IOSUD – "DUNAREA DE JOS" UNIVERSITY OF GALATI

Doctoral School of Biomedical Sciences

DOCTORAL DISSERTATION

THE THERAPEUTIC APPROACH IN CRITICAL PATIENTS WITH SARS CoV 2 RESPIRATORY INFECTION

Doctoral Student,

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Doctoral Supervisor,

Prof. univ. dr. habil. FIRESCU DOREL

Series M No. 5

ANUL

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- DOCTORAL DISSERTATION ABSTRACT -

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1.1 SHORT HISTORY

The COVID-19 pandemic represented the worldwide spread of an infectious disease caused by the SARS-CoV-2 virus. The first confirmed case of infection with the new coronavirus was identified in December 2019 in China, the virus spreading rapidly afterwards in all countries of the world. This led the World Health Organization to declare the occurrence of this disease a Public Health Emergency of International Concern on 30th January 2020 and to characterize this spread as a pandemic on 11th March 2020 (World Health Organization / overview). Since the onset of the pandemic, around 2 million people in European countries have lost their lives.

1.2 ETIOLOGICAL AND PATHOPHYSIOLOGICAL ASPECTS

1.2.1 Etiology

Coronaviruses (CoV) are positive-sense, single-stranded encapsulated RNA viruses (+ssRNA). Their genome is about 30 kb long and is among the largest RNA viruses known. CoV belong to the order *Nidovirales*, suborder *Cornidovirineae* and family *Coronaviridae*. This family of viruses is further classified into four different genera, based on genetic and antigenic studies of human and animal coronaviruses. While *Alphacoronaviruses* and *Betacoronaviruses* mainly infect mammalian species, including humans, *Gammacoronaviruses* and *Deltacoronaviruses* mainly infect avian species (V'kovski P., Kratzel A, 2021). Alphacoronaviruses include HCoV-229E and HCoV-NL63, while Betacoronaviruses include HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV and SARS-CoV-2 (Heinz F.X., Stiasny K,2020).

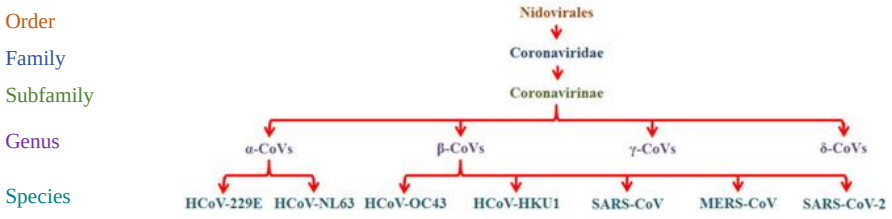

Figure 1.2.1.1 Classification of coronaviruses (Balasubramanian Ganesh,et al.,2021)

HCoV viral particles are spherical-shaped, with a diameter of 80-120 nm. Both membrane glycoproteins (M) and envelope protein (E) are incorporated into the host's lipid bilayer (envelope) surrounding the virus particle (virion) surface. The virion surface contains prominent Spike (S) trimeric glycoproteins formed by subunits S1 and S2, which gives the virus its crown-like appearance, viewed under electron microscopy. In the case of SARS-CoV-2, the S1 subunit containing the receptor-binding domain (RBD) directly binds the cell surface receptor, such as angiotensin-converting enzyme 2 (ACE2) for SARS-CoV-2, which is expressed on the surface of cells in the human respiratory and gastrointestinal tract and mediates viral penetration. Meanwhile, the S2 subunit mediates membrane fusion. The S protein is also the primary target of neutralizing antibodies against SARS-CoV-2. Inside the virion, the nucleocapsid protein (N) binds the viral RNA genome, which together form a helical structure (Magan Solomon, et at.,2022).

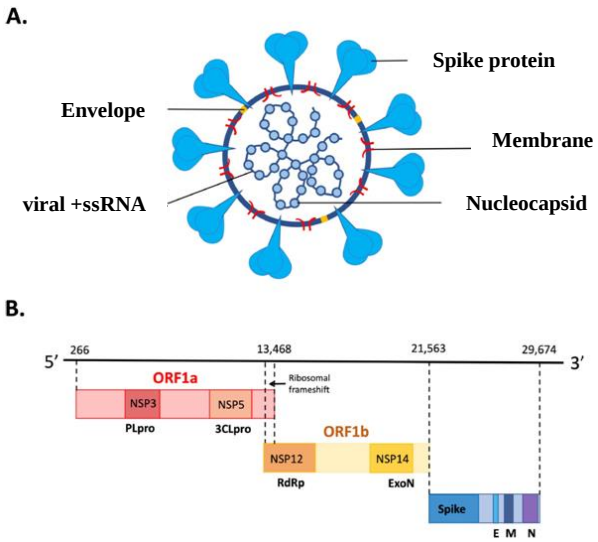

Figure 1.2.1.2 Scheme of HCoV viral particle and genome. (A) HCoV virions contain membrane proteins and envelope embedded in the double lipid layer surrounding the viral particle. S proteins exit the surface of the viral particle. The +ssRNA genome is encapsulated by protein nucleocapsids. (B) SARS-CoV-2 genome schema. Viral NSPs are predominantly involved in viral replication and are encoded by ORF1a and ORF1b. The remaining ORFs encode accessory and structural proteins, including spike, envelope, membrane, and nucleocapsid proteins (Magan Solomon, et al.,2022).

SARS-CoV-2 variants

Different variants of COVID-19 have been identified since 2019. The mutations in the Spike protein are called S key mutations because of the S protein's role in binding to the angiotensin 2 receptor, antigenic effect, cell entry, transmissibility, virulence, and protection against the host's immunity. The neutralizing antibodies that bind themselves to the S protein are important in the humoral immune response against SARS-CoV-2 (Z. Jia, W. Gong, 2021).

At the end of 2020, the WHO classified the new variants of SARS-CoV-2 based on significant amino acid substitution, using the Greek alphabet to classify them. Based on the latest update of 7th June 2022, SARS-CoV-2 variants are classified into variants of concern (VOC), variants being monitored (VOB), variants of interest (VOI), VOC lineages under monitoring (VOC-LUM) and variants of high consequences (VOHC).

The B 1.17 variant, also known as the Alpha variant, is the first variant introduced in December 2019 and the variant with the lightest and fastest extension (A. Muik, A. K. Wallisch, 2021).

The B.1.351 variant, also known as the Beta variant, the previously circulating VOC, was first detected in South Africa in late December 2020 and showed an increase in the transmissibility of the virus. This variant is capable of reinfecting people with a history of COVID-19 infection.

The P.1 variant, also known as the Gamma variant, was first reported in Manaus, Brazil, in January 2021 and later reported in Japan, Korea and the Faroe Islands (K. Kai-Wang To, S. Sridhar, et. al., 2021).

The B.1.427 and B.1.429 variant, also known as the Epsilon variant, was first reported in the United States in July 2020. The Epsilon variant is now classified as the previous VOI.

The P.2 variant, also known as the Zeta variant, is now classified as the previous VOI. It was first detected in Brazil in April 2020.

The B.1.525 and B.1.526 variants, also known as the Eta and Lota variants, respectively, share common mutations of the S protein. The Eta variant was first identified in Nigeria in December 2020, and Lota was first reported in November 2020 in the United States. They are now classified as previous VOI.

The B.1.617.1 variant, also known as the Kappa variant, was first identified in October 2020 in India and is now classified as the previous VOI and the B.1.617.1 variant,

also known as the Kappa variant, was first identified in October 2020 in India and is now classified as the previous VOI.

The B.1.617.1 variant, also known as the Kappa variant, was first identified in October 2020 in India and is now classified as the previous VOI, and the B.1.621 variant, also known as the Mu variant, was first identified in January 2021 in Colombia and became the predominant variant during that time. It is now classified as previous VOI.

The Delta variant, also known as the B.1.617.2 variant, was first detected in India in October 2020 and considered the previously circulating VOC until 7th June 2022 (https://www.who.int/activities/tracking-SARS-CoV-2-variants). The Delta variant has spread rapidly around the world and has caused large numbers of infections, hospitalizations, and mortality rates. The COVID-19 variant currently circulating, according to WHO, is the Omicron variant (VOC).

The Omicron variant, also known as B.1.1.529, was first detected in Botswana and South Africa and spread fairly quickly to several countries in November 2021 and was considered a VOC on 26th November 2021. Compared to the Delta variant, the Omicron variant has mostly affected the younger population and those with higher vaccination rates. In a retrospective cohort study conducted on a group of 699 patients diagnosed with the Omicron variant, the severity of clinical manifestations of the disease in vaccinated versus unvaccinated patients was compared, finding a much lower rate of hospitalization and a favorable evolution in vaccinated subjects (Manole C., Baroiu L., et al., 2023).

1.2.2 PATHOPHYSIOLOGY

The COVID-19 pandemic is a complex problem and should not be considered as a single unit, but as a heterogeneous group of infections. Several disease- and patient-related factors are involved in the development of COVID-19. The complications of COVID-19 include Acute Respiratory Distress (ARDS) (J. Stebbing, et al., 2020), arrhythmias, shock, acute kidney injury, acute heart injury, liver dysfunction, and secondary infection. The poor clinical response has been linked to the disease severity (X. Yang, et al., 2020).

The pathophysiology of acute respiratory distress in SARS-CoV-1 or MERS-CoV infection has not been fully understood. Previous studies have indicated that high levels of proinflammatory cytokines in serum (e.g., IL6, IL12, IFNγ, IP10, and MCP1) have been associated with inflammation and extensive lung damage in SARS patients (C. Wong, et al.,

2004). Progression to ARDS signifies worsening of respiratory symptoms and eventually leads to respiratory failure. ARDS occurs as a complication within a week of clinical signs appearing. Arterial blood oxygen partial pressure values/inspired oxygen fraction (PaO_2/FiO_2) are used to differentiate the severity of ARDS based on varying degrees of hypoxia. PaO_2/FiO_2 values less than 100 mmHg indicates severe ARDS. PaO_2/FiO_2 values between 100 mmHg and 200 mmHg indicate moderate ARDS, and those between 200 mmHg and 300 mmHg support the diagnosis of mild ARDS. The levels of aspartate transaminases (AST) and alanine transaminases (ALT) at the time of admission are correlated with the clinical worsening of ARDS symptoms. Therefore, higher levels at admission betray respiratory deterioration, with progression to ARDS (S.A. Hassan, et al., 2010).

A research group in China studied the pathological features of a patient who died from a serious SARS-CoV-2 infection through post-mortem biopsy. The patient was a 50-year-old man hospitalized with fever, chills, dry cough and shortness of breath. Biopsy samples were taken from the patient's lungs, and the biopsy of the left lung tissue revealed pulmonary edema and the formation of hyaline membranes, which indicates ARDS. Inflammatory infiltrates of interstitial mononuclear cells were observed in both lungs (Z. Xu, et al., 2020).

1.3 CLINICAL MANIFESTATIONS

The clinical characteristics specific to SARS – Cov 2 infection or COVID – 19 diseases are similar to those of Severe Acute Respiratory Syndrome (SARS): dry cough, fever, dyspnea, myalgia, fatigue and radiological evidence of opacities in "frosted glass", also found in atypical pneumonia (Cheng VC, 2007).

1.4 PRINCIPLES OF TREATMENT

1.4.1 Antiviral therapy

The onset of the pandemic triggered a series of unprecedented social, economic and healthcare challenges. To control and reduce the rate of infections, several non-pharmacological measures, such as social distancing, isolation, quarantine, use of masks and

hand and surface disinfectants, have been applied. The often-severe clinical evolution of patients infected with the new SARS-COV 2 and the lack of a safe and effective treatment have generated the motivation to search and identify treatments for this new disease in order to prevent its mortality and morbidity (M.A. Martinez, 2019).

Several antiviral medicines pre-existing at the time of the pandemic have been reused as antiviral agents against SARS-CoV2, but none of these have clearly demonstrated their effectiveness so far.

