MASTER IN BIOMEDECINE

PROGNOSIS OF PATIENTS SUFFERING FROM SARS-COV-2 PNEUMONIA REQUIRING HIGH-FLOW OXYGEN THERAPY AS THE HIGHEST THERAPEUTIC SCALE (PATIENTS WITH A "DO NOT INTUBATE" STATUS). A MONOCENTRIC RETROSPECTIVE STUDY

TAKPAH, Anani

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TAKPAH Anani

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Université de Namur
FACULTE DE MEDECINE
Secrétariat des départements
Rue de Bruxelles 61 - 5000 NAMUR
Téléphone: + 32(0)81.72.43.22
E-mail: manon.chatillon@unamur.be - http://www.unamur.be/

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ABSTRACT

Background. The severe acute respiratory failure and hypoxemia induced by the COVID-19 disease has led to a widespread need for mechanical ventilation by orotracheal intubation. However, the choice of a do not intubate (DNI) order is recommended in some cases. This makes non-invasive respiratory support interventions such as high-flow oxygen therapy (HFOT) a possible alternative to invasive ventilation as the highest therapeutic scale in patients with severe COVID-19 infection and a DNI order. There is however a paucity of data on the prognosis of patients requiring HFOT with a DNI. As HFOT is also a limited resource, such data are useful for resource allocation, particularly in a situation of pandemic.

Aims. This study aimed to assess the vital prognosis of patients admitted in tertiary care hospital for acute respiratory failure due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who were offered HFOT as the highest therapeutic scale because of a DNI order.

Moreover, other aims are to assess characteristics or comorbidities of these patients associated with mortality and to compare the vital prognosis of these patients to that of patients who were offered HFOT for a SARS-CoV-2 infection but without a DNI order.

Methods. We performed a retrospective monocentric cohort study by reviewing the medical charts of patients admitted at the CHU-UCL-Namur-Site Godinne hospital for a SARS-CoV-2 infection who were offered HFOT with a DNI order to assess their prognosis. Prognostic factors are related to patient's demographic data namely: age, gender, weight, height, living in a health facility, COVID-19 vaccination status; as well as clinical data, in particular comorbidities. Groups comparison followed by multivariate cox regression and ROC analysis were performed to identify predictors of mortality.

Results. The results of the comparative analysis in the group of DNI patients indicated, at first a mortality rate of 76.2%. Only age ($p = 0.001$; r^2 change: 0.22) and D-dimers levels ($p = 0.0015$; r^2 change: 0.14) on admission were significantly associated with a higher mortality rate in DNI patients. Furthermore, mortality rate was significantly higher in patients in the DNI group than in those eligible for intubation (76.2% vs. 13%; $p<0.001$). There was a significant difference between DNI and non DNI groups according to age, body mass index (BMI) and hypertension.

Conclusion. To conclude, our results suggest a higher in-hospital mortality for COVID-19 patients with a DNI requiring HFOT as the highest therapeutic scale. The ROC analysis confirmed that age was the most important and discriminative factor predicting death. However, our multivariate analysis results are not exclusive, given the presence of numerous missing data for certain risk factors. It is necessary to perform studies with larger cohorts and fewer missing data to have a more complete multivariate analysis.

Running-title: High-flow oxygen therapy in COVID-19 do not intubate patients
Keywords: COVID-19, High-flow oxygen therapy, ARDS, do-not resuscitate, elderly

