# CONVALESCENT PLASMA INFUSION DOES NOT APPEAR TO CHANGE THE PROGNOSIS IN ITALIAN PATIENTS HOSPITALIZED WITH SARS-COV-2 PNEUMONIA.

**Short Title: CCP in Patients with COVID-19 Peumonia**


## Abstract

Aims: This case-control prospective study aimed to describe the effects of COVID convalescent plasma (CCP) on late mortality in hospitalized patients with coronavirus disease 2019 (COVID-19) pneumonia.

Study Design: In this study were enrolled 214 consecutive patients with moderate to severe COVID-19 pneumonia hospitalized during the fourth trimester of 2020 in Venice Prefecture (North-East Italy). admitted to COVID-19 Hospitals of our district were enrolled.

Methodology: Confirmation of SARS-CoV-2 infection was made through reverse transcription-polymerase chain reaction test in nasopharyngeal swabs. The severity of each patient's clinical condition was determined considering the Berlin score radiological findings and ventilatory data. Clinical data, risk factors and comorbidity, laboratory test reports and imaging diagnosis of all patients were recorded at hospitalization. In Italy, during the fourth trimester 2020 standard therapy for COVID-19 Pneumonia was: NSAIDs, ventilator support, LMWH, steroids, antibiotics and antiviral drugs; 108 patients received standard therapy alone and 106 received standard therapy in combination with CCP. The endpoint was mortality at 30 days.

Results: Patients series were comparable for gender, age, comorbidity and risk factors, Berlin score, PaO2/FiO2. Data concerning radiological findings and data concerning ventilatory support suggested a higher severity of patients treated with standard therapy plus CCP. Mortality rate at 30 days was 30.6% among subjects treated with standard therapy versus 30.2% among subjects treated with standard therapy plus CCP. The mortality observed in the two groups did not differ significantly. In the present study, however, we observed a higher mortality than reported in the literature. This result may be attributable to the greater severity of the patients considered.

Conclusions: This case-control prospective study showed that in a cohort of hospitalized patients suffering from severe 19 pneumonia, the addition of CCP to the standard therapy did not impact the mortality rate at 30 days. However, we believe that further studies are needed to evaluate the effectiveness of convalescent plasma therapy.



**Keywords:** COVID-19, Serotherapy, Mortality, Pneumonia, Risk factors.

## Introduction

At the end of 2019, a new coronavirus strain was reported in the Chinese province of Wuhan and was named SARS-CoV-2, its subsequent disease was named COVID-19. Italy was the first Western Country where the SARS-CoV-2 infection assumed an epidemic trend with the first two outbreaks in Lombardy and Veneto. The rapid spread COVID-19 led to a high number of hospitalizations and deaths, and the response capacity of our National Health System was almost overwhelmed [1-3]. Moreover, all available antiviral treatments, designed mainly for treatment of HIV, HBV, HCV and Herpes Virus infections, proved to be only partially effective [4-6]. Previous data on the use of convalescent plasma during the recent Ebola, SARS and MEV outbreaks suggested that the administration of plasma obtained from convalescent subjects, containing neutralizing antibodies could be useful in patients with COVID-19. [7-9]. Effectiveness of Covid Convalescent Plasma (CCP) therapy in COVID-19 patients is currently being discussed, with some authors reporting a satisfactory therapeutic impact when treating COVID-19 patients with CCP [10-13], while analysis of two large open-label randomized trial: CONCOR-1 [14] and RECOVERY [15] demonstrated that convalescent plasma did not reduce the risk of intubation or death at 30 days in hospitalized patients with COVID-19. Comparison of published studies is made more complex by a lot of variables: patients selection, different end point, clinical conditions, data recorded, variability of the volume of CCP administered. Furthermore, the definition of CCP appears to be ambiguous. From a methodological perspective, neutralization is considered the reference method for antibody quantification [16-18]. Recommendations regarding antibody titer differ, with the Istituto Superiore di Sanità (ISS) strictly recommending a titer > 1/160 [16], the FDA allowing for a titer >1/80 [17] and the European guidelines prescribing a titer > 1/320 [18]. However, in the studies published, the authors not only treated patients with very different volumes of CCP and with very different titers, but often the quantification of the antibodies was not carried out by titration of the neutralizing activity [10-18].