Medication	Original indication	Target at virus level
Favipiravir	Influenza virus	RNA polymerase
Remdesivir	HCV, Ebola, MERS-CoV	RNA polymerase
Lopinavir/ritonavir	HIV-1	Protease
Darunavir/cobicistat	HIV-1	Protease
Hydroxychloroquine	Malaria	Cell entry
Azithromycin	Antibiotic	Undefined
Ivermectin	Parasitic diseases	Undefined

Table 1.4.1.1 Examples of antiviral medicines created for other pathologies but also used for Covid-19 (J.-T.Jan, et al.,2021; Martinez M. A., 2020;).

Azithromycin, Hydroxychloroquine and **Lopinavir/Ritonavir** were in the first months of the pandemic the medicines most commonly used in most centers in the fight against Covid-19 and, although their choice was not based on clear evidence, they were used primarily in empirical therapy against the SARS CoV-2 virus. All of these medicines have been associated with corrected QT interval prolongation as an adverse effect, which has raised concerns about the risk of ventricular arrhythmias occurrence, particularly Torsades de Pointes and sudden cardiac death (E.P. Rock, 2009).

The use of **Ivermectin** in the treatment of Covid 19 has sparked a number of controversies in the medical world, being a medicine mainly used in veterinary medicine. Initially, there were a few studies that demonstrated Ivermectin's potential of shortening the duration of illness, but later studies had conflicting results regarding its effectiveness (Sabeena Ahmed, et al., 2021).

1.4.2 Anti-inflammatory and immunomodulatory therapy

Tocilizumab is a monoclonal antibody that acts against Interleukin-6 and thus reduces inflammation, increased IL-6 concentrations have been shown to be a negative prognostic factor in Covid-19 infections. Before the Covid-19 pandemic, Tocilizumab was a medicine used in several inflammatory conditions such as rheumatoid arthritis, giant cell arteritis, and systemic juvenile idiopathic arthritis (The RECOVERY Collaborative Group, 2021).

The use of this medicine in SARS-CoV-2 infection has been considered by multidisciplinary teams after an inadequate response to systemic corticoids and disease progression with the need for Hy-Flow or CPAP-NIV use and admission to intensive care units was demonstrated in a significant number of patients (HSE interim guidance, 2021). Two large randomized trials, RECOVERY and REMAP-CAP, analyzed and demonstrated the benefits of survival with Tocilizumab compared to the standard medical care (Recovery Collaborative Group, 2021). But not all studies have shown the same results. In the randomized COVACTA trial, for the hospitalized patients with COVID-19 disease, tocilizumab did not demonstrate improvement in mortality at 28 days or 60 days, but showed the shortening of the hospitalization period, as well as of the days spent in Intensive Care (Ivan O., 2022).

Another medicine used during the Covid-19 pandemic with an immunomodulatory role is **Anakinra**, the first biologically recombinant medicine, IL-1 receptor antagonist with inhibiting power at both IL-1α and IL-1β levels, approved for the treatment of rheumatoid polyarthritis. The medicine has several unique advantages over other medicines used in Covid-19, demonstrated by a superior safety profile (P. Mehta, 2020). A meta-analysis of 3179 patients showed promising results by reducing the need for mechanical ventilation and reducing mortality. It is recommended to be used more in mild and moderate forms of the disease to avoid potential complications related to immunosuppression (Aliae A.R, 2023).

Other systemic corticosteroids have also been studied in several randomized trials such as: **Methylprednisolone** and **Hydrocortisone,** but the sample size in many of the trials was not large enough to assess the effectiveness of these medicines in the treatment of COVID-19. Currently based on the available evidence, guidelines recommend the following: alternative glucocorticoids such as Prednisone, methylprednisolone and hydrocortisone can only be used only in case dexamethasone is not available.

1.4.3 Anticoagulant and antithrombotic treatment

Since the beginning of the Covid-19 pandemic, there has been an increased number of thrombotic events identified in both non-hospitalized and hospitalized patients, with the highest frequency reported in critical patients (D. Jiménez, 2021). Heparin-based products have been the first line of treatment for hospitalized patients, their main advantages being represented by low cost, increased availability and known side effects, being frequently used in other pathologies for their prophylactic but also curative role (B.K. Tan, 2021).

A number of studies have looked at the optimal anticoagulation dose and compared the effects of anticoagulation in the prophylactic, therapeutic and intermediate dose, but increasing the dose above the prophylactic dose failed to demonstrate any clinical benefit (COVID-19 Treatment Guidelines Panel, 2019).

In the randomized meta-analysis "Optimal dosing of heparin for prophylactic anticoagulation in critically ill COVID-19 patients", the results of anticoagulation with prophylactic dose versus intermediate dose of anticoagulation with low molecular weight heparins were analyzed on a group of 2130 patients.

The results show that there is no significant difference in mortality between the two groups; instead, there were significant reductions in pulmonary embolism in patients with the augmented dose, but at the same time, hemorrhagic risk events were also recorded in the same group (U.S. Perepu, 2021). Currently, the recommendations of the Covid-19 treatment guidelines are as follows: in hospitalized patients, heparin-based products are preferred over oral anticoagulants due to the shorter half-life and potential for rapid antagonization. The therapeutic anticoagulation dose is recommended only if the D-Dimer level is elevated above the upper limit and there is no increased risk of bleeding.

1.4.4 COVID-19 convalescent plasma transfusion

COVID-19 convalescent plasma transfusion is a passive immunization process based on the artificial transfer of the immune survivor's plasma, plasma containing antibodies to the infectious disease. A meta-analysis of 25 clinical trials with a total patient count of 22,591 initially concluded that compared to no treatment or placebo, convalescent plasma was able to reduce mortality with a risk ratio of 0.78. In contrast, after applying corrections by excluding trials with different design, the results were less obvious and the statistical significance of the result was borderline (Paola de Candia, et al, 2021), the real benefit of using plasma with antibodies in the treatment of Covid-19 remaining unknown to date.

1.4.5 Therapeutic plasma exchange

Therapeutic plasma exchange is an extracorporeal blood cleansing method designed to remove high molecular weight substances over 15000 Daltons, thus reversing the pathological processes generated by the presence of these substances in the blood (A.A. Kaplan, 2013). Despite the lack of solid evidence supporting the usefulness of plasma exchange in severe infectious context such as sepsis, the practical experience by applying the method in multiple clinical situations has been a favorable indicator to be tried in the treatment of severe forms of Covid-19.

Several studies have found that plasma exchange therapy is not only a rescue therapy, but even an alternative therapy that needs to be applied even earlier in the clinical evolution of Covid-19 cases, with signs of rapid worsening and characteristics of cytokine storm syndrome. When the pro-inflammatory status given by the Coronavirus infection was identified, it became obvious that the elimination of large amounts of cytokines and the blocking of cytokine storm activation before systemic endothelial dysfunction and the appearance of multiple organ dysfunction syndrome, have a therapeutic potential with positive valence during the healing of Covid-19 (P. Keith, 2020).

1.4.6 Treatment of hypoxemia

The Covid-19 pandemic has posed a great challenge in treating hypoxia translated into inefficient tissue oxygenation. The initial stages of Covid-19 were characterized by the phenomenon of “happy hypoxemia” which translates into happy or silent hypoxemia whereby, although the oxygen level in the arterial blood was low, the patient did not present dyspnea or any other type of respiratory discomfort. At the histopathological level at this stage, pneumocyte desquamation, diffuse alveolar damage with hyaline membrane formation - common features with acute respiratory distress syndrome - have been identified (L. Gattinoni, et al., 2020; Y. Zheng, et al., 2021).

1.4.6.1 Conventional oxygen therapy

It was the first strategy in combating hypoxemia of patients infected with SARS-CoV2. Oxygen can be administered to the patient through several interfaces such as nasal cannula, simple facial mask, face mask with reservoir and Venturi mask. Oxygen’s

administration by nasal cannula can be done with a flow that varies between 1 and 6 liters / minute and achieves the inspiratory fraction of oxygen, FiO_2, between 25 and 40%.

1.4.6.2 High-Flow Nasal Cannula (HFNC)

It is a ventilatory support system whereby a special cannula is placed in the patient's nostrils to ensure relatively airtight delivery of oxygen, with a flow rate of up to 60 liters/minute, with a concentration ranging from 21 % to a maximum of 100 %. It has an air humidifier and an adjustable heater with the possibility of heating the air to a temperature between 31ºC and 37ºC (A. Eden, 2005).

With the use of these devices during the Covid-19 pandemic, clinicians have noted not only an improvement in patient comfort, but also an improvement in clinical progression. A study published in June 2022 shows that early use of HFNC therapy in patients with increasing oxygen needs, but prior to the development of ARDS, was associated with a statistically significant decrease in the number of intensive care days and the decrease in mortality was very close to the statistically significant threshold (Laura García-Pereña, et al., 2022). In another study of 170 patients, which compared the effects of conventional oxygen therapy with HFNC, it was found that the need for oro-tracheal intubation was lower in the HFNC group.

1.4.6.3 Non-Invasive Ventilation with Continuous Positive Airway Pressure (CPAP-NIV)

Non-invasive ventilation is the delivery of oxygen or ventilatory support by means of a face mask, eliminating or otherwise delaying the need for endotracheal intubation (Nava S, Hill N., 2009). Physiologically, non-invasive ventilation has benefits comparable to invasive ventilation by reducing the respiratory labor and improving gas exchange. Non-invasive ventilation works by creating a positive pressure in the airways, the pressure outside the chest exceeding that inside and thus will cause a movement of the air flow in the direction of the pressure gradient, so towards the inside of the lungs, thus decreasing the patient's respiratory effort (Guideline BT, 2002).

At the same time, it helps to keep the chest expanded, which translates into an increase in residual functional capacity after a normal exhalation, the air remaining in the pulmonary

alveoli being available for gas exchanges, but at the same time has a special role in preventing the phenomenon of atelectasis (Lumb A., 2005).

Throughout the pandemic, non-invasive ventilation techniques have been the gold standard in moderate and severe cases of Covid-19, without having irrefutable evidence of the superiority of the method. At the end of 2022, the results of a meta-analysis of 7 relevant studies with 2831 patients included, comparing the effectiveness of conventional oxygen therapy with non-invasive ventilation in patients infected with SARS-CoV2, were published. The results reveal a reduction in the risk of endotracheal intubation and mortality in the invasive ventilated group, without showing a decrease in the number of days of hospitalization in either group (Vinesh Kumar, et al., 2022).

1.4.6.4 Invasive ventilation

At the onset of the Covid-19 pandemic, mechanical ventilation was proposed as one of the main lifesaving therapeutic options. However, it was soon observed that the mortality of mechanically ventilated patients had varied between 30 and 97% despite the application of protective ventilation methods. (G. Bellani, et al., 2016). For this high mortality rate, complications associated with the evolution of respiratory distress syndrome and the development of multiple organ failure can be blamed, but at the same time, invasive mechanical ventilation and its complications have been shown to play an important role in increasing mortality as an independent factor. Although many of the complications associated with invasive mechanical ventilation are common for Covid-19 and non-Covid patients, some of these complications occurred more frequently during the pandemic, thereby increasing the severity and worsening the prognosis of Covid-19 patients who experienced higher mortality (G. Bellani, et al., 2016; S. Richardson, 2020).

The indications of invasive mechanical ventilation are respiratory arrest, acute respiratory failure and acute respiratory distress syndrome, tachypnea (respiratory rate over 30 breaths/minute) and vital capacity less than 15ml/kg.

Among pulmonary complications, Ventilator-Associated Pneumonia (VAP) was frequently encountered, especially in the case of Covid-19 patients with prolonged need for mechanical ventilation (J. Udi, C.N. Lang, V. Zotzmann, et al., 2021). Studies have shown that the frequency of occurrence of this complication was higher in Covid-19 patients than in non-covid patients with other causes of acute respiratory distress syndrome, such as Influenza virus. Common causes generating VAP are oro-pharyngeal microaspirations

facilitated by low patient immunity, decreased mucociliary activity secondary to the use of deep sedation and prolonged ventilation (A.I. Ritchie, A. Singanayagam, 2020).

1.4.7 ECMO – Extracorporeal membrane oxygenation

After exhausting all conventional oxygenation methods and the failure of using maximum ventilatory parameters, ECMO can be considered a rescue therapy (A. Zangrillo, et al., 2013). Its concept is a simple one, the oxygenation of the patient's blood takes place through an extracorporeal membrane, at the same time removing carbon dioxide, but putting the therapy into practice can be a real challenge that requires a laborious technique, qualified personnel and special equipment, all the above adding to the risks that the therapy has: bleeding, thromboembolism, coagulopathies, infections, limb ischemia, convulsions, ischemic or hemorrhagic stroke.