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ABBREVIATIONS TABLE

ACE-2	Angiotensin-Converting Enzyme 2
AD	Alzheimer Disease
AEDs	Antiepileptic Drugs
aHR	Adjusted Hazard Ratio
AIDS	Acquired Immunodeficiency Syndrome
AKI	Acute Kidney Injury
ALT	Alanine Transaminase
APP	Awake Prone Position
ARDS	Acute Respiratory Distress Syndrome
ARF	Acute Respiratory Failure
AST	Aspartate Aminotransferase
ATN	Acute Tubular Necrosis
BiPAP	Bilevel Positive Airway Pressure
BMI	Body Mass Index
CAD	Coronary Artery Disease
CCOS	Critical Care Outreach Service
CD8+	Cluster of Differentiation 8 or Cytotoxic T-cells
CFS	Clinical Frailty Scale
CHF	Chronic Heart Failure
CI	Confidence Interval
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CLD	Chronic Liver Disease
CND	Chronic Neurological Disease
COPD	Chronic Obstructive Pulmonary Disease
COT	Conventional Oxygen Therapies
COVID-19	Coronavirus Disease of 2019
CPAP	Continuous Positive Airway Pressure
CPR	Cardiopulmonary Resuscitation
CRP	C-reactive protein
DIC	Disseminated Intravascular Coagulation
dL	Deciliter
DNI	Do Not Intubate
DNR	Do Not Resuscitate
ECMO	Extracorporeal Membrane Oxygenation
EMA	European Medicines Agency
ESRD	End-Stage Renal Disease
FEU	Fibrinogen Equivalent Units
FiO2	Fraction of inspired Oxygen
FSGS	Focal Segmental Glomerulosclerosis
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	Gamma-Glutamyl Transferase
HFNC	High-Flow Nasal Cannula
HFOT	High-Flow Oxygen Therapy
HIV	Human Immunodeficiency Virus
H1N1	Swine flu
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
INF-γ	Interferon Gamma
IL	Interleukin
IQR	Interquartile Range
IMV	Invasive Mechanical Ventilation
JAK	Janus Kinase
KDIGO	Kidney Disease Improving Global Outcomes
Kg	Kilogram

LDH	Lactate dehydrogenase
m^2	Square meter
MERS	Middle East Respiratory Syndrome
mg	Milligram
ml	Milliliter
NF-κB	Nuclear Factor Kappa-light-chain-enhancer of activated B cells
ng	Nanogram
NIRS	Non-Invasive Respiratory Supports
NIV	Non-Invasive Ventilation
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratio
OSA	Obstructive sleep Apnea
P	p-value
RNA	Ribonucleic Acid
ROC Curve	Receiver Operating Characteristic Curve
ROS	Reactive Oxygen Species
RR	Risk Ratio
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS-CoV2	Severe Acute Respiratory Syndrome-related Coronavirus 2
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment
SpO2	Saturation of Peripheral Oxygen
TLR7	Toll-like receptor 7
TNF-α	Tumor Necrosis Factor Alpha
VA	Veterans Affairs
WHO	World Health Organization
4C Score	Coronavirus Clinical Characterization Consortium
%	Percentage

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INTRODUCTION

Since the first cases of novel SARS-CoV-2 coronavirus pneumonia occurred in Wuhan, Hubei Province, China, in December 2019-January 2020, the number of cases has increased rapidly. According to the World Health Organization (WHO), which regularly publishes reports on global health trends and data analysis, more than 767 million cases and 6947192 deaths have been recorded worldwide as of June 27, 2023. Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. The virus can be spread through droplets of saliva or nasal secretions emitted by an infected person when coughing, sneezing, breathing, talking, or singing. Most people infected with the virus have mild to moderate respiratory illness and recover without needing special treatment or hospitalization. Some, however, become seriously ill and require medical attention. On average it takes 5-6 days, but sometimes up to 14 days, for symptoms to appear in a person infected with the virus. Common clinical manifestations are a non-productive cough, fever, fatigue, loss of taste or smell. Less common are sore throat, headache, body aches, myalgias, diarrhea, skin rash or discoloration of fingers or toes, redness, or irritation of eyes. These manifestations may progress to organ dysfunction, i.e., shock, difficult breathing or shortness of breath, chest pain, loss of speech, difficulty moving or confusion, acute respiratory failure (ARF), acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), acute cardiac injury in severe cases, and death [1, 2].
Acute respiratory failure and acute respiratory distress syndrome are common reasons for admission to an intensive care unit, accounting for approximately 1/3 of admissions. In order to effectively control the pandemic and to avoid the lack of availability of resources resulting in triage of intensive care unit (ICU) beds and ventilators to other patients, especially those with risk factors, a range of treatment and therapeutic decisions have been put in place at any point in the patient's medical pathway (in the outpatient department, in the medical ward or emergency department, or when the patient is suffering from respiratory failure in the ICU) [3, 4].