The aim of this case-control prospective study was to report some considerations about our experience in treatment of hospitalized COVID-19 patients with moderate to severe pneumonia. . The study was performed in the Venice Prefecture area between October - December 2020, during the second epidemic wave in Italy.

## Materials and Methods

*Study Design*: This was a single center case-control prospective study on the long-term effectiveness and safety of the infusion of CCP in hospitalized patients with COVID-19 pneumonia with moderately to severely compromised respiratory function, according to the Berlin score [19]. Moreover the radiological findings were classified as follow 1) bilateral pneumonia, 2) presence of ground-glass opacities, 3) evidence of pulmonary consolidations. The primary endpoint of the study was 30-day mortality. For each subject enrolled in the study, personal data such as age and gender were recorded; as well as data relating to potential risk factors and comorbidities: obesity, with a BMI greater than 30, tobacco smoke, hypertension, diabetes, dyslipidemia, cardiovascular pathologies, cancer, chronic kidney disease, previous pathologies of the respiratory system. The extent of lung involvement evaluated both with imaging methods and by arterial blood gas analysis were taken into consideration; as well as the need for ventilatory support and finally the need for admission to an intensive care unit. Data were recorded at hospital admission as reported in clinical documentation.

*Setting and population*: The study was conducted in Venice Prefecture (North East Italy) and was approved by the local ethical committee. Patients were enrolled from October 01, 2020 to December 31, 2020. All patients underwent a 30-day follow-up which, for the last enrolled patients, ended on March 31, 2021. All of the 214 patients admitted to Hospital with COVID-19 pneumonia were recruited in this study and received standard treatment with steroids (ST), low molecular weight heparin (LMWH), non-steroidal anti-inflammatory drugs (NSAID), antibiotics (AB) and antiviral drugs (AV); of these, 106 received CCP infusion as well. Patients received standard therapy alone or in combination with CCP, according to the indications of the clinicians who were treating them, meaning no randomization was involved (Figure 1). All subjects considered in this study were at least 18 years old. The enrolment protocol in the group treated with CCP provided for the consent to the infusion of plasma, the absence of previous phenomena of intolerance to the transfusion of blood components. Furthermore, the maximum time interval allowed between the onset of symptoms and the start of the CCP infusion had to be less than twelve days.

*Convalescent donors and plasma*: Males and females aged from 18 to 60 years and with no history of blood transfusions or pregnancies who had recovered after a symptomatic (respiratory symptoms, fever, anosmia, ageusia, flu like syndrome, etc.) and microbiologically confirmed (positive molecular nasopharyngeal swabs) SARS-CoV-2

infection were recruited. Each donor gave specific written consent to the procedure after receiving adequate information in a confidential interview with a doctor. Eligibility for plasma donation was assessed according to current Italian National transfusion regulamentations. [20]. Further enrollment criteria were: complete clinical recovery, two consecutive negative nasopharyngeal molecular swabs performed between 7 - 30 days before potential recruitment as donors and a neutralizing titer of anti SARS-CoV-2 antibody $\geq$80 [21]. In addition to the tests required by law, CCP donors were tested for SARS-CoV-2-RNA, HAV-RNA, HEV-RNA, Erytrovirus-DNA, Anti-SARS-CoV-2 antibodies. Plasma (650-700 mL) was collected using latest-generation cell separators (Aurora – Fresenius Kabi), and, after each procedure, was immediately equally divided into three bags (about 200 mL) using a sterile tubing welder. Plasma pathogen reduction was performed with the INTERCEPT processing system (Cerus Europe BV) [22]. The units collected were stored at a controlled temperature ranging from - 40°C to - 30°C.

*Plasma infusion*: Plasma was delivered ready-for-use by the Transfusion Medicine Service to Clinical Units and was administered to patients over 30 to 60 minutes, on three consecutive days, under supervision of the treating physician. Each patient gave specific written consent to the procedure after receiving adequate information in a confidential interview with a doctor.