It is worth mentioning that this procedure does not have a therapeutic role in itself, but only supports the oxygenation of the patient with severe lung damage and gives him/her the necessary time for healing or, in some cases, until lung transplant (A. Bharat, et al., 2021).

1.4.8 Vaccine

Because prevention is the best treatment, since the beginning of the pandemic, researchers have been looking for potential immunogenic molecules, epitope or antigen, to develop an effective vaccine to stop the pandemic.

Starting with 22nd September 2022, a global vaccination program has begun using a vaccine with a safe and effective design that stimulates both humoral immune response with antibody production and cellular immune response with secondary production of CD4 and CD8. To enhance immunity to emerging new strains, an additional third dose was recommended approximately six months after the second dose (A Vitiello, et al., 2021).

Despite the undeniable benefits brought by the vaccine, a series of speculations without scientific basis were launched followed by an anti-vaccination trend, the topic of vaccination remaining even today an intensely debated one.

2 CHAPTER 2 – The therapeutic approach in critical patients with SARS-CoV-2 respiratory infection

2.1 Motivation for choosing the theme

The motivation behind selecting the theme "The therapeutic approach in critical patients with SARS-CoV-2 respiratory infection" is driven by the urgent need to address the complex challenges posed by the pandemic. Through a rigorous exploration of this topic, this research aims to clarify some theoretical aspects, improve clinical outcomes and contribute to the broader scientific effort to combat the impact of Sars-Cov-2 virus infection on the patient.

Taking into account all these considerations mentioned above, we decided to conduct this clinical research as a private, personal study, whereby we want to expose the relationship and efficiency existing between the various therapy methods approached in the case of critical patients diagnosed with acute SARS-CoV-2 infection.

2.2 General research methodology

Ethical considerations

The collection and processing of data was carried out respecting the anonymity of patients. The approval of the Bioethics Committee of "Sf. Apostol Andrei" County Emergency Hospital in Galati was obtained in order to access and collect patients' personal information from the hospital and AICU Clinical Department database, archived electronically or on paper (observation sheets, observation registers), as well as the images obtained from imaging evaluations.

The consents were made taking into account the legislation currently in force of the World Health Organization and the European Union on human research in the medical field, but also taking into account the latest version of the Helsinki Declaration of Human Rights. Therefore, the present study was started after obtaining the approval of the Ethics Commission of "Sf. Apostol Andrei" County Emergency Hospital, Galati.

Study's design

The design chosen for this research is a retrospective cohort study that uses quantitative components as the main study methodology to properly investigate the therapeutic interventions in critical patients with SARS-CoV-2 respiratory infection. This design is particularly suitable for collecting real-time event data and provides a retrospective analysis of the outcomes of different therapeutic approaches.

2.3 Purpose and Objectives

The purpose of this research is to investigate and understand in detail the therapeutic strategies applied to critical patients affected by acute infection with the SARS-CoV-2 virus, aiming to improve the understanding and complex dynamics between interventions and clinical outcomes. Exploring a diverse dataset from the analysis of 108 cases, this study seeks to contribute valuable insights into the management of severe COVID-19 cases and improve evidence-based medical practices in real-world clinical settings.

The objectives of this study are as follows:

- Assessing the impact of demographic variables
- Analysis of the effectiveness of different types of ventilation
- Correlation between laboratory investigations and therapeutic results
- Examining the relationship between imaging results and treatment's success
- Analyzing the parameters of the acid-base balance and their correlation with the clinical evolution
- Identifying the predictors of the therapeutic success in multivariate analyses
- Subgroup-based analysis, relying on demographic and clinical characteristics

3 CHAPTER 3 - EPIDEMIOLOGICAL ASPECTS OF PATIENTS DIAGNOSED WITH SARS-CoV-2

3.1 Introduction

Infection with the SARS-CoV-2 virus, which causes the disease known as COVID-19, has been the subject of a pandemic unprecedented in our century. Since the first cases emerged in the Chinese city of Wuhan in late 2019, the virus has spread rapidly globally, affecting millions of people and challenging health systems around the world. In this context, the epidemiological aspects of patients diagnosed with SARS-CoV-2 have become essential for understanding the evolution of the disease, risk factors and for developing effective prevention and control strategies.

3.2 Material and methods

The final study group consists of a final number of 108 subjects. It consists of individuals diagnosed with SARS-CoV-2 who, during the course of the disease, had been hospitalized in the Anesthesia and Intensive Care Unit (AICU). The reference medical unit for this research is, as previously stated, represented by "Sf. Apostol Andrei" County Emergency Hospital, Galati.

3.3 Results

In this subchapter we analyzed the distribution of the sample dependent on socio-demographic characteristics, comorbidities, performed a statistical analysis materialized on the chronology of SARS-CoV-2 diagnosis, the admission to AICU and the number of days of illness, the reasons for admission and the condition of the subjects at the time of registration, the statistical evaluation of clinical, paraclinical parameters in dynamics, as well as of the use of oxygen therapy or other therapeutic means.

3.4 Discussions

The study group included 57.4% men and 42.6% women. The predominance of male participants in the studied group shows their increased impairment in relation to the female sex and helps to interpret the data in the context of SARS-CoV-2. Studies such as Mukherjee & K., 2021 and Kushwaha, et al., 2021 also report a male-dominated sample in SARS-CoV-2 research, consistent with these findings. However, Kopel, et al., 2020 observed a more balanced gender ratio, highlighting potential demographic differences between studies.

The mean age was 68.87 years, with a standard deviation of 14.426, indicating a significant age variability. The average age in this study is relatively higher compared to Boehmer, et al., 2020, which reported a decrease in average age from 43 to 37 years.

Statistics

Age in years

N	Valid	108
	Missing	0
Mean		68.87
Std. Deviation		14.426
Skewness		-.930
Std. Error of Skewness		.233
Kurtosis		1.364
Std. Error of Kurtosis		.461
Minimum		20
Maximum		99

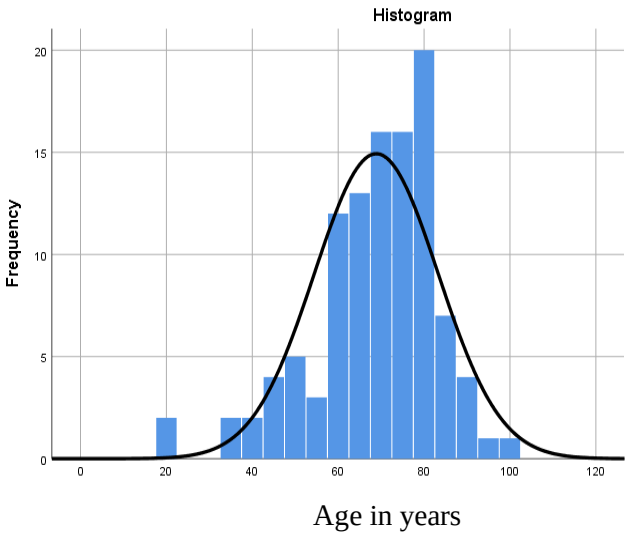

Figure 1.4.8 Descriptive statistics of age distribution and the histogram by age

Both the Pearson Chi-Square tests and the Probability Ratio suggest that there is no significant association between age and sex in the studied population. However, the precautionary note on expected counts requires careful consideration and further analysis or adjustments may be justified to ensure the robustness of the conclusions drawn from this assessment.

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	40.869[a]	44	.607
Likelihood Ratio	53.189	44	.161
N of Valid Cases	108		

a. 90 cells (100.0%) have expected count less than 5. The minimum expected count is .43.

Figure 3.4.2 Chi-square independence test between patients' age and sex

The symptomatology present at AICU admission is shown in the underlying table:

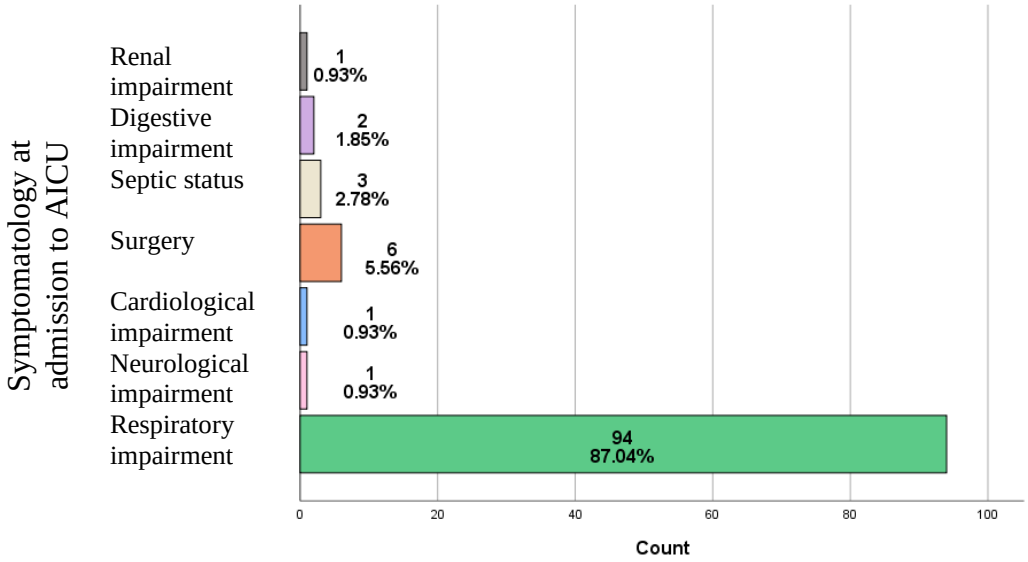

Figure 3.4.3 Symptomatology found in the group at the time of admission to the AICU

The study of comorbidities in patients infected with SARS-CoV-2 is of paramount importance in unraveling the complicated interaction between pre-existing health conditions and the course of COVID-19.

- The existence of strokes shows a quasi-equal distribution at the level of the group, the value of the Chi-Square test being .0619
- Chronic kidney disease predominates in male patients (72.7%)
- Among the 32 subjects who associated BMI values above the maximum permissible limit, the largest share (68.8%) belongs to the subgroup of male patients
- Approximately the same distribution is noted in the case of those who have a history of cardiac pathology such as chronic ischemic heart disease (60.7%, weight predominant for males), congestive heart failure, atrial fibrillation (quasi-equal distribution reported to sexes), hypertension (61.5% majority for male subjects).
- Finally, for male patients, a history of increased incidence of diabetes mellitus is noted (with a percentage difference of about 10%)

		Sex				Chi-Square Test Value
		Male		Female		
		Count	Row Valid N	Count	Row Valid N	
Stroke	No	57	58.2%	41	41.8%	0.619
	Yes	5	50.0%	5	50.0%	
Chronic Kidney Disease	No	46	53.5%	40	46.5%	0.103426717
	Yes	16	72.7%	6	27.3%	
Obesity	No	40	52.6%	36	47.4%	0.121905264
	Yes	22	68.8%	10	31.3%	
Chronic Ischemic Cardiomyopathy	No	45	56.3%	35	43.8%	0.680953654
	Yes	17	60.7%	11	39.3%	
Chronic Heart Failure	No	42	56.8%	32	43.2%	0.840122486
	Yes	20	58.8%	14	41.2%	
Atrial Fibrillation	No	50	58.1%	36	41.9%	0.760961515
	Yes	12	54.5%	10	45.5%	
Arterial hypertension	No	22	51.2%	21	48.8%	0.285772378
	Yes	40	61.5%	25	38.5%	
Diabetes Mellitus	No	41	58.6%	29	41.4%	0.739865656
	Yes	21	55.3%	17	44.7%	

This research paper also analyzes the biomarker profiles in patients infected with SARS-CoV-2. The results reveal dynamic changes in physiological markers and their implications for recovery, with insights that can be compared to other studies.