1- TREATMENTS

With the overflow of patients and shortage of intensive care staff due to COVID-19, there was an urgent need for effective and specific treatment for this disease. Several clinical trials have attempted to identify the most potent drug or treatment strategy for the disease. Several agents including antiviral agents (polymerase inhibitors (Remdesivir, Favipiravir), protease inhibitors (Lopinavir/ritonavir), inhibitors of nucleoside and nucleotide reverse transcriptase (Azvudine, Molnupiravir), entry and uncoating inhibitors (Amantadine, Enfuvirtide) and others antivirals such as hydroxychloroquine with or without azithromycin), several targeting host therapies (neutralizing monoclonal and polyclonal antibodies therapies (convalescent plasma, Bamlanivimab, Tocilizumab, Etesevimab, Bebtelovimab), Janus Kinase (JAK) inhibitors (Baricitinib, Tofacitinib, Ruxolitinib, Nezulcitinib), corticosteroids (Dexamethasone, Budesonide, Ciclesonide, hydrocortisone, prednisolone and methylprednisolone) and non-steroidal anti-inflammatory drugs (NSAIDs)), antisense RNA, bronchodilators/vasodilators, respiratory supports such as invasive or non-invasive mechanical ventilation, high-flow oxygen therapy (HFOT), extracorporeal membrane oxygenation (ECMO) and preventive methods such as vaccine have been evaluated [5, 68]. In the present study, the only treatments used in patients with COVID-19 during the observation period were dexamethasone and respiratory supports such as oxygen therapy (either low or high flow), non-invasive ventilation, invasive ventilation, or ECMO.

1.1- Dexamethasone

Dexamethasone is a potent glucocorticoid recommended in many medical fields. It is a synthetic corticosteroid composed of chemically produced hormones that are very similar to cortisol. It also has 25 times more anti-inflammatory power than cortisol naturally secreted by the adrenal glands (above the kidney) [49].

It acts by suppressing neutrophil migration to inflammatory sites and reducing the proliferation of lymphocyte colonies. It can also bind to the receptors present on several proteins involved in the inflammatory reaction and modulate their gene expression [6].
It has been found useful in treating acute exacerbation of allergic and particularly anaphylactic reactions, inflammation, polytraumatic and anaphylactic shock, patients with conditions such as asthma, multiple sclerosis, hypersensitivity reactions to drugs, atopic and contact dermatitis. It is also indicated in the treatment of chemotherapy-induced nausea and vomiting, the prevention and treatment of altitude sickness [6]. In the COVID-19 pandemic, it has been found useful for severely ill patients with COVID-19 who are on supplemental oxygen or ventilatory supports by modulating inflammation-mediated lung injury and thereby reducing progression to respiratory failure and death [49].
On September 18, 2020, the European Medicines Agency (EMA) validated its use in adults and adolescents (from 12 years old and weighing at least 40 kg) infected with COVID-19 and who require additional oxygen therapy [48]. It is administered orally or intravenously at a dose of 6mg once daily, for ten days or less until hospital discharge if it occurs sooner [49].
In a clinical trial designed to evaluate the effects of potential treatments in patients hospitalized with Covid-19 in 176 National Health Service organizations in the United Kingdom, the use of dexamethasone resulted in lower 28-day mortality in those receiving either invasive mechanical ventilation or oxygen alone at randomization, but not in those receiving no ventilatory support [49].
When taken over the long term, dexamethasone-based drugs may weaken the immune system and cause serious adverse effects, which may or may not be reversible. For example, they can lead to weight gain caused by water and salt retention, high blood pressure, hypokalemia, swelling of the face and chest, the appearance of purplish hairs or skin patches, acne, sleep disorders weakness and muscle wasting, agitation, depression, osteoporosis, hormonal and metabolic disorders, reversible diabetes, cessation of growth in children, menstrual disorders, digestive disorders (gastritis, ulcers), certain eye diseases (glaucoma) [6].