*SARS-CoV-2 micro neutralization assay*: The titer of neutralizing antibodies against SARS-CoV-2 was determined as previously described [23]. In summary, 50 mL of a serum sample from each donor, starting from 1:10 in a serial 4 - fold dilution series, were added to two wells of a flat-bottomed tissue culture microtiter plate mixed with an equal volume of 50, 50% tissue culture infectious dose ($TCID^{50}$) of a previously titrated, SARS-CoV-2 strain. Plates were incubated at 33°C in 5% $CO^2$. After 1 h of incubation, VERO E6 cells were added to each well. After 48 additional hours of incubation the wells were scored to evaluate the degree of cytopathic effect compared to that of the virus control. Blue staining of the wells denoted the presence of neutralizing antibodies. The neutralizing titer was the maximum dilution that presented a 90% reduction of the cytopathic effect. A positive titer was defined as equal or greater than 1/10. Positive and negative controls were included in all test runs [24,25 ].

*Statistical Analysis:* Data were analyzed using MedCalc Ver.8.0.0 (Medcalc SW Bvda, Ostend, Belgium). In a first stage data distribution was evaluated using the Skewness (CS) and Kurtosis (CK) coefficients, “normality” was evaluated using the D’Agostino-Pearson (DP) test. Having found that the distribution of the results was not "normal", we

used a non-parametric statistical approach: categorical data are presented as numbers (percent) and continuous data as median (I and III quartiles) and Interquartile range (IQR).. Proportions comparison was performed using a Chi square test; median comparison was performed using a Mann-Whitney test. A p=.05 was considered statistically significant. The primary outcome was analyzed using a two-sided Wald test of the null hypothesis that probability of death at 30 days is the same among patients receiving standard therapy or standard therapy plus CCP.

**Results**

We recruited 214 patients, 108 were treated with standard therapy (ST) as reported above (ST) and 106 also received CCP. As reported in table I, at hospital admission, the two series were comparable for age and gender ; comorbidity: hypertension, hyperlipemia, diabetes, cardiovascular disease, respiratory disease (RD), neoplastic disease, chronic kidney disease (CKD); such as for risk factors: tobacco smoke and obesity (BMI>30).

As reported in table II, at hospital admission the two series of were comparable for PaO2/FiO2, SpO2, tachypena (respiratory rate > 30/ minute), presence of fever (over 37°C). We observed lower median PaO2/FiO2 ratio ($p<0.05$) and a higher prevalence ($p<0.01$) of subjects with PaO2/FiO2 rate <200 in patients treated with CCP. Practically all yje considered patients had a O2 blood saturatio in ambient air (SpO2) lower than 93% As matter of facts in these patient series all subjects required O2 support. Among patients treated with CCP, we observed 14 patients (13.2%) that needed low flow O2 with a simple mask, 22 (20.7%) needed high flow O2 with a reservoir or a Venturi mask, 70 (66.1%) needed C-Pap and/or intubation. Among patients treated with ST, we observed 23 patients (21.3%) that needed low flow O2 with a simple mask, 21 (19.4) needed high flow O2 with a reservoir or a Venturi mask, 65 (60.3%) needed C-Pap and intubation. Among patients treated with CCP we observed a statistically significant higher ($p=0.01$) prevalence of subjects needing intubation.

Comparing the severity of pulmonary function impairment evaluated using the Berlin score, none significant difference could be detected among the two patients groups. As a matter of fact, we observed a moderate ARDS (Acute Respiratory Distress Syndrome) in 57 (53.7%) patients treated with CCP infusion versus 59 (54.6%) patients treated without CCP, and a severe ARDS in 49 (46.3%) patients treated with CCP infusion versus 51 (45.4%) patients treated without CCP. On the other hand, regarding chest imaging study we observed a higher ($p=0.02$) prevalence of evidence of pulmonary consolidations in patients treated with CCP.

As reported in Table III all patients received AB and NSAIDs, no significant difference was observed between the two patient series for ST, LMWH and Tozicilizumab. A higher percentage of subjects treated with ST alone was treated with Remdesivir, compared to patients that received CCP therapy (88.9% versus 76.4%, p=0.01).

Among 106 patients treated with CP, collateral effects were observed in 4 (3,7%): 3 urticaria and 1 dyspnoea.

With regards to mortality within 30 days from diagnosis, we recorded 32 deaths (30.2%) among patients treated with CCP infusion versus 33 (30.6%) among patients treated without CCP plasma infusion (a two-sided Wald test did not allow to exclude the null hypothesis).