Statistics

		Value of leukocytes at admission to AICU	Value of neutrophils at admission to AICU	Value of C-reactive protein at admission to AICU	Value of ESH at admission to AICU	Value of Procalcitonin at admission to AICU	Value of LDH at admission to AICU	Value of D-Dimer at admission to AICU	Value of INR at admission to AICU	Value of APPT at admission to AICU
N	Valid	107	108	104	107	103	108	108	108	108
	Missing	1	0	4	1	5	0	0	0	0
Mean		13.0297	86.7722	113.1798	77.5701	3.3890	1392.4815	3.6447	1.4203	36.5704
Std. Deviation		7.83054	11.00848	80.71447	39.53768	8.03898	929.47412	1.28139	0.46844	16.66440
Skewness		1.867	-4.955	1.186	.091	3.917	1.426	.640	1.630	2.331
Std. Error of Skewness		.234	.233	.237	.234	.238	.233	.233	.233	.233
Kurtosis		4.757	35.967	1.947	-.510	15.957	3.825	1.068	5.932	7.516
Std. Error of Kurtosis		463	.461	.469	.463	.472	.461	.461	.461	.461
Minimum		0	.00	0	.00	0	.00	.00	.00	.00
Maximum		48.05	97.50	425.00	178.00	45.00	5855.00	7.76	3.72	114.40

Figure 3.4.3 Statistical evaluation of paraclinical investigations at the time of admission to the AICU

Statistics										
		Value of leukocytes at discharge from AICU	Value of neutrophils at discharge from AICU	Value of C-reactive protein at discharge from AICU	Value of ESH at discharge from AICU	Value of Procalcitonin at discharge from AICU	Value of LDH at discharge from AICU	Value of D-Dimer at discharge from AICU	Value of INR at discharge from AICU	Value of APPT at discharge from AICU
N	Valid	107	108	107	107	104	108	108	108	108
	Missing	1	0	1	1	4	0	0	0	0
Mean		9.8163	57.0935	66.7493	44.2243	3.1496	992.5500	41.0414	1.0799	25.2435
Std. Deviation		9.11397	43.71876	81.73597	47.37751	9.70497	1364.93440	303.96648	1.17604	24.76014
Skewness		.568	-.519	1.142	.669	5.887	3.484	8.601	2.953	1.498
Std. Error of Skewness		.234	.233	.234	.234	.237	.233	.233	.233	.233
Kurtosis		-.254	-1.704	.422	-.835	41.835	20.429	77.507	17.073	5.595
Std. Error of Kurtosis		.463	.461	.463	.463	.469	.461	.461	.461	.461
Minimum		.00	.00	.00	.00	.00	.00	.00	.00	.00
Maximum		38.57	97.60	302.70	164.00	81.04	10416.00	2905.00	8.83	154.40

Figure 3.4.4 Evolution of paraclinical investigations in the studied group

Compared to similar studies, the mean count of leukocytes at discharge (9.82 *1000/microliter) demonstrates a significant decrease, indicating a resolution of the acute immune response. The count of neutrophils also decreases (mean 57.09*1000/microliter), aligning with reduced inflammation. The CRP levels remain high (average: 66.75), highlighting persistent inflammation during recovery.

COVID-19 continues to evolve, the treatment protocols can be updated to reflect the most current knowledge and guidelines. This underlines the importance of healthcare professionals staying informed about the latest research and evidence-based practices to ensure optimal patient care.

As for corticosteroid therapy in the treatment of COVID-19, it plays a vital role in managing the inflammatory response triggered by the virus, especially in severe cases. Dexamethasone, in particular, has been extensively studied and recommended for severe cases of COVID-19 requiring respiratory support. Its ability to modulate the immune response has been shown to reduce mortality in these cases.

It is essential to stress that the use of corticosteroids in the treatment of COVID-19 is not universally applied and should be carefully evaluated based on individual patient profiles and disease progression. Although they have been shown to be effective in reducing mortality in severe cases, their use in mild or moderate cases is not recommended and may even pose potential risks.

The data presented show the diversity of corticosteroid therapy in the studied cases, a significant proportion having no corticosteroids (28.7%). Dexamethasone is the most commonly used corticosteroid (63.0%), in line with its established benefits in severe cases. In some cases, combinations of corticosteroids have been administered, reflecting an individualized approach to treatment.

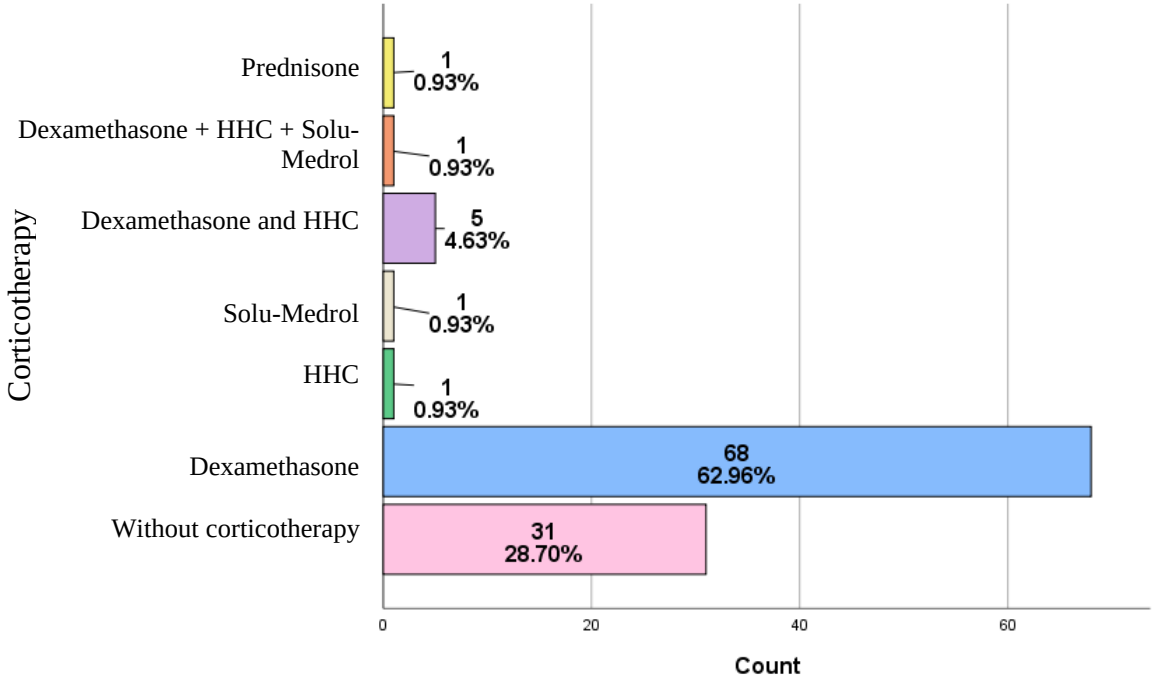

Figure 3.4.5 Corticotherapy used in the group

3.5 Conclusions

The study revealed a significant predominance of male patients compared to female. The higher mean age of the participants in this study, compared to other research, was due to the fact that the first outbreaks of Covid -19 in Galati County occurred in two nursing homes and confirm the importance of age as a severity factor in COVID-19.

The study highlighted the aggravating effects of stroke, often accompanied by cardiovascular pathologies, on COVID-19, due to increased inflammatory responses and clotting disorders. This observation aligns with previous research and highlights the increased mortality rate in patients with both stroke and COVID-19.

The research provided insights into the prevalence of specific antiviral and antibiotic treatments. Antiviral medicines such as Remdesivir have been administered to a significant portion of the population, highlighting ongoing efforts to combat the virus. Antibiotics have also been prescribed, stressing the importance of judicious management of secondary bacterial infections.

In conclusion, this study contributes with information on demographic data, clinical profiles, treatment strategies and physiological markers of COVID-19 patients. These data highlight the complexity of COVID-19 management, the importance of individualized care, and the continuous need for research to improve the understanding of the disease and optimize treatment protocols. Additional studies with larger samples are essential to validate and extend these protocols.

4 CHAPTER 4 - STUDY ON THE USE OF VENTILATION METHODS IN PATIENTS IN THE ANALYZED GROUP

4.1 Introduction

In recent years, the medical community has shown increasing interest in exploring advanced respiratory support strategies in critical patients with Sars-Cov-2 infection admitted to intensive care units, where choosing between Continuous Positive Airway Pressure (CPAP) and High-Flow Nasal Oxygen therapy (HFNO) remains a first-intent decision. This subchapter reviews the study conducted to evaluate the efficacy and outcomes of CPAP versus HFNO in critical patients infected with the SARS-CoV-2 virus.

4.2 Material and methods

The study included a total of 108 subjects, all of whom were diagnosed with COVID-19. Patient data, including demographics, medical history, and baseline respiratory parameters (SpO_2, blood CO_2, and blood O_2), were collected from the observation sheets. The primary focus was on monitoring the use of non-invasive CPAP, HFNO, and invasive mechanical ventilation throughout the study. In addition, the number of days when each ventilation method was used per patient was recorded and subsequently analyzed using descriptive statistics. The duration of each ventilation method, expressed in days, was summarized using the mean and standard deviation, characteristics specific to descriptive statistics.

4.3 Efficiency of non-invasive CPAP and HFNO use in critically ill patients with COVID-19 (Manole et al., 2024)

The conventional oxygen therapy is insufficient for most COVID-19 patients in intensive care services. Although the prognosis of patients with respiratory failure of other etiologies improves by initiating invasive mechanical ventilation, the mortality rate is extremely high among intubated COVID-19 patients.

Personal experience has shown that optimal oxygenation, either by administering high-flow oxygen on the nasal cannula or by non-invasive mechanical ventilation, gave better results in critical Covid-positive patients admitted to the Intensive Care Unit of Galati County Emergency Clinical Hospital. HFNO is a relatively new technique used in the management of acute respiratory failure, providing previously heated and humidified

oxygen via a nasal cannula at a flow rate from 60 to 100 L per minute and a concentration of up to 100%.

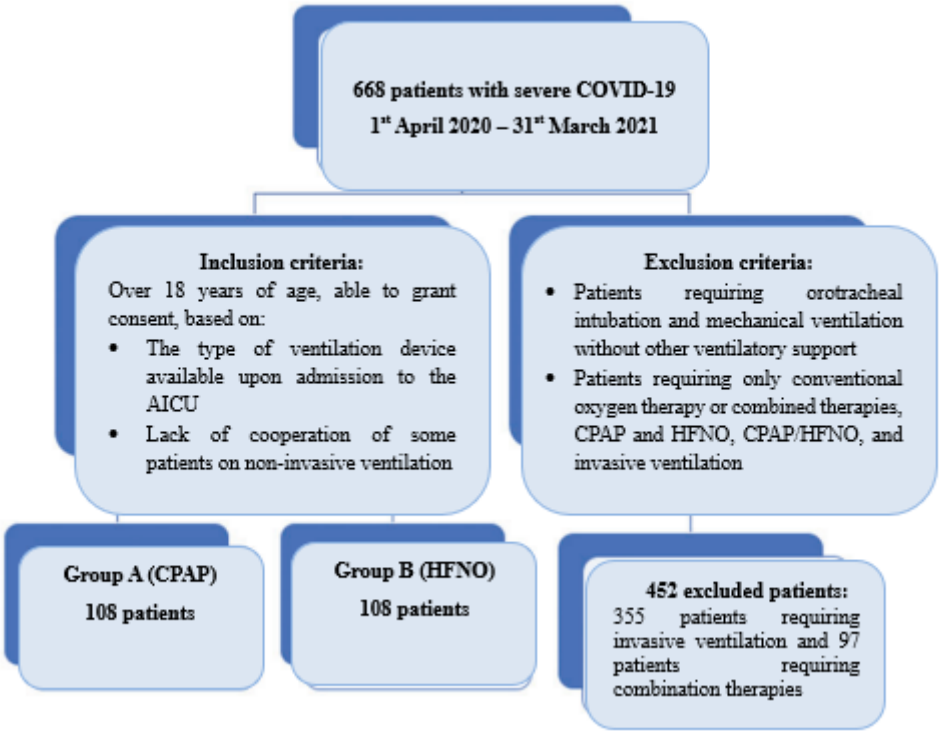

Figure 4. Selection of the group of patients. AICU, Anesthesia and Intensive Care Unit; CPAP, Continuous Positive Airway Pressure; HFNO, High Flow Nasal Oxygen Therapy (Manole C., et al., 2024)

Non-invasive positive, continuous pressure ventilation is a ventilatory support technique that uses an interface other than the orotracheal probe, such as facial mask, full-face mask or a face tent. Clinical results showed that the use of non-invasive CPAP and HFNO for the treatment of hypoxemic acute respiratory failure due to Covid were associated with good outcomes, decreasing the need for orotracheal intubation, the invasive mechanical ventilation and the mortality rates (Manole C. et al.,2024).