1.2- Invasive Mechanical Ventilation (IMV)

Acute hypoxemic respiratory failure is one of the most common clinical manifestations that determine clinical outcomes in patients with COVID-19. Although a large proportion of COVID-19-infected patients have asymptomatic or mild respiratory disease, a small but significant proportion of patients present with acute respiratory distress syndrome (ARDS) requiring hospitalization and/or intensive care unit (ICU) admission and mechanical ventilation support. The severe acute respiratory failure and hypoxia due to the SARS-CoV-2 infection has led to a widespread need for invasive mechanical ventilation [7].
During inspiration, the lung expands due to a positive trans-pulmonary pressure. In spontaneous ventilation, where the patient breathes until the end of expiration, this gradient is produced by a negative pleural pressure created by the inspiratory muscles, mainly the diaphragm. In contrast, mechanical ventilation relies on positive airway pressure to push gas into the lungs, with positive transpulmonary pressure depending on increased alveolar pressure and passive chest wall movement. The trans-pulmonary pressure is generated by a combination of a negative pleural pressure and a positive alveolar pressure, and the work of breathing is shared in various proportions between the respiratory muscles and the mechanical ventilator [51].
IMV has some potential harmful effects on the pulmonary system. It has been associated with severe muscle weakness depending on the intubation duration and a high mortality rate for older individuals. In some circumstances, patients are not eligible for invasive mechanical ventilation, because of their own wishes or severe comorbidity and/or frailty [8].
The increased risk of Invasive mechanical ventilation use in elderly patients may be attributed to the chronic pro-inflammatory state of the immune system related to aging and weakened immune defenses against infections.

In the context of COVID-19, several studies have found that older age was strongly associated with an increased risk of invasive mechanical ventilation. In a longitudinal cohort study of 10131 patients in the Department of Veterans Affairs (VA) national health care system with SARS-CoV-2 infection, advanced age was strongly associated with the risk of mechanical ventilation (adjusted hazard ratio [aHR] 4.32; 95% CI = 2.88-6.47) [52].
In addition, invasive mechanical ventilation has been associated with various adverse events, such as ventilator-associated pneumonia and barotrauma. Intubations are well-known generators of considerable amounts of aerosol, which place nursing staff and caregivers at increased risk of infection transmission [9].

1.3- Extracorporeal Membrane Oxygenation (ECMO)

The WHO suggested the use of extracorporeal membrane oxygenation (ECMO) for assisting respiration (and circulation if necessary) in critically ill patients with COVID-19 based on its basic knowledge and review of its evidence on use in MERS and H1N1 influenza. It may serve as life-saving rescue therapy. With ECMO, venous blood is drained out of the body, oxygenated by an extracorporeal membrane, and transfused back into the body, with the entire process driven by a pump. The purpose of the ECMO is to resolve hypoxemia and improve blood perfusion in critically ill patients with ARDS, particularly in COVID-19 patients with persistent severe hypoxemia despite invasive mechanical ventilation [10]. Some studies showed that an early use of ECMO in respiratory distress, considering mechanical ventilation < 7 days for example may minimize breathing-induced pressure and reduce pulmonary and severe multi-organ dysfunction. Therefore, ECMO is a good therapeutic alternative in patients with COVID-19 who do not respond to conventional interventions including invasive mechanical ventilation, resulting in improved outcome and lung protection [11].
However, potential harms or complications are commonly observed in patients with severe COVID-19 receiving ECMO, such as an increased risk of bleeding complications and thromboembolic events. In a multicenter cohort study including 302 patients admitted to ECMO in 17 intensive care units in Paris between March 8 and June 3, 2020, a 90-day mortality of 54% was observed. They reported a high rate of pulmonary embolism under ECMO, reflecting thromboembolic events. They also reported a high rate of multifactorial severe bleeding or bleeding complications (thrombocytopenia, disseminated intravascular coagulation, acquired von Willebrand syndrome or COVID-19-associated endotheliitis) [70].