**Discussion**

Based on experience gained during the SARS-CoV epidemic in 2002 [9] and Ebola virus outbreak in 2015 [8], the use of convalescent plasma has been considered a possible therapeutic solution for COVID-19 patients especially in the first year of the pandemic when antiviral treatments did not appear to be effective, monoclonal antibodies were not available and vaccines were still being studied. Obviously, CCP must meet the safety requirements established by Italian National transfusion regulations as well as the specific product standard agreed upon by the National Blood Centre [20,26]; it must also adhere to specific characteristics and quality requirements (e.g. treatments or presence of adequate concentration of neutralizing anti-SARS-CoV-2 antibodies) [26,27].

At present, despite the numerous clinical studies and meta-analysis conducted so far, while the safety of therapy with CCP has been confirmed, conclusive results with respect to its effectiveness have not yet been provided [29-31]. A recent WHO document recommended against administering CCP except in the context of clinical trial [32].

During the second epidemic wave in Italy, therapeutic protocols for the treatment of patients with COVID-19 were not fully defined and they were based on: ventilatory support, NSAIDs [33], LMWH [34], steroids [35], antibiotics [36] and antivirals (mainly Remdesivir) [37]. In Italy, CCP has never been considered a standard therapy for COVID-19 patients, its use was initially limited in clinical trials, although it was sometimes used "for compassionate use". In any case, PCC has never been recommended as first-line therapy, but its use has always been considered as "auxiliary" to standard therapy, therefore meaning its use largely depended on the clinician's "beliefs" on its effectiveness [16,21,22]. Therefore, in this study, patients were not randomized and CCP was assigned as required by the clinical departments. Our case-control prospective study was performed

to compare the outcome of patients with COVID-19 pneumonia and moderate to severe ARDS. 214 patients were enrolled; 108 subjects received ST alone and 106 ST plus CCP. At hospital admission the two patient groups were comparable for age, gender distribution, comorbidity and risk factors. Moreover, at first evaluation the two groups were also similar for disease severity classification using the Berlin score [19,39-41]. The two series of subjects had comparable PaO2/FiO2 values, however, in patients treated with CCP it was possible to detect a higher percentage of subjects with PaO2/FiO2 <200. Some of the data collected in the present study would seem to suggest that patients treated with standard therapy alone had less severe disease than patients also treated with CCP. For example, considering radiological findings, we found a higher prevalence of patients with evidence of pulmonary consolidations among subjects treated CCP plus standard therapy than in subjects treated with standard therapy alone. Furthermore, patients treated with CCP infusion in addition to standard therapy more frequently presented the need for more aggressive ventilatory support using high flows of oxygen, venturi mask and the need to proceed with intubation.These observations would seem to suggest that clinicians, in our operating setting, tended to request CCP in more compromised patients, probably believing they had a reduced probability of responding favourably to conventional therapy.

In the authors' experience, considering 30-day mortality as the endpoint, no effectiveness in the use of CCP could be highlighted. In fact, in the 108 patients treated with standard therapy the mortality at 30 days was 30.6% while in patients treated with standard therapy plus convalescent plasma the mortality at 30 days was 30.2%. As a matter of fact, a two-sided Wald test did not allow to exclude the null hypothesis. These conclusion were strongly supported by results obtained in two large open-label randomized trial: CONCOR-1 [14] and RECOVERY [15] who have demonstrated how convalescent plasma did not reduce the risk of intubation or death at 30 days in hospitalized patients with COVID-19 pneumonia.

In our patient series we detected a mortality ratio higher than data reported by other authors [42,43]. We believe that the poor prognosis observed should be related to the high prevalence of patients with severe disease enrolled in this study. It should be noted that, in the group of 108 subjects treated only with standard therapy, 38 (35.2%) patients were admitted to Intensive Care Units (ICU); while, among 106 subjects treated with standard therapy plus CP, 39 (36.8%) were admitted to ICU. As reported in table IV in subjects treated only with standard therapy, we observed 23 deaths out of 38 patients admitted to ICU (60.5%), versus 10/70 (14.3%) patients who did not need intensive care,

whereas in subjects treated with CCP plus standard therapy, we observed 23 deaths out of 39 patients admitted to ICU (59.1%), against 9/67 (13.4%) among patients who did not need to be admitted to ICU. it is interesting to note how the prevalence of deceased patients in subjects admitted to ICUs and of patients not admitted to ICUs is very similar in subjects treated with standard therapy and in subjects also treated with cob CCP infusion. This observation which on the one hand seems to suggest a high prognostic value to the criticality of the conditions at the time of hospital admission while on the other hand it seems to suggest a reduced capacity of the available therapeutic options to significantly affect the evolution of the disease. As reported in table II, all patients considered in this study, were classified, using the Berlin score, as subjects with moderate or severe ASDS. .A mortality of around 30% good agreement with what is expected for patients classified with moderate - severe ARDS according to the Berlin score [16,21]..