A meta-analysis of 58 studies concluded that there is no consensus on the use of non-invasive ventilatory support in covid-positive patients and that information on the indications for initiating or suppressing these therapies is unclear.

Due to the lack of consensus regarding the use of different ventilatory support modalities in patients with severe forms of COVID-19, the purpose of this study was to compare the results of CPAP-NIV and HFNO use in patients treated in the AICU of Galati Emergency Clinical Hospital. We decided to broaden the studied group, compared to the one initially used at the beginning of the research, to see if the mortality rate in the group of

intubated and mechanically ventilated patients remains as high and if survival is higher in those ventilated non-invasively. The results of this doctoral dissertation study were published in Journal of International Medical Research 2024, vol.52, DOI:I0. II77/03000605231222I5I, Manole C. et al.

4.3.1. METHODS

We used a retrospective comparative cohort study, involving 668 adult patients with COVID-19 who were admitted to the AICU of Galati Emergency Clinical Hospital, between 1st April 2020 and 31st March 2021. 2 groups of patients were analyzed, the first receiving non-invasive CPAP (n=108) and the second using high-flow oxygen administered via nasal cannula (n=108). The criteria for inclusion in the study were acute respiratory failure associated with Sars-CoV-2 infections, hypoxemia, and moderate or severe dyspnea.

The inclusion criteria for patients receiving HFNO were:

- Anxiety associated with the method, claustrophobia caused by the CPAP mask and implicitly the patient's refusal.
- Higher tolerance for HFNO than for CPAP.
- Pre-existing lung disease that predisposes to the occurrence of pneumothorax / pneumomediastinum (i.e., pathologies associated with pulmonary emphysema, bronchopulmonary neoplasm, sequelae of pulmonary tuberculosis or bronchial asthma).
- Limited number of ventilators required for CPAP.

The CPAP selection criteria were as follows:

- Low degree of anxiety and high tolerance for CPAP.
- Absence of pre-existing pathologies that predispose to the occurrence of pneumothorax / pneumomediastinum during the use of positive-pressure mechanical ventilation.

Patients in both groups required frequent small doses of sedation to reduce their anxiety levels without affecting their state of consciousness. The patients in the HFNO group adopted prone position for 10 to 16 hours per day.

The criteria for invasive oxygen therapy were an altered state of consciousness, severely increased respiratory effort requiring the use of accessory muscles or a respiratory

rate of >30 breaths/minute, risk of aspiration pneumonia, and severely decompensated acidosis (pH < 7.2-7.25). Orotracheal intubation was required shortly before death for the selected patients (since orotracheal intubation is also required during resuscitation maneuvers).

The study exclusion criteria were the inability to provide written informed consent for study participation, pregnancy and lactation, and outliers (patients with extreme routine laboratory test results, including erythrocyte sedimentation rate and procalcitonin, fibrinogen, ferritin, and C-reactive protein concentrations). Patients who had recently undergone surgical procedures or had other non-respiratory conditions requiring intensive care were also excluded.

We considered the following exclusion criteria for both groups:

- Patients with indication for orotracheal intubation since presentation to the AICU.
- Patients admitted to the AICU who required any combination of the following therapies: conventional oxygen therapy, CPAP, HFNO, or initial orotracheal intubation followed by any of the three therapies mentioned above.

Regarding the initial choice of CPAP or HFNO for the patients admitted to AICU, due to the small number of existing COVID-19 AICU beds in our region, the County Clinical Hospital being the only one with a functional AICU with permanent on-call shift, we could not include age, sex or comorbidities as criteria. Therefore, the therapy was chosen based on the availability of a bed equipped with CPAP or HFNO and the criteria mentioned above.

The patients had been monitored during hospitalization in the AICU, and complete data were not available for all patients. The end point of the study was the total number of deaths in the AICU. The failure of CPAP and HFNO contributed to mortality in the AICU, as the patients transferred from the AICU to the medical ward required neither orotracheal intubation nor invasive ventilation. The patients who died in the AICU were those intubated since admission, those whose condition worsened due to respiratory failure under HFNO or CPAP, requiring invasive ventilation for several days, or those who required intubation during cardiorespiratory resuscitation. It is worth mentioning that the first recommendations of SRATI included orotracheal intubation and invasive mechanical ventilation, as the first intention in the critical Covid patient. Our experience has shown a high mortality rate in

these cases, an increased length of days in the AICU with increasing costs and often exceeding the financial resources available at that time.

This study was conducted in accordance with the guidelines of the Declaration of Helsinki (following the STROBE guidelines) and approved by the Ethics Committee of the "St. Apostol Andrei" Emergency Clinical Hospital in Galati (approval number 20924 on 22nd September 2021). Informed written consent for publication was obtained from all patients involved in the study.

The patient data extracted from the observation sheets were analyzed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). All patient data has been anonymized. Gross descriptive statistical parameters were calculated for all analyzed variables. Continuous variables are presented as mean ± standard deviation and categorical variables are presented as absolute frequency (relative frequency). The test used in the inferential analysis is specified for each variable. We calculated the φ, V and C coefficients to analyze the correlation of variables measured at the nominal level. The chi-square test was performed to measure the association between two categorical variables, and Pearson's coefficient (r) was used for continuous variables. Comparisons were made between patients in the CPAP and HFNO groups. For all statistical tests, the two-tailed p-value of <0.05 was considered statistically significant.

4.3.2. RESULTS

Of the 668 patients admitted to the AICU from 1st April 2020 to 31st March 2021, 355 patients required orotracheal intubation and mechanical ventilation, without any other respiratory support, CPAP or NIV, respectively, in percentage of 53.1%. Of these 355 patients, only 11.5% survived, so the mortality rate was 88.5% in this group. The mortality rate in this group was much higher than in the entire group of patients. Of all 668 patients, 252, or 37.7% survived.

A total of 97 patients underwent various oxygenation strategies, including conventional oxygen therapy, combined therapies such as CPAP and HFNO, interventions involving CPAP/HFNO and invasive ventilation.

We compared the CPAP group (n=108) and HFNO group (n=108) against demographic data, paraclinical status at AICU admission, comorbidities, antiviral and immunosuppressive therapies, and number of deaths (Table 4.3.1(a), (b); Table 4.3.2).

The mean age in both groups was > 65 years. The mean age in the CPAP group was 68.56 years (range between 37 and 99 years old) and in the HFNO group was 66.44 years (range between 20 and 86 years old) (Table 4.3.1(a)).

Male sex prevailed in both groups (Table 4.4.2).

The Radiographic Assessment for Lung Edema (RALE) score for lung lesion severity imaging was slightly higher in the CPAP group (Table 4.4. 1(a)), but the difference was not statistically significant.

In the CPAP group, the mean ratio of oxygen arterial partial pressure (PaO_2) to the inspired oxygen fraction (FiO_2) (PaO_2/FiO_2, also known as the Horowitz index) was 92.56 (range between 44 and 216), which was significantly lower than that in the HFNO group (109.78; range between 45 and 305) (p = 0.0093) (Table 4.3.1(a)). In both groups, the ratio was close to the threshold of 100 that differentiates between moderate and severe respiratory failure.

In the initial assessment of the inflammatory syndrome, statistically significant differences were found for the following parameters: procalcitonin values (p = 0.0296), fibrinogen concentration (p = 0.0009) and erythrocyte sedimentation rate (p = 0.309) (Table 4.3.1(a)).

The incidence of comorbidities was not significantly different between the two groups. Among patients with chronic lung disease, the mortality rate was 100% in both the CPAP and HFNO groups. In addition, mortality was higher among patients with neurological, metabolic, renal and hepatic disorders in the CPAP group and among patients with oncological comorbidities in the HFNO group (Tables 4.3.2 and 4.3.3).

	CPAP (n = 108)		**HFNO (n=108)**		**P (T-t)**
	Mean	**SD**	**Mean**	**SD**	
Age (years)	68.56	13.73	66.44	14.27	0.2674
PaO_2/FiO_2 on admission	92.56	38.55	109.78	56.26	***0.0093***
RALE score	35.31	8.18	33.94	8.33	0.2241
Serum lactate, mmol/L	3.02	1.53	2.73	1.01	0.1017
Procalcitonin, ng/mL	3.83	6.89	2.15	4.00	***0.0296***
ESR, mm/h	66.83	33.26	76.85	34.51	***0.0309***
C-reactive protein, mg/L	107.22	75.48	111.53	85.43	0.6948
Fibrinogen, mg/dL	505.92	230.88	601.44	183.72	***0.0009***
Ferritin, ng/mL	1331.02	1441.14	2352.77	5545.32	0.0652

	CPAP (n = 108)		HFNO (n=108)		P (T-t)
	Mean	SD	Mean	SD	
Lactate dehydrogenase (LDH)	1296.81	1063.86	1115.03	688.75	0.1375
Lymphocytes, × 10^9/L	6.63	4.81	6.59	4.15	0.9479

CPAP, continuous positive airway pressure; HFNO, high-flow nasal oxygen therapy; SD, standard deviation; T - t, Student's t-test for differences between means; PaO_2/FiO_2, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; RALE, Radiographic Assessment of Lung Edema; ESR, erythrocyte sedimentation rate.

Reference ranges: PaO_2/FiO_2, 400–500; serum lactate, 0.5–2.2 mmol/L; procalcitonin, 0–0.15 ng/mL; ESR, 0–15 mm/hour; C-reactive protein, 0–1 mg/L; fibrinogen, 200–400 mg/dL; ferritin, 0–400 ng/mL; lactate dehydrogenase, 0–4.2 U/L; lymphocytes, 1000–4000/μL.

Boldface italicized p values are statistically significant.

Table 4.3. 1(a). *Baseline characteristics of COVID-19 patients treated with CPAP compared to HFNO*

	CPAP (n = 108)		HFNO (n=108)		P (T-t)
	Mean	SD	Mean	SD	
Duration of hospitalization in intensive care, days	4.96	4.17	5.98	4.84	0.0998
Number of days of invasive ventilation	1.20	1.45	1.39	2.09	0.4403

CPAP, continuous positive airway pressure; HFNO, high-flow nasal oxygen therapy; SD, standard deviation; T-t, Student's t-test for differences between means; AICU, Anesthesiology and Intensive Care Unit

Table 4.3.1(b). Resulting characteristics of COVID-19 patients treated with CPAP compared to HFNO

	CPAP (n = 108)		HFNO (n=108)		p (chi-square test)
	n	%	n	%	
Sex					
Female	42	38.89	48	44.45	0.4897
Male	66	61.11	60	55.55	
Cardiovascular comorbidities	82	75.92	89	82.40	0.3150
Metabolic comorbidities	64	59.25	62	57.40	0.8905
Neurological comorbidities	39	36.11	32	29.62	0.3840
Renal and hepatic comorbidities	40	37.03	32	29.62	0.3121
Oncological comorbidities	9	8.33	18	16.66	0.0999
Pulmonary comorbidities	8	7.40	3	2.77	0.2154
Tocilizumab treatment	28	25.92	30	27.77	0.8782
Remdesivir therapy	54	50	76	70.37	***0.0035***
Corticosteroids	90	83.33	94	87.03	0.5661
Deaths	80	74.07	70	64.81	0.1837

CPAP, continuous positive airway pressure; HFNO, high-flow nasal oxygen therapy.

Boldface italicized p value is statistically significant.

Table 4.3.2. Comparison of categorial variables in COVID-19 patients treated with CPAP compared to HFNO

Remdesivir and Favipiravir were used as antiviral therapies, but the number of patients treated with Remdesivir was significantly higher in the HFNO group than in CPAP ($p = 0.0035$). There was no significant difference in immunosuppressive therapy between the two groups (Table 4.3.2).