1.4- Non-invasive respiratory supports (NIRS)

The use of non-invasive respiratory supports i.e., non-invasive ventilation (NIV), continuous positive airway pressure (CPAP) and HFOT is a good compromise for patients with severe COVID-19 and a do not intubate order. These supports have been shown to be efficacious in critically ill patients with conditions such as acute exacerbation of chronic obstructive pulmonary disease COPD, acute cardiogenic pulmonary edema, obstructive sleep apnea (OSA) and hypercapnic respiratory failure, whereas their utility is less clear in the management of patients with pneumonia, ARDS and particularly in COVID-19. When utilized with precaution and under appropriate conditions, non-invasive respiratory support is an acceptable alternative to early invasive mechanical ventilation in the management of mild to moderate acute hypoxemic respiratory failure secondary to COVID-19 [12].

1.4.1- High Flow Oxygen Therapy (HFOT)

HFOT is an innovative and effective modality for early treatment of adults with respiratory failure with diverse underlying diseases such as hypoxemic respiratory failure, exacerbation of chronic obstructive pulmonary disease (COPD), postextubation, preintubation oxygenation, acute heart failure and conditions entailing a DNI order.

Administered via an air-oxygen blender, active humidifier, single heated inspiratory circuit, and nasal cannula, HFOT has become an alternative means of respiratory support for critically ill patients. It is an oxygen system capable of delivering up to 100% humidified and heated oxygen at a flow rate up to 60-100 liters per minute. It is useful for treating hypoxemic respiratory failure and is better tolerated than other non-invasive respiratory assistance systems [14].
The active humidifier heats and humidifies the gas delivered through the heated inspiratory circuit. This is ultimately connected to the nasal cannula which allows the patient to breathe adequately. It is considered to have several physiological advantages compared with the other conventional oxygen therapies (COT), including a reduced anatomical dead space, constant FiO2 and good humidification [15].

