Gupta, Z. Zhao, SL. Lightman, Terry JR Rapid intra-adrenal feedback regulation of glucocorticoid synthesis. J R Soc Interface. vol. 12(102),pp.20140875,2015.

[23] 23- C. Wagner, M. Griesel, A. Mikolajewska, A. Mueller, M. Nothacker, K. Kley, MI. Metzendorf, AL. Fischer, M. Kopp, M. Stegemann, N. Skoetz, F. Fichtner. Systemic corticosteroids for the treatment of COVID-19. Cochrane Database Syst Rev.vol. 16;8(8),pp.CD014963,2021.

[24] 24- M. Diamond, HL. Peniston, D. Sanghavi, acute respiratory distress syndrome. [Updated]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan

[25] 25- O. Gajic, O. Dabbagh, PK. Park, Adesanya. Critical Illness, and Injury Trials Group: Lung Injury Prevention Study Investigators (USCIITG-LIPS). Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. Am J Respir Crit Care Med.vol. 15;183(4),pp.462-70,2011.

[26] 26 – NJ. Meyer, JD. Christie. Genetic heterogeneity and risk of acute respiratory distress syndrome. Semin Respir Crit Care Med.vol.34(4),pp.459-74,2013.

[27] 27- GS. Shrestha, S. Khanal, S. Sharma, G. Nepal. COVID-19: Current Understanding of Pathophysiology. J Nepal Health Res Counc.vol. 13;18(3),pp.351-359,2020.

[28] 28- NS. Sharma, CV. Lal, JD. Li, XY. Lou, L. Viera, T. Abdallah, RW. King, J. Sethi, P. Kanagarajah, R. Restrepo-Jaramillo, A. Sales-Conniff, S. Wei, PL. Jackson, JE. Blalock, A. Gaggar, X. Xu. The neutrophil chemoattractant peptide proline-glycine-proline is associated with acute respiratory distress syndrome. Am J Physiol Lung Cell Mol Physiol.vol. 01;315(5),pp. L653-L661,2018.

[29] 29- BT. Thompson, RC. Chambers, KD. Liu. Acute Respiratory Distress Syndrome. N Engl J Med. 2017 Aug 10;377(6):562-57290-Rawal G, Yadav S, Kumar R. Acute Respiratory Distress Syndrome: An Update and Review. J Transl Int Med.vol.6(2),pp.74-77,2018.

[30] 30- D. Huang, H. Ma, Z. Xiao, M. Blaivas, Y. Chen, J. Wen, W. Guo, J. Liang, X. Liao, Z. Wang, H. Li, J. Li, Y. Chao, XT. Wang, Y. Wu, T. Qin, K. Su, S. Wang, N. Tan. Diagnostic value of cardiopulmonary ultrasound in elderly patients with acute respiratory distress syndrome. BMC Pulm Med.vol. 13;18(1),pp.136,2018.

[31] 31- G. Rawal, S. Yadav, R. Kumar. Acute Respiratory Distress Syndrome: An Update and Review. J Transl Int Med.vol.6(2),pp.74-77,2018.

[32] 32- E. Fan, L. Del Sorbo, EC. Goligher, CL. Hodgson, L. Munshi. American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med .vol.01,pp.195(9):1253-1263,2017.

[33] 33- SK. Gadre, A. Duggal, E. Mireles-Cabodevila, S. Krishnan, XF. Wang, K. Zell, J. Guzman. Acute respiratory failure requiring mechanical ventilation in severe chronic obstructive pulmonary disease (COPD). Medicine (Baltimore).vol.97(17),pp.e0487,2018.

[34] 34- SJ. Tzotzos, B. Fischer, H. Fischer, M. Zeitlinger. Incidence of ARDS and outcomes in hospitalized patients with COVID-19: a global literature survey. Crit Care.vol.24(1),pp.1–4,2020.

[35] 35- W. Bain, H. Yang, FA. Shah, T. Suber, C. Drohan, N. Al-Yousif.COVID-19 versus non–COVID-19 acute respiratory distress syndrome: comparison of demographics, physiologic parameters, inflammatory biomarkers, and clinical outcomes. Ann Am Thoracic Soc.vol.18(7),pp.1202,2021.

[36] 36- Y. Shimizu. Understanding the immunopathogenesis of COVID-19: its implication for therapeutic strategy. World J Clin Cases.vol.8(23),pp.5835,2020.