The mean duration of hospitalization in the AICU was shorter in the CPAP group (4.96 days; range between 1 and 18 days) than in the HFNO group (5.98 days; range between 1 and 25 days), but the difference was not statistically significant (Table 4.3.1(b)).

In particular, some patients had a very short stay in the AICU for the following reasons:

- A significant number of patients developed a sudden clinical worsening that required invasive oxygen ventilation, and their condition rapidly progressed towards death thereafter.
- Patients who showed a marked respiratory improvement were transferred relatively quickly to a respiratory recovery service that provided standard oxygen therapy with a flow rate of up to 30 L/min, due to the constant pressure of admitting patients into the AICU and the limited number of beds; in addition, a higher number of newly admitted patients with more severe forms of respiratory failure required admission than the patients who evolved favorably.

	Deaths CPAP (n=108)		**Deaths HFNO (n=108)**		**p**
	n	**%**	**n**	**%**	
Sex					
Female	42	66.66	48	62.50	0.8488
Male	66	78.78	60	66.66	0.1836
Cardiovascular comorbidities (present)	82	73.17	89	64.04	0.2634
Metabolic comorbidities (present)	64	78.12	62	61.29	0.0624
Neurological comorbidities (present)	39	79.48	32	62.50	0.1877
Renal and hepatic comorbidities (present)	40	75.00	32	68.75	0.7462
Oncological comorbidities (present)	9	66.66	18	88.88	0.3813
Pulmonary comorbidities (present)	8	100	3	100	-
Tocilizumab therapy (present)	28	57.14	30	73.33	0.3078
Remdesivir therapy (present)	54	74.07	76	73.68	0.8787
Corticosteroids (present)	90	75.55	94	65.95	0.2050

CPAP, Continuous Positive Airway Pressure; HFNO, High Flow Nasal Oxygen therapy

Table 4.3.3. Proportions of deaths between CPAP and HFNO groups by sex, comorbidity and therapy subgroups (Manole C. et al.,2024)

The mean duration of invasive ventilation after CPAP was 1.20 days (range between 1 and 11 days), which was shorter than that after HFNO (1.39 days; range between 1 and 10 days). However, the difference was not statistically significant (Table 4.3.1(b)).

The shorter period of artificial ventilation after CPAP than after HFNO can be explained by the fact that some of the patients developed sudden cardiorespiratory arrest due to various COVID-19 complications and required orotracheal intubation during cardiorespiratory resuscitation maneuvers. In addition, the condition of some patients worsened under noninvasive oxygen therapy, and their condition did not improve even after orotracheal intubation and assisted ventilation, and they died after several days of intubation. The intubation criteria used in this study were altered consciousness, severe increase in respiratory effort with use of accessory muscles or a respiratory rate of >30 breaths/minute, a risk of aspiration pneumonia and severe decompensated acidosis (pH < 7.2-7.25). In addition, at the time of this study, there was neither consensus nor sufficient clinical trials establishing clear criteria for stopping non-invasive oxygen therapy and initiating assisted ventilation. Finally, very few intensive care beds were available to COVID-19 patients in our geographic region.

Although the mortality rate was slightly higher in the CPAP group than in the HFNO group, the difference was not statistically significant (Table 4.3.2). In addition, there was no statistically significant difference in the mortality between the two study groups or between subgroups by sex, comorbidities, or antiviral and immunosuppressive therapies (Table 4.4.3).

The mortality rates in both the CPAP (64.81%) and HFNO groups (74.07%) were significantly lower than in the orotracheal intubation group (88.50%) ($p < 0.0001$ and $p = 0.0004$, respectively) (Table 4.3.1(b))).

	Mortality: CPAP group	
	Coefficient value	**Test - associated probability**
Sex		
Pearson's chi-square test	0.982	0.249
Phi	0.135	0.322
Cramer's V	0.135	0.322
Contingency coefficient	0.134	0.322
Cardiovascular comorbidities		
Pearson's chi-square test	0.072	0.550
Phi	0.037	0.788
Cramer's V	0.037	0.788
Contingency coefficient	0.037	0.788
Metabolic comorbidities		

	Mortality: CPAP group	
	Coefficient value	**Test - associated probability**
Pearson's chi-square test	0.671	0.305
Phi	-0.111	0.413
Cramer's V	0.111	0.413
Contingency coefficient	0.111	0.413
Neurological comorbidities		
Pearson's chi-square test	0.363	0.397
Phi	-0.082	0.547
Cramer's V	0.082	0.547
Contingency coefficient	0.082	0.547
Renal and hepatic comorbidities		
Pearson's chi-square test	0.014	0.585
Phi	-0.016	0.905
Cramer's V	0.016	0.905
Contingency coefficient	0.016	0.905
Oncological comorbidities		
Pearson's chi-square test	0.002	0.726
Phi	-0.006	0.965
Cramer's V	0.006	0.965
Contingency coefficient	0.006	0.965
Pulmonary comorbidities		
Pearson's chi-square test	1.512	0.289
Phi	-0.167	0.219
Cramer's V	0.167	0.219
Contingency coefficient	0.165	0.219
Tocilizumab therapy		
Pearson's chi-square test	2.821	0.095
Phi	0.229	0.093
Cramer's V	0.229	0.093
Contingency coefficient	0.223	0.093
Remdesivir therapy		
Pearson's chi-square test	0.000	0.621
Phi	0.000	1.000
Cramer's V	0.000	1.000
Contingency coefficient	0.000	1.000
Corticosteroid therapy		
Pearson's chi-square test	0.309	0.427
Phi	-0.076	0.579
Cramer's V	0.076	0.579
Contingency coefficient	0.075	0.579

CPAP, Continuous Positive Airway Pressure

Table 4.3.4. Correlation tests in the CPAP group (Manole C.et al.,2024)

Correlation tests in both groups revealed no significant relationship between mortality and sex, between mortality and comorbidities, or between mortality and antiviral/corticosteroid therapies. In the HFNO group, correlation tests for nominal variables highlighted a correlation between mortality and remdesivir therapy ($\chi 2 = 4.424$, $p = 0.038$, $\varphi = 286$, $V = 286$ and $C = 0.275$, $p = 0.035$) (Tables 4.3.4 and 4.3.5).

4.3.3. DISCUSSION

The European Respiratory Society recommends the use of HFNO for patients with acute respiratory failure of various etiologies as follows: (Oczkowski S, Ergan B, et al., 2022).

1. HNFO versus conventional oxygen therapy and NIV ventilation for hypoxemic acute respiratory failure
2. HFNO instead of oxygen therapy during breaks from NIV ventilation
3. Either HFNO or oxygen therapy in surgical patients at low risk of developing lung complications
4. Either HFNO or NIV in surgical patients at high risk of lung complications
5. HFNO versus oxygen therapy in nonsurgical patients with a low risk of extubation failure
6. NIV versus HFNO ventilation for patients at high risk of developing extubation failure unless there are relative or absolute contraindications for NIV
7. Testing the effectiveness of NIV ventilation prior to HFNO use in patients with chronic obstructive pulmonary disease and hypercapnic acute respiratory failure

	Mortality: HFNO group	
	Coefficient value	**Test - associated probability**
Sex		
Pearson's chi-square test	0.102	0.486
Phi	0.043	0.750
Cramer's V	0.043	0.750
Contingency coefficient	0.043	0.750
Cardiovascular comorbidities		
Pearson's chi-square test	0.016	0.609
Phi	0.017	0.899
Cramer's V	0.017	0.899
Contingency coefficient	0.017	0.899
Metabolic comorbidities		
Pearson's chi-square test	0.396	0.368
Phi	0.086	0.529
Cramer's V	0.086	0.529
Contingency coefficient	0.085	0.529
Neurological comorbidities		
Pearson's chi-square test	0.053	0.527
Phi	0.031	0.817
Cramer's V	0.031	0.817
Contingency coefficient	0.031	0.817
Renal and hepatic comorbidities		
Pearson's chi-square test	0.154	0.473
Phi	-0.053	0.694
Cramer's V	0.053	0.694
Contingency coefficient	0.053	0.694
Oncological comorbidities		
Pearson's chi-square test	2.745	0.097
Phi	-0.225	0.098
Cramer's V	0.225	0.098
Contingency coefficient	0.220	0.098
Pulmonary comorbidities		
Pearson's chi-square test	0.553	0.648

	Mortality: HFNO group	
	Coefficient value	**Test - associated probability**
Phi	-0.101	0.457
Cramer's V	0.101	0.457
Contingency coefficient	0.101	0.457
Tocilizumab therapy		
Pearson's chi-square test	0.661	0.315
Phi	-0.111	0.416
Cramer's V	0.111	0.416
Contingency coefficient	0.110	0.416
Remdesivir therapy		
Pearson's chi-square test	4.424	0.038
Phi	-0.286	0.035
Cramer's V	0.286	0.035
Contingency coefficient	0.275	0.035
Corticosteroid therapy		
Pearson's chi-square test	0.208	0.474
Phi	-0.062	0.649
Cramer's V	0.062	0.649
Contingency coefficient	0.062	0.649

Table 5.4.5. HFNO Group Correlation Tests (Manole C.et al.,2024)

The European Respiratory Society considers HFNO an effective therapy for acute respiratory failure of various etiologies (Oczkowski S, Ergan B, et al., 2022).

For acute respiratory failure developing in COVID-19 patients, existing clinical trials are insufficient and there is no consensus on the use of different oxygen therapy methods.

Clinical studies have shown that patients receiving HFNO have better adherence to therapy; more specifically, they are able to feed more effectively and communicate with medical staff and have lower levels of anxiety. By contrast, CPAP is associated with higher levels of anxiety, posing a risk for developing ventilator asynchrony; difficulties in oral nutrition, requiring additional parenteral nutrition; difficulties in maintaining the prone position; discomfort due to decubitus cutaneous lesions secondary to mask pressure, which can sometimes overlap with lesions produced by SARS-CoV-2 (Tatu AL, Nadasdy T and Bujoreanu FC., 2020; Tatu AL, Baroiu L, Fotea S, et al., 2021) and other complications of mechanical ventilation such as barotrauma, aspiration pneumonia, and healthcare-associated infections. (Peng Y, Dai B, Zhao HW, et al., 2022). The prone position improves oxygenation by reducing ventilation/perfusion disorders, decreasing hypoxemia, and slowing the progression of respiratory failure. However, further studies are needed to prove its long-term effectiveness.

In the present study, we observed a lower mortality rate in AICU, in the HFNO group (64.81%) than in the CPAP group (74.07%), but the difference was not statistically

significant. This is consistent with other studies. However, the mortality rate in the AICU was significantly lower in both groups than in the invasive ventilation group with orotracheal intubation (88.5%).

A meta-analysis of 23 studies involving 5354 patients, published before February 2022, showed lower mortality rates in the HFNO group than in the NIV group ($p = 0.0008$) (Peng Y, Dai B, Zhao HW, et al., 2022). The NIV group was divided into two subgroups: one with face tent ventilation and the other with CPAP; however, the mortality rate was not significantly different between the two subgroups. In addition, the meta-analysis showed no statistically significant differences in the PaO_2/FiO_2 ratio, in the total number of days of hospitalization or intensive care, and in the intubation rate between HFNO and NIV groups (Peng Y, Dai B, Zhao HW, et al., 2022).

A literature review of COVID-19 patients showed that HFNO can reduce the need for intubation, the severity of complications related to mechanical ventilation and the duration of hospitalization in the AICU (Görün Kaya A, Öz M, Erol S, et al., 2020).

It should be noted that the results of other studies are contradictory. In the randomized COVIDISCUS trial involving French patients with severe forms of COVID-19, CPAP and HFNO did not significantly alter the risk of invasive ventilation at 28 days, compared to patients who received invasive ventilation from the start of admission (Bouadma L, Mekontso-Dessap A, Burdet C, et al.; 2022).

The SOHO study, which involved 711 French patients with severe forms of COVID-19 from January to December 2021, showed a mortality rate of 10% at day 28 in the HFNO group and of 11% in the standard oxygen therapy group; however, the difference was not statistically significant (Frat JP, Quenot JP, Badie J, et al., 2022).

Many factors can influence the success of NIV, such as the degree of patient cooperation, the type of interface used, the etiology of respiratory failure, and the experience of the medical staff (Ship S and Hill N., 2009).