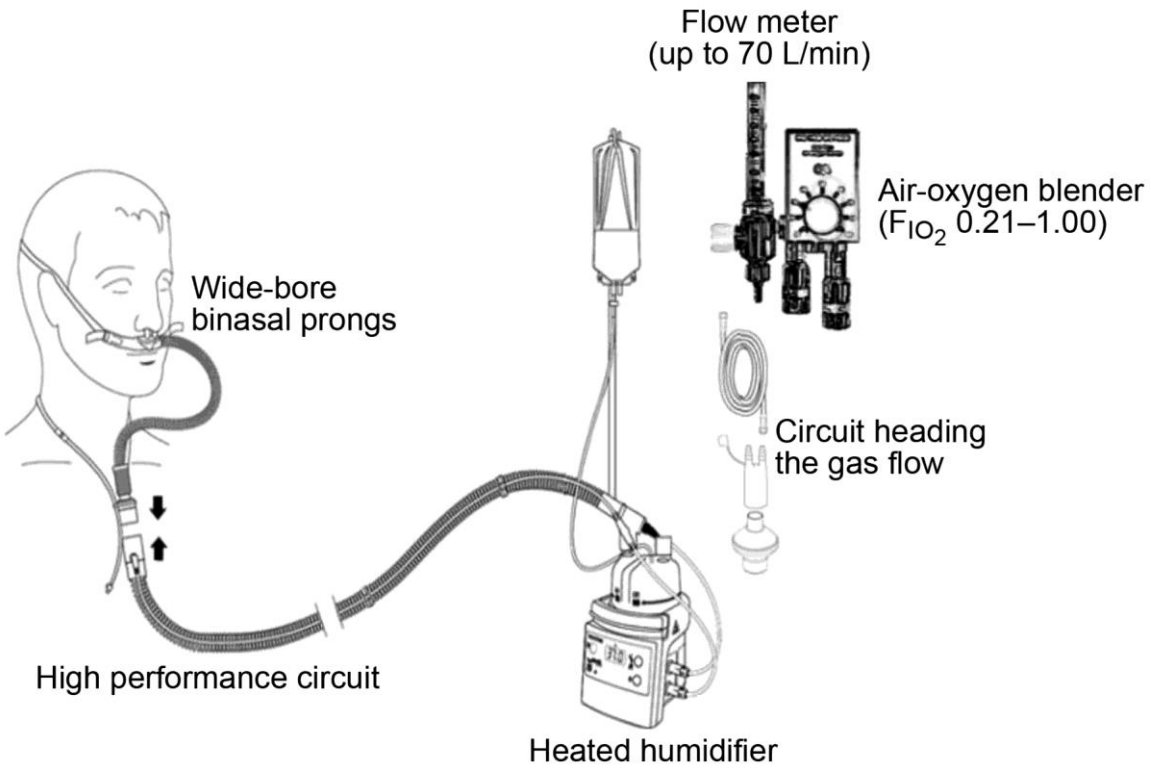


Figure 1: Nasal High-Flow Oxygen Therapy devices

Among other advantages, HFOT is often well tolerated. Furthermore, in an observational study of 122 matched critically ill adult patients with COVID-19-associated acute respiratory failure receiving either HFOT or early intubation on intensive care unit admission, the use of HFOT was associated with increased ventilator free days and reduced intensive care unit length of stay, with no difference in all-cause hospital mortality. So, HFOT reduces the need for intubation in patients with acute respiratory failure and this may in turn help to avoid the associated risks such as delirium and cognitive impairment, ICU acquired weakness and secondary infections [16].
Accordingly, HFOT can preserve the much-needed critical care ventilators, which have been in short supply in some regions during several waves of the pandemic.
HFOT allows better communication and easier oral or enteral feeding for these patients compared to the other conventional oxygenation therapy (COT) [19].
In older patients suffering from this dramatic clinical situation with such a poor prognosis, acute care should focus at least as much on patient quality of life as on survival. HFOT can help to maintain comfort as much as possible and possibly to decrease mortality [18].

1.4.2- Non-invasive ventilation: Continuous or Bilevel Positive Airway Pressure (CPAP, BiPAP)

Continuous positive airway pressure (CPAP) can be used as a first- or second-line treatment if HFOT is insufficient, and its use in intensive care units (ICUs) as well as in conventional wards has grown considerably. It is used as a quick solution to breathe pauses during sleep known as obstructive sleep apnea. CPAP uses adjustable air pressure generated by a machine and delivered through a tube in a mask that fits over the face. Alternatively, BiPAP (Bi-level Positive Airway Pressure) as its name indicates refers to the positive airway pressure at two levels: a pressure on inspiration and a lower pressure on expiration. Generally, BiPAP is often used to treat complex sleep apnea when CPAP is not tolerated or acute respiratory acidosis due to chronic obstructive pulmonary disease (COPD) exacerbation [17].
Compared with HFOT, CPAP has the advantage of providing a high fraction of inspired oxygen (FiO2), which is an estimate of the oxygen content that a person inhales and thus participates in alveolar gas exchange at higher pressures, increasing alveolar oxygenation and decreasing respiratory muscle work [17].
However, these devices have also been reported to be potentially dangerous due to the generation of high tidal volumes and excessive transpulmonary pressure variations, which may induce a risk of late intubation. One of the major problems with CPAP is that it cannot be used continuously for several days because, even when optimally applied, the interface can be uncomfortable [7]. As compared to HFOT, non-invasive ventilation (NIV) is uncomfortable and requires significant human-machine cooperation. In an experiment of five patients with COVID-19 who were treated with a HFOT after CPAP or NIV failure, the results convincingly suggest that, in the management of COVID-19-associated acute respiratory distress syndrome, HFOT is a better treatment option than CPAP, especially for some frail COVID-19 patients with respiratory failure, particularly for elderly and/or uncooperative patients [17]. At the Mont-Godinne hospital, HFOT was preferred to CPAP for patients with a DNI order.