In this patients series plasma infusion was generally well tolerated, we observed only 4 (3.7%) mild adverse reactions , none of which required the suspension of therapy, these results were in good accord with literature data suggesting a good safety of convalescent plasma therapy [44,45].

The main limitation of this study is its design: in fact it is not a randomized prospective study but a single center case-control prospective study. Therefore the patients were not assigned to the group treated with standard therapy or to that also treated with CCP on the basis of a randomization process but according to the indications of the attending physician who required or not plasma infusion. . Moreover unfortunately, we do not have any data about the treatments carried out at home before admission to the hospital.

However, we believe that our study has some strengths. Undoubtedly, in our opinion, the main one is the fact that, contrary to what has been done by other authors, we used two groups that were found to be well comparable in terms of age, gender, lifestyle habits, risk factors and comorbidities [ 38-43]. Another point of extreme interest seems to us to be the considerable number of clinical parameters detected upon enrollment of patients, data relating to pulmonary imaging, respiratory function, general coenaesthesia. Furthermore, data relating to antiviral and supportive therapies carried out during hospitalization and, in patients treated with CCP infusion, data relating to any side effects were also collected and compared. A further aspect that deserves consideration is the level of competence of the staff and the technological equipment of the hospitalization units, in fact it seems obvious that the experience of the clinical staff and the available technology could only influence the result [38-43]. In our study, all patients were admitted and treated in the

same two COVID-19 hospitals in our Prefecture. We therefore believe that any influence related to the level of expertise of the clinical staff and the available technology has been minimized as much as possible. The variables related to the administration of the plasma were also minimized as much as possible (obviously it is still a biological product and not a drug): the antibody quantification was carried out by titration of the neutralizing antibodies carried out at a regional reference laboratory, we only used PCCs with a neutralizing antibody titre equal to or greater than 1/80, the plasma was obtained exclusively by apheresis as described above, each patient was treated with one 200 ml unit per day for three consecutive days, each patient received the three "daughters" units obtained from the processing of the same plasma unit from "mother" apheresis, the assignment of the plasma is carried out centrally by adopting uniform criteria for its selection [10,11,16,33].

**Conclusions**

In conclusion, SARS-CoV-2 has spread rapidly across the globe and preparedness of National Health System in the Western World proved to be inadequate. In the absence of a specific and effective treatment during the current pandemic, thousands of patients died, thousands more needed intensive care and the Hospital system nearly crashed. In these critical conditions it seems CCP therapy should be effective for a better outcome of COVID-19 infection in severe and critically ill patients.

Before any efficacy analysis, our results have confirmed that treatment of severe COVID-19 patients is very safe, in accordance with other reports [44,45].

The data obtained in the present study do not seem to confirm the efficacy of CCP therapy in hospitalized patients with moderate to severe COVID-19 pneumonia, at least using 30-day mortality as an end point. in fact, it was not possible to observe a decrease in the 30-day mortality rate. However, we believe that more studies are needed to evaluate the utility of convalescent plasma therapy, the selection criteria for patient selection needed to evaluate the efficacy of convalescent plasma therapy, the criteria for patient selection, the evaluation of the CCP title, the administration schedule deserve further consideration [46-53].

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**Authorship**: All co-authors have read and approved the attached manuscript and shared the choice of the journal to submit it to. All co-authors contributed significantly to the elaboration of the manuscript. In particular:

- GESSONI Gianluca designed the study and revised the manuscript,
- MORO Lauretta and ROSSI Carla collaborated in the drafting of the manuscript,
- PIVETTA Michela, COLUCCIA Enza, COLLODEL Luca and ROVERONI Giovanni carried out the data collection and statistical processing.
- CARRETTA Giovanni contributed in identification of risk factor and in definition of the methodological approach.
- TESSARIN MICHELE created the logistical and organizational conditions for the establishment of the convalescent plasma bank,
- BAGNARA Domenico provided the specific morbidity and mortality statistics for ULSS 3 Serenissima.
- VALVERDE Sara performed laboratory data collection and analysis
- VALLE Roberto performed multivariate analysys and assigned clinical scores.