Two meta-analyses of non-COVID-19 respiratory failure showed that CPAP can reduce both the need for intubation and the mortality rate, compared to simple oxygen therapy. (Ferreyro BL, Angriman F, Munshi L, et al., 2020; Chaudhuri D, Jinah R, Burns KEA, et al., 2022).

The RECOVERY-RS Randomized Clinical Trial in the United Kingdom of Great Britain and Northern Ireland, involving 1273 adults with COVID-19 and respiratory failure, showed a mortality rate of less than 30 days and a lower need for intubation in the CPAP group than in the conventional oxygen therapy group. However, there was no significant

difference in HFNO's initial strategy versus conventional oxygen therapy. (Perkins GD, Ji C, Connolly BA, et al., 2022).

Acute respiratory failure in COVID-19 patients can be triggered by many factors, including vaccines, which can exacerbate comorbidities such as psoriasis. When severe COVID-19 is associated with cardiovascular disease, diabetes or even systemic sclerosis, patients tend to experience higher degrees of severity and increased mortality (Ständer S, Zirpel H, Bujoreanu F, et al., 2022).

Consequently, a multidisciplinary medical team should treat these patients according to a personalized plan, and oxygen therapy should include consecutive ventilation strategies tailored to the patient's specific needs. Further studies are needed to obtain personalized guidelines for these patients.

This study had a few limitations. It was an observational study where no match or randomization was performed and included a relatively small number of patients, preventing us from drawing precise conclusions. Another limitation is that the population studied was Europid; the results cannot be generalized to patients of other races. In addition, there were some minor differences in comorbidity profiles at COVID-19 onset between the two groups. Finally, the study was initiated rapidly early in the pandemic, prior to the development of a set of baseline outcomes for COVID-19 studies on the initiation of different types of oxygen therapy, criteria for AICU and hospital discharge, or patient recovery protocols after severe COVID-19 treatment (Manole C. et al.,2024).

4.4 Discussions

The use of High-Flow Nasal Oxygen therapy (HFNO) in the treatment of COVID-19 patients is an important modality of respiratory support, providing a large flow of heated and humidified oxygen through small nasal cannulas. This technique is often applied to patients with acute respiratory failure, especially those who require high oxygen flows. HFNO were not used in the majority of patients in the study group, which may suggest that these patients were treated with conventional oxygen therapy or other respiratory support methods (Manole C. et al., 2024).

Overall, the use of HFNO can be a valuable respiratory support strategy for COVID-19 patients experiencing respiratory distress. The duration of HFNO use may vary considerably depending on the patient's clinical condition and response to therapy. It is important to note that this represents only part of the means of treatment and supports

available for COVID-19 patients, and the decision to use HFNO must be made in the specific context of each case.

The data on the use of noninvasive mechanical ventilation with positive pressure (VM-NIV CPAP) in the treatment of COVID-19, showed that this respiratory support modality was used in a significant number of cases. VM-NIV CPAP is used to deliver continuous positive pressure into the airways, aiding in alveolar recruitment, improving oxygenation and reducing respiratory distress. The decision to use VM-NIV CPAP or other respiratory support strategies depended on several factors, including severity of respiratory distress, arterial blood gas values, patient tolerance, and especially resource availability (Manole C. et al., 2024).

The data on the use of invasive mechanical ventilation in the treatment of COVID-19 revealed that most cases required this type of respiratory support, either due to recommendations of initial therapeutic guidelines or due to severe respiratory distress with imminent respiratory arrest upon admission to intensive care. These data reflect the diversity of respiratory support modes available to COVID-19 patients, with therapeutic decisions being made based on individual patient needs and their clinical evolution. The variability in duration of use and the presence of data outliers, underline the complexity of managing these patients and the need for a personalized approach in the treatment of COVID-19 (Manole C et al., 2024).

The analysis of data on the relationship between the use of non-invasive ventilation with continuous positive airway pressure (VM-NIV CPAP) and oxygen saturation (SpO_2) values at the time of admission to the Intensive Care Unit provides important insight into the impact of this treatment on critical patients with COVID-19. Here are the results and associated conclusions:

Upon admission to AICU, the Chi-Square test for the relationship between CPAP VM-NIV and SpO_2 value did not indicate any statistical significance. This suggests that there is no strong relationship between VM-NIV CPAP use and baseline SpO_2 levels upon admission to the ICU in this dataset. However, 24 hours after admission into intensive care unit, Chi-Square tests showed a significant association between VM-NIV CPAP therapy and SpO_2 levels. These results suggest that CPAP VM-NIV may have a notable impact on improving oxygen saturation in critical patients during the first 24 hours of staying in the AICU. 72 hours after admission to AICU, Chi-Square tests also showed a significant association between CPAP VM-NIV use and SpO_2 levels. This underlines the clinical relevance of CPAP VM-NIV, as an effective intervention for maintaining and improving the

oxygen saturation in critical patients during the first 72 hours after admission to the ICU (Manole C et al.,2024).

The analysis shows that VM-NIV CPAP therapy can have a significant impact on SpO_2, CO_2 and O_2 levels in critical patients with COVID-19, especially 24 and 72 hours after admission to AICU. These results highlight the importance of using CPAP VM-NIV in the management of respiratory function in patients with COVID-19 in critical stages, but also the need for adequate monitoring adapted to the individual evolution of patients.

It has also been demonstrated that, based on available data and chi-square tests performed, there is no strong evidence to suggest a significant relationship between the use of invasive mechanical ventilation and SpO_2, CO_2 or O_2 levels in the patients admitted to the AICU at that time. It is important to emphasize that these results specifically reflect the situation in this dataset and require further investigation to establish more precise conclusions or evaluate other factors that may influence these relationships.

The results of the tests and risk estimates provided in the analysis of the relationship between the state of discharge from the Intensive Care Unit (ICU) and the use of invasive mechanical ventilation (VMI) and non-invasive ventilation with continuous positive airway pressure (VM-NIV CPAP) are significant and have important implications. The risk estimation for the state of discharge from the AICU indicates higher odds for patients discharged to another ward compared to those who died. However, the 95% confidence interval is relatively wide, which indicates some uncertainty in the estimate.

Chi-Square tests revealed statistically significant and convincing results. The existence of a very significant relationship between the status at discharge from the ICU and the use of CPAP VM-NIV was supported by all tests used (Pearson Chi-Square, continuity correction and Fisher's exact test). The risk estimation reveals that the use of CPAP VM-NIV may be associated with an increased risk of death upon discharge from AICU, as indicated by the wide confidence interval for this group.

These results suggest that the use of CPAP VM-NIV and HFNO is not associated with the status when being discharged from AICU, but there is a significant association between CPAP VM-NIV use and risk of death at discharge from AICU.

4.5 Conclusions

In conclusion, HFNO is an essential respiratory support method for COVID-19 patients, providing heated and humidified oxygen through nasal cannulas. It is commonly used for patients experiencing acute respiratory failure or requiring higher oxygen levels.

Interestingly, most of the cases discussed do not involve the use of HFNO, indicating that alternative approaches such as standard oxygen therapy or other respiratory support methods may have been preferred in these cases. Finally, an analysis of the relationship between the status when being discharged from the ICU and VM-NIV CPAP and HFNO use indicates that use of VM-NIV CPAP is associated with a higher risk of death upon discharge from ICU. However, it is important to note that the confidence interval for this group is relatively wide, highlighting a certain level of uncertainty in the estimate.

5 CHAPTER 5 – STUDY OF ASSOCIATED RISK FACTORS / POTENTIAL INFLUENCE OF THERAPEUTIC APPROACHES

5.1 Introduction

The landscape of medical research is constantly evolving, requiring a dynamic understanding of the complicated interaction between risk factors and therapeutic

approaches in managing various medical impairments. This subchapter embarks on a comprehensive exploration, delving deeper into the multifaceted field of underlying risk factors while assessing the potential influences of therapeutic strategies. Recognizing the essential role these elements play in shaping patient outcomes, this study aims to decipher the links between risk factors and subjects' evolution.

5.2 Material and methods

This study used a retrospective observational design to investigate the use of antiviral therapies, antibiotics, and corticoids in the treatment of COVID-19, with a focus on their relationship to patients' condition upon admission and discharge from the AICU. In addition, the study aimed to explore the associations between known pathological medical conditions and subsequent patient evolution. The analyses involved Chi-Square and Odds Ratio tests with risk estimates.

5.3 Results and discussion

Chi-Square test results and risk estimates provided in the analysis of the relationship between the patient's condition at admission to the Intensive Care Unit and the use of antiviral therapy are important and provide significant clues regarding the decision to administer antiviral therapy. Chi-Square tests produced Pearson Chi-Square values and associated significance values that did not reach conventional significance levels ($p > 0.05$). This indicates that there is no statistically significant association between the patient's baseline condition and the administration of antiviral therapy.

The risk estimation indicates that patients who received antiviral therapy were approximately 1,694 times more likely to have a positive outcome (survival or transfer to another facility) compared to those who did not receive antiviral therapy. For the cohort of patients who did not receive antiviral therapy, the probability to have a positive result was smaller compared to the reference group.

These findings suggest that the administration of antiviral therapy may influence the outcomes upon discharge from the AICU, with a greater likelihood of having a positive outcome. However, it should be borne in mind that this does not necessarily imply causality, and other factors or interactions may play a role in the decision to administer antiviral therapy to patients in the AICU based on their baseline condition. It is essential that these outcomes are considered in the overall context of critical patient management and are

supported by further research to assess in more detail the impact of antiviral therapy on AICU patient outcomes.

Based on these analyses, there is no strong evidence to suggest a significant association between antibiotic therapy administration and the patient's condition at admission or discharge from the AICU. However, it should be borne in mind that these findings are specific to the data analyzed and there may be specific changes.

Regarding the absence of personal pathological history, Chi-Square test results did not indicate a significant association with the status when being discharged from AICU ($p = 0.782$). This suggests that the absence of this personal history does not significantly influence patient's outcomes at the time of discharge from AICU. However, it is important to note that sample size can influence the statistical strength of the test, and further research with a larger number of patients could provide more robust data.

5.4 Conclusions

Patients who received antiviral therapy were more likely to have a positive outcome (survival or transfer to another facility) compared to those who did not receive antiviral therapy.

Administration of antibiotic therapy has no statistically significant influence on patient outcomes at ICU admission or at the time of discharge from ICU. The absence of personal pathological history is not significantly associated with patient outcomes at the time of discharge from the AICU.

6 CHAPTER 6 – DISCUSSION

6.1 General discussions

Within the statistical analysis carried out within the research on the "*Therapeutic Approach in Critical Patients with SARS-CoV-2 Respiratory Infection*", the essential results of the dissertation will be debated in the current subchapter, connecting each aspect of the research, in order to provide a complete perspective on the contribution to the studied field. As our answers to the proposed questions have evolved over the course of this study, the final conclusions aiming to provide a clear and balanced view of the impact of this research

in the broader context of the management of critical patients with SARS-CoV-2 respiratory infection.

6.2 The limits of the research

In the complex exploration of the "*Therapeutic Approach in Critical Patients with SARS-CoV-2 Respiratory Infection*", the doctoral dissertation aimed to contribute to the improvement of known therapeutic approaches in the case of critical Covid-positive patients, in Intensive Care Units. However, like any scientific endeavor, this research is not without limitations that need to be recognized and explored in depth.

This section is dedicated to the careful analysis of the limitations encountered during the research, providing a balanced perspective on the context where the results should be interpreted. Despite the efforts made to shed light on key aspects of the therapeutic approach, it is important to confront openly the obstacles and challenges that may affect the interpretation and applicability of the findings.

By honestly acknowledging these limitations, we aim to outline a realistic and responsible framework for interpreting the results, while opening the doors for future research to address these challenges. So, hereinafter, we will carefully and transparently explore the limits highlighted in this research and their impact on the validity and generalizability of the results obtained.