1.4.3- Awake Prone Position (APP)

There is also the awake prone position (APP). Prone positioning involves turning a patient, with precise and safe movements, from the back onto the abdomen so that the patient is lying in a prone position. During the COVID-19 pandemic, it is extremely beneficial for patients with compromised respiratory comfort. It improves ventilation, keeps the alveolar units open and makes breathing easier. This technique is only necessary when the patient is having trouble breathing and the pulsed oxygen saturation (SpO2) drops below 94%. This technique is avoided in conditions such as pregnancy, deep vein thrombosis, major heart disease, unstable spine, femur, or pelvic fractures.
There is no evidence of a substantial mortality benefit for this non-invasive respiratory therapy technique. With low certainty, awake prone position appears to have little or no effect on mortality, while moderate certainty evidence shows that it reduces the need for endotracheal intubation which is considered invasive [13].

2- PROGNOSTIC FACTORS

Identifying potential risk factors that predict disease progression can be of great value to health care professionals to effectively triage patients, personalize treatment, monitor clinical course, and use appropriate resources at all levels of care to reduce morbidity and mortality.

2.1- Age

Age has consistently been implicated as one of the main risk factors for poor prognosis in COVID-19. Accordingly, a comprehensive approach that accounts for geriatrics-focused indicators is crucial when evaluating prognosis and treatment decisions for hospitalized older patients with COVID-19 [20]. Advanced age has been defined as one of the strongest risk factors for poor outcomes, complications, and mortality in COVID-19 [21].
Elderly patients are more likely to be hospitalized or admitted to the intensive care unit. From the pulmonary aspect, they are more likely to develop severe pneumonia or ARDS and more vulnerable to poor outcomes. In this elderly population, men had higher mortality than women [22].
Mortality of elderly COVID-19 patients decreases when there is greater access to hospital.
In a large-scale, multicenter Japanese retrospective study, clinical characteristics associated with mortality were assessed among patients who died during hospitalization (n=158) and those who were alive at hospital discharge (n=2736). Patients who died during hospitalization were older (63% of patients aged over 70 versus 16% of patients aged over 70 alive at hospital discharge, $p<0.001$). These patients also had independent risk factors for mortality, notably age over 70 [23].
In another national, multicenter, retrospective observational study in patients ≥ 80 years of age hospitalized with severe COVID-19 in 150 Spanish hospitals, some clinical characteristics at admission, were associated with higher all-cause mortality. Age, male sex, poor functional status before admission, and severe symptoms-but not comorbidities were independently associated with in-hospital mortality [24].
Overall, the results suggest that mortality in older adults with COVID-19 is related to the disease itself and not to a lack of appropriate care. Therefore, functional assessment is critically important in establishing a prognosis for elderly patients with COVID-19 [(23, 24)].