**Ethical Statement**: The study was authorized by the Ethics Committee for Clinical Research of the province of Venice with decree N ° 196828 of 15/05/2020.
All the procedures described in the study, and which involved human beings were implemented in accordance with the ethical standards established by the Helsinki Declaration of 1964 and subsequent amendments.
Each patient / donor has issued written informed consent for enrolment in the convalescent plasma collection project.
Each patient / recipient gave written informed consent for enrolment in the arm that involved the administration of convalescent plasma.
No animal studies were performed in the conduct of the study.
**Conflict of Interest**: The authors are all employees of the National Health Service and are not carriers of conflict of interest.

**Table I: Description of demographic data, risk factosr and comorbidity at hospital admission**

| | Plasma Infusion YES | Plasma Infusion NO | Statistical Significance |
|---|---|---|---|
| **Patients** | 106 | 108 | p>0.05 |
| **Demographic data** | | | |
| **Male** | 83 (78.3%) | 79 (73.1%) | p>0.05 |
| **Age (median)** | 63 (from 32 to 86) | 64 (from 35 to 91) | p>0.05 |
| **Risk factors** | | | |
| **Tobacco Smoke** | 19 (17.9%) | 20 (18.5%) | p>0.05 |
| **Obesity (BMI>30)** | 21 (19.8%) | 25 (23.1%) | p>0.05 |
| **Comorbidities** | | | |
| **Hypertension** | 65 (61.3%) | 63 (58.3%) | p>0.05 |
| **Hyperlipemia** | 20 (18.9%) | 17 (15.7%) | p>0.05 |
| **Diabetes** | 23 (21.7%) | 21 (19.4%) | p>0.05 |
| **Cardiovascular diseases** | 8 (7.5%) | 9 (8.3%) | p>0.05 |
| **Respiratory diseases** | 7 (6.6%) | 4 (3.7%) | p>0.05 |
| **Tumor** | 7 (6.6%) | 9 (8.3%) | p>0.05 |
| **Chronic kidney impairment** | 9 (8.5%) | 11 (10.2%) | p>0.05 |

No statistically significant difference was observed comparing the two groups.

**Table II: Patients' clinical characteristics at hospital admission**

| | Plasma Infusion YES | Plasma Infusion NO | p |
|---|---|---|---|
| **Patients** | 106 | 108 | |
| **Ventilatory data** | | | |
| **PaO2/FiO2** | 166 (IQ113 – IIIQ220) | 171 (IQ125 - IIIQ234) | p>0.05 |
| **PaO2/FiO2 < 200** | 95 (89.6%) | 87 (80.5%) | P<0.01 |
| **SpPO2 <93%** | 101 (95.2%) | 99 (91.6%) | p>0.05 |
| **Tachypnea (>30 rr)** | 100 (94.3%) | 99 (91.6%) | p>0.05 |
| **Fever (>38°C)** | 94 (88.7%) | 97 (89.8%) | p>0.05 |
| **Berlin score** | | | |
| **Moderate** | 57 (53.7%) | 59 (54.6%) | p>0.05 |
| **Severe** | 49 (46.3%) | 51 (45.4%) | p>0.05 |
| **Chest Imaging** | | | |
| **Bilateral Pneumonia** | 18 (17.1%) | 23 (21.3%) | p>0.05 |
| **Ground Glass Opacities** | 31 (29.2%) | 36 (33.3%) | p>0.05 |
| **Pulmonary Consolidation** | 57 (53.7%) | 49 (45.4%) | p=0.02 |
| **Ventilatory support** | | | |
| **Low flow** | 14 (13.2%) | 23 (21.3%) | P<0.01 |
| **High flow** | 22 (20.7%) | 21 (19.4%) | p>0.05 |
| **Intubation** | 70 (66.1%) | 65 (60.3%) | P<0.01 |
| **Hospital admission criteria** | | | |
| **Ordinary Care Units** | 22 (20.8%) | 33 (30.6%) | P<0.01 |
| **Sub Intensive Care Units** | 45 (42.5%) | 37 (34.3%) | P<0.01 |
| **Intensive Care Units** | 39 (36.8%) | 38 (35.2%) | p>0.05 |

As reported in the table in the group of patients treated with CCP we observed a percentage of subjects with PaO2/FiO2 lower than 200 significantly lower ($p<0.01$) compared to the patients treated with standard therapy alone. Patients treated with CCP had a higher prevalence of severe lung imaging (consolidation); they also tended to require more intensive ventilatory support than patients not treated with CCP. Furthermore, subjects treated with standard therapy alone were less likely to be admitted to a sub-intensive care units.