- ✓ The diversity of Treatment Protocols
- ✓ The rapid evolution of scientific research
- ✓ The variability of population characteristics
- ✓ The limitations of available data
- ✓ The confusion factors and variables' control
- ✓ The emotional impact on patients

Recognizing and openly discussing these limitations is essential to ensure a proper assessment of the contribution of the doctoral dissertation and to guide future research in this area. These limitations do not diminish the importance of discoveries, but serve as starting points for improving methodologies and identifying future research directions. Researchers, medical professionals and decision-makers need to be aware of these limitations to encourage a balanced and correct approach in applying and interpreting the results of the research in the therapeutic approach in critical patients with SARS-CoV-2 respiratory infection.

6.3 Future research perspectives

This paper represents a deep commitment to understand and improve the management of patients affected by SARS-CoV-2 infection. In a world substantially affected by the COVID-19 pandemic, this research is in the midst of the efforts to address the significant challenges posed by this disease.

This thesis covered several important aspects of the therapeutic approach, trying to make contributions to the correct management of patients in Intensive Care Units. However, despite the successes recorded, it is essential to recognize that the field of therapy for critical COVID-19 patients is constantly evolving. In this context, this approach aims to explore the future research perspectives that open up as a result of this thesis, to new horizons of medical knowledge and innovation.

In the following, we will explore in detail future research perspectives that could help strengthen and expand our understanding of therapy for critical patients with SARS-CoV-2 respiratory infection:

- ✓ Personalization of therapy according to genetic characteristics
- ✓ Innovative Therapies based on Advanced Technologies
- ✓ Impact of viral variants on the therapy
- ✓ Integration of Non-Pharmacological Therapies into the Treatment Protocol
- ✓ Evaluation of the Long-Term Effects of the Therapy
- ✓ Patient-Centered Therapies and Involving Patients and Families in Decision Making
- ✓ Socio-Economic Impact and Home Health Care
- ✓ Evaluation of the Effects of Therapy in Different Population Groups
- ✓ Holistic Approach to Health

The future research perspectives in the field analyzed in this scientific paper are vastly expanded and full of challenges and opportunities. Further to this dissertation, researchers are called upon to explore the new frontiers of medical science, adapting to continuous changes in our knowledge of COVID-19 and engaging in a collective effort to improve the management and treatment of critical patients. Through these efforts, we hope to provide more effective, personalized and integrated solutions for the patients affected by this global pandemic.

7 CHAPTER 7. CONCLUSIONS AND PERSONAL CONTRIBUTIONS

Through this paper, we aimed to analyze the therapeutic approach of patients admitted to the Covid-AICU of the Galati County Emergency Hospital, the only functional ward in the county, permanently on-duty, opened on 28th March 2020 when the first critical patient with Sars-Cov-2 virus infection, coming from the Clinical Hospital of Infectious Diseases, was admitted.

Initially, the Covid-AICU functioned with 9 beds, and subsequently, depending on the epidemiological evolution, the number increased to 12-14-16 beds. In the following period, the staff had been under great pressure determined by the increased number of cases and the lack of available places in the AICUs, our department also taking patients from other counties of the country. Between 28th March 2020 and 31st March 2021, a number of 681

patients had been admitted to the Covid-AICU, the peak of admissions being in December 2020, respectively 116.

The male sex was predominant, 58% and the incidence of cases according to the age group was as follows: 3% between 0 and 40 years, 19% between 41 and 60 years, 55% between 61 and 80 years and a percentage of 23% fell into the age group over 81 years. As a particularity, it can be noted that the highest age values were associated with the transfers made from another health unit (Hospital of Infectious Diseases in Galati), and patients with the youngest age were transferred from another ward of the County Hospital to AICU.

As a place of origin, the vast majority of cases admitted to our ward were from the Clinical Hospital of Infectious Diseases (36.42%), followed by the Emergency Unit of our hospital (25.70%), nursing homes in the city (11.89%), other wards from the County Hospital (13.95%), TB hospital (6.61%) and Railway Hospital (5.43%). As a recommendation, for Galati County, we consider imperative to organize Intensive Care Units at the Hospital of Infectious Diseases and at the Pulmonology Hospital in order to prevent overcrowding the AICU of the County Emergency Hospital in the future.

Based on the radiographic assessment score of pulmonary edemas (RALE), 24% of patients had less than 50% lung impairment, 50% had lung injury between 50-80%, and in 26% of subjects, the lung impairment was over 80%, associated with an increased mortality rate. It should be specified that the access of Covid-positive patients to imaging investigations and especially to computer tomography examination was made with difficulty during that period of time due to the presence of a single device that also served the other non-Covid patients hospitalized in emergency regime.

This huge pressure on health services, and especially on intensive care units, shows the importance of providing high-performance medical equipment, which must be a permanent concern of decision-makers.

Most patients had increased values of inflammatory markers (CRP, ESR, fibrinogen, LDH, ferritin), neutrophilia, lymphopenia, increased D-dimers and the conversion to a decreasing trend near the time of transfer, and the evolution in dynamics of ferritin, C-reactive protein and procalcitonin was a predictive factor for the prognosis of the critical patient.

In the initial assessment of the inflammatory syndrome, statistically significant differences were found for the following parameters: procalcitonin values ($p = 0.0296$), fibrinogen concentration ($p = 0.0009$) and erythrocyte sedimentation rate ($p = 0.309$).

Of the 668 patients admitted to the AICU from 1st April 2020 to 31st March 2021, 355 patients required orotracheal intubation and mechanical ventilation, without any other respiratory support, CPAP or NIV, respectively, a percentage of 53.1%. Of these 355 patients, only 11.5% survived, so the mortality rate was 88.5% in this group. The mortality rate in this group was much higher than in the entire group of patients. Of all 668 patients, 252, or 37.7% survived.

Among the patients with chronic lung disease, the mortality rate was 100% in both the CPAP and HFNO groups. In addition, mortality was higher among patients with neurological, metabolic, renal and hepatic disorders in the CPAP group and among patients with oncological comorbidities in the HFNO group.

The mortality rates in both the CPAP (64.81%) and HFNO groups (74.07%) were significantly lower than in the orotracheal intubation group (88.50%) ($p < 0.0001$ and $p = 0.0004$, respectively). We mention that the mortality rate of Covid-positive patients treated in our ward was relatively similar to that reported in clinical trials at that time.

The intubation criteria used in this study were increased respiratory rate exceeding 30 breaths/minute, altered consciousness with risk of aspiration pneumonia, severe increase in respiratory effort using accessory muscles, severe decompensated acidosis (pH < 7.2-7.25) and use of ROX (respiratory rate oxygenation) index values (oxygen saturation ratio) for patients with HFNO. At the time of this study, there was no consensus nor sufficient clinical trials to establish clear criteria for stopping non-invasive oxygen therapy and initiating assisted ventilation, the first recommendations being even early orotracheal intubation, at admission to intensive care to prevent aerosol dispersion and contamination of the medical staff.

For acute respiratory failure developing in COVID-19 patients, existing clinical trials are insufficient and there is no consensus on the use of different oxygen therapy methods.

Our observations were similar to other clinical trials and showed that patients receiving HFNO have better adherence to therapy, are able to feed more effectively and communicate with healthcare professionals, and have lower levels of anxiety. By contrast, CPAP is associated with higher levels of anxiety, posing a risk for developing ventilator asynchronism, difficulties in oral nutrition, requiring additional parenteral nutrition, difficulty maintaining the prone position, discomfort due to decubitus cutaneous lesions secondary to mask pressure, which can sometimes overlap with the lesions produced by SARS-CoV-2.

Personal experience has shown that optimal oxygenation, either by administering high-flow oxygen on the nasal cannula or by non-invasive ventilation, gave better results than invasive ventilation in critical Covid-positive patients admitted to the AICU of Galati County Emergency Clinical Hospital.

Although the prognosis of patients with respiratory failure of other etiologies improves by initiating invasive mechanical ventilation, the mortality rate is extremely high among intubated COVID-19 patients, our recommendation being to avoid using it as the first alternative respiratory support.

As personal contribution, we propose the following recommendations for the respiratory support therapy in Covid-positive critical patients:

- avoidance of early orotracheal intubation, less than 12 hours after admission to the ICU, in the absence of severe hypoxemia (PaO_2<50 mmHg) in patients who tolerate well the non-invasive support
- implementation of using ROX index as a predictor of the intubation risk in patients with therapy with high oxygen flows on the nasal cannula. The ROX index is defined as the ratio of oxygen saturation (SpO_2) / inspiratory oxygen fraction (FiO_2) to respiratory rate (Roca O, et al., 2016). ROX index values are determined at 2, 4 and 12 hours after the initiation of HNFO, guiding the clinician in choosing the moment for orotracheal intubation.

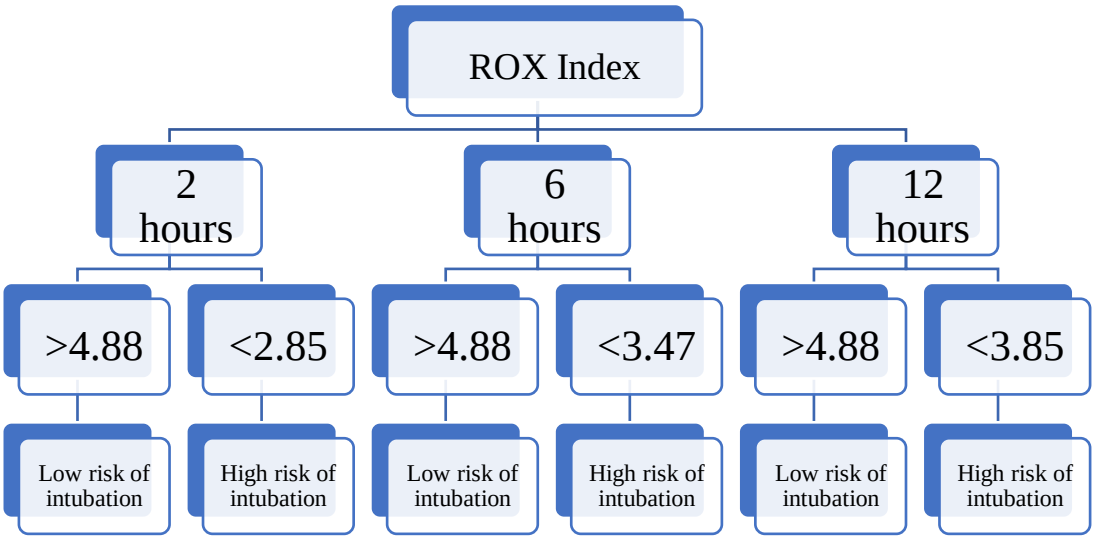

Figure 1 - Prediction of intubation in COVID-positive patients with HFNO, according to ROX index values (Roca O., et al., 2016)

- the radiological severity of pneumonia (RALE score) should not be considered a "per se" criterion for orotracheal intubation

- avoiding excessive sedation in patients with non-invasive CPAP and continuously adjusting the oxygen inspiratory fraction to maintain PaO_2>50 mmHg

We also want to mention the presence of silent hypoxemia as an unfavorable prognostic factor in critical patients infected with the Sars-Cov-2 virus. Silent hypoxemia or "happy hypoxemia" represents the paradox of being free of dyspnea. (Couzin-Frankel, 2020). In the absence of scientific evidence, the cause of this paradox is a viral invasion of the central nervous system. (Nouri-Vaskeh et al, 2020; Gopal et al., 2021). The absence of dyspnea despite severe hypoxemia is also found in other lung diseases, not being specific to Sars-Cov-2 infection. (Tobin et al., 2020). We observed its presence especially in male patients, included in the age group 41-50 years, without associated diseases, admitted to the ICU with severe ARDS and lung impairment greater than 80%, without respiratory symptoms and without dyspnea. The presentation of these patients in emergency services was late, the evolution unfavorable and the mortality rate extremely high.

We propose that Covid-positive patients fitting into these criteria be carefully monitored from the first days of the disease, an important role being played in these cases by the primary medicine network, respectively family physicians.

Globally, managing Sars-Cov-2 infection has been a real challenge for Intensive Care Units, which have often been insufficient to treat the large number of critical patients. The Covid-19 pandemic in Romania has brought into discussion the importance of endowing the Intensive Care Units with equipment, highlighting the work done by the intensivists, who very often put patients' lives above their own, to the detriment of their safety.

We would like to thank to all colleagues who, through their often superhuman effort, saved lives!

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