[37] 37- JJ. Marini, L. Gattinoni. Management of COVID-19 respiratory distress. Jama.vol.323(22),pp.2329–30,2020.

[38] 38- J. Van Paassen, JS. Vos, EM. Hoekstra, KM. Neumann, PC. Boot, SM. Arbous. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Crit Care.vol.24(1),pp.1–22, 2020.

[39] 39- J. Villar, C. Ferrando, D. Martínez. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir .vol.8,pp.267-276,2020.

[40] 40-41- SA. Fatima, M. Asif, KA. Khan, N. Siddique, AZ. Khan. Comparison of efficacy of dexamethasone and methylprednisolone in moderate to severe covid 19 diseases. Ann Med Surg (Lond). Dec.vol.60,pp.413-416,2020.

[41] 41- JM. Michot, L. Albiges, N. Chaput, V. Saada, F. Pommeret, F. Griscelli, C. Balleyguier, B. Besse, A. Marabelle, F. Netzer,

M. Merad, C. Robert, F. Barlesi, B. Gachot, A. Stoclin. Tocilizumab, an anti-IL-6 receptor antibody, to treat COVID-19-related respiratory failure: a case report. Ann Oncol.Vol.31(7),pp.961-964,2020.

[42] 42- K. Ranjbar, M. Moghadami, A. Mirahmadizadeh, MJ. Fallahi, V. Khaloo, R. Shahriarirad. Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial. BMC Infect Dis.vol.21(1),pp.1–8,2021.

[43] 43- TRF. Smith, A. Patel, S. Ramos,D. Elwood, X. Zhu.Immunogenicity of a DNA vaccine candidate for COVID-19. Nat Commun.vol.20;11(1),pp.2601,2020.

[44] 44- Z. Pasquini, R. Montalti, C. Temperoni, B. Canovari, M. Mancini, M. Tempesta, D. Pimpini, N. Zallocco, F. Barchiesi. Effectiveness of remdesivir in patients with COVID-19 under mechanical ventilation in an Italian ICU. J Antimicrob Chemother.vol. 1;75(11),pp.3359-3365,2020.

[45] 45- R. Fadel, AR. Morrison, A. Vahia, ZR. Smith, Z. Chaudhry, P. Bhargava, J. Miller, RM. Kenney, G. Alangaden, MS. Ramesh; Henry Ford COVID-19 Management Task Force. Early Short-Course Corticosteroids in Hospitalized Patients With COVID-19. Clin Infect Dis. Vol.19.pp,71(16):2114-2120,2020.

[46] 46- K. Wu, AP. Werner, JI. Moliva, M. Koch, A. Choi, GBE. Stewart-Jones, H. Bennett, S. Boyoglu-Barnum, W. Shi, BS. Graham, A. Carfi, KS. Corbett, RA. Seder, DK. Edwards. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. bioRxiv, 2021.

[47] 47- VCC. Cheng, SC. Wong, KKW. To, PL. Ho, KY. Yuen. Preparedness and proactive infection control measures against the emerging novel coronavirus in China. J Hosp Infect. .vol. 104(3),pp.254-255,2020.

[48] 48- MA. Pinzón, S. Ortiz, H. Holguín, JF. Betancur, D. Cardona Arango, H. Laniado, C .Arias Arias, B. Muñoz, J. Quiceno, D. Jaramillo, Z. Ramirez. Dexamethasone vs methylprednisolone high dose for Covid-19 pneumonia. PLoS One.vol.25;16(5),pp.e0252057,2021.

[49] 49- M A. Rana, M. Hashmi, A. Qayyum. Comparison of Efficacy of Dexamethasone and Methylprednisolone in Improving PaO2/FiO2 Ratio Among COVID-19 Patients. Cureus .vol.12(10),pp.e10918,2020.

[50] 50- JJ. Ko,C. Wu,N. Mehta,N. Wald-Dickler, W. Yang, R. A. Qiao Comparison of Methylprednisolone and Dexamethasone in Intensive Care Patients With COVID-19. J Intensive Care Med.vol.36(6),pp.673-680,2021.

[51] 51- EM. Du Plessis, U. Lalla, BW. Allwood, EH. Louw, A. Nortje, A. Parker, JJ. Taljaard, BT. Ayele, PS. Nyasulu, CFN. Koegelenberg. Corticosteroids in critical COVID-19: Are all corticosteroids equal? S Afr Med .vol.6;111(6),pp.550-553,2021.