**Table III: Comparison of therapeutic approach in the two patient groups**

| | Plasma Infusion YES | Plasma Infusion NO | p |
|---|---|---|---|
| **Patients** | 106 | 108 | -- |
| **Ventilatory support** | 106 (100%) | 108 (100%) | p>0.05 |
| **NSAIDs** | 106 (100%) | 108 (100%) | p>0.05 |
| **LMWH** | 104 (98.1%) | 104 (96.3%) | p>0.05 |
| **Steroids** | 102 (96.2%) | 106 (98.1%) | p>0.05 |
| **Antibiotics** | 106 (100%) | 108 (100%) | p>0.05 |
| **Remdesivir** | 81 (76.4%) | 96 (88.9%) | P<0.01 |
| **Tocilizumab** | 10 (9.4%) | 12 (11.1%) | p>0.05 |
| **Colchicine** | 1 (0.9%) | 0 (0.0%) | p>0.05 |
| **Plasma Infusion** | 106 (100%) | 0 (0.0%) | -- |

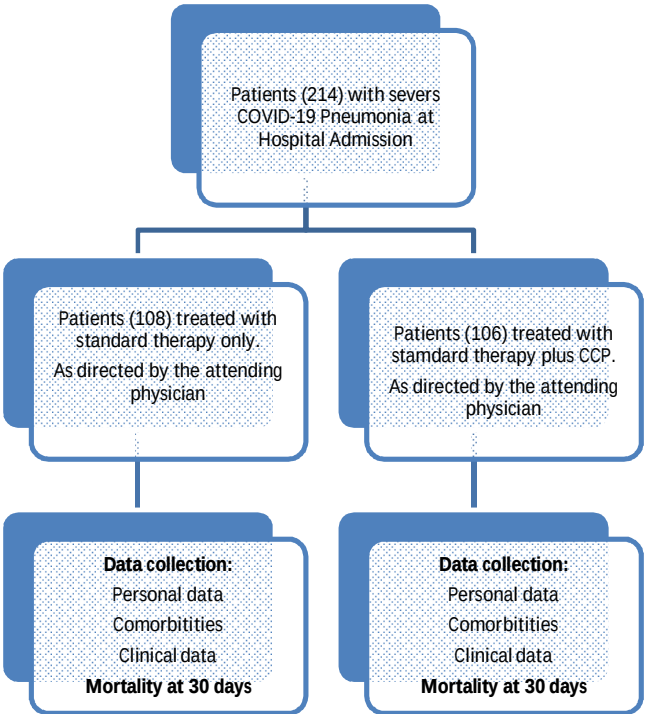
As reported in the table, in the group of patients treated with CCP we observed a significantly lower percentage of subjects treated with the antiviral drug Remdesivir ($p<0.01$) compared to patients treated with standard therapy alone.

**Table IV: Data concerning mortality in patients treated with standard therapy alone or standard therapy plus CCP andimte or not admitted in an Intensive Care Units**

| | Plasma Infusion YES | Plasma Infusion NO | p |
|---|---|---|---|
| **Patients** | 106 | 108 | -- |
| Overall Mortality | 32 (30.2%) | 33 (30.6%) | p>0.05 |
| Patients admitted in ICU | 39 (36.8%) | 38 (35.2%) | p>0.05 |
| Mortality in ICU patients | 23 (59.1%) | 23 (60.5%) | p>0.05 |
| Patients not admitted in ICU | 67 (63.2%) | 70 (64.6%) | p>0.05 |
| Mortality in not ICU patients | 9 (13.4%) | 10 (14.3%) | p>0.05 |

As shown in the table, the mortality detected was much higher in patients admitted to the ICU but the mortality data were practically superimposable in the series of patients treated with standard therapy alone compared to patients treated with standard therapy plus CCP.

**Figure 1: Patients enrollment**




The flow chart shows the criteria for enrollment of patients in the study

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