2.2- Frailty

One of the potential prognostic indicators in patients with COVID-19 is frailty. It reflects a state of vulnerability resulting from a lifetime accumulation of physiological deficits that lead to a limited capacity to respond to organic stressors. Frailty can be characterized by fatigue, accumulated deficits, sedentary behavior, weight loss, cognitive impairment, and social isolation. It is often associated with both malnutrition and sarcopenia, which is linked to skeletal muscle loss and poor muscle quality. Patients with sarcopenia tend to have the features of cachexia, which is characterized by a very low BMI [(69, 87)].
It is used as a measure of morbidity, to guide clinicians in prognostication and resource allocation in hospitalized patients with COVID-19. The degree of frailty could be used to assist both the triage into intensive care and decisions regarding treatments limitations. So, frailty provides essential prognostic information in COVID-19 patients in addition to old age (>70 years old) and comorbidities [25]. Frailty can be measured with the clinical frailty scale (CFS). It grades the patient from very fit (CFS1) and minimal frailty to terminally ill and maximal frailty (CFS9) i.e., someone whose life expectancy is below 6 months. Frailty was associated with a 2-fold to 3-fold increased risk of in-hospital death due to COVID- 19 independent of age, sex, and major comorbidities [26].
Most studies have shown that the frailty of hospitalized COVID-19 patients is a risk factor for short-term outcomes, such as in-hospital mortality (30- or 60-day mortality) [27]. In a literature search of articles including 21 studies with 26652 patients hospitalized with COVID-19 and reporting the association between frailty and mortality in this population, 51.4% were frail. A higher rate of short-term mortality was observed in frail compared to non-frail patients (OR =2.8; 95% CI: 2.3-3.5; $P<0.001$) [71].
In another mini-analysis summarizing discussions from meta-analyses (7 studies) regarding the impact of frailty in hospitalized older adults with COVID-19, frail COVID-19 patients had an increased risk of short-term mortality compared with non-frail COVID-19 patients. Frailty assessment should be performed in COVID-19 patients to help clinicians allocate healthcare

resources while managing the risk-benefit approach, reducing, and avoiding poor health outcomes [72].

2.3- Obesity

Obesity is defined as an abnormal or excessive accumulation of fat that presents a health risk. According to World Health Organization (WHO) standards, a person with a body mass index (BMI) >30 kg/m^2 is classified as obese. Achieving a healthy weight is considered as a risk modifier and has a favorable effect on blood pressure, glucose metabolism, and cardiac and vascular function [(31,73)].

A growing number of studies have attempted to establish an association between obesity and severity and/or death in COVID-19. In a single center retrospective cohort study of 469 African American COVID-19 patients in the USA, obesity was significantly associated with an increased risk of morbidity and mortality [73]. A retrospective observational monocentric study including 131 COVID-19 patients hospitalized in France, reveals that overweight and obesity are significantly associated with the risk of severe forms of the disease [74]. In a multicenter observational study of 2054 COVID-19 patients in Italy, obesity (BMI<30kg/m2) was associated with poor outcomes and a higher prevalence of in-hospital mortality [54].

Severe obesity was also shown to be a significant independent risk factor for in-hospital mortality from COVID-19 in studies including a small number of patients with severe obesity and focused on specific illnesses. During the COVID-19 pandemic, severe obesity was the highest mortality risk factor in the medical wards. The decreased functional residual capacity and hypoxemia observed in these patients with severe obesity make them vulnerable to a more severe COVID-19 illness [31].

2.4- Smoking status

Smoking status is also considered in the assessment of prognostic factors.

SARS-CoV-2 enters epithelial cells through the angiotensin-converting enzyme 2 (ACE-2) receptor. Some studies suggest that gene expression and subsequent receptor levels are elevated in the airways and oral epithelium of current smokers, putting smokers at higher risk for SARS-CoV-2. Other studies, however, suggest that nicotine downregulates the ACE-2 receptor. Despite these suggestions, smoking, both past and present, is known to increase the risk of respiratory viral and bacterial infections and is associated with worsening health outcomes once infection has occurred. Cigarette smoke reduces respiratory immune defenses through peribronchiolar inflammation and fibrosis, impaired muco-ciliary clearance, and disruption of the respiratory epithelium. There is also reason to believe that behavioral factors (e.g., regular hand-to-mouth movements) related to smoking may increase infection and transmission of SARS-CoV-2 in current smokers [55].

In an observational, multicenter, retrospective cohort study of 14260 patients admitted for COVID-19 in 123 Spanish hospitals, patients who were active or former smokers had a poor prognosis, with a higher rate of in-hospital death (22.5 vs. 16.4%), intensive care unit admission (10.4 vs. 8.1%) and 30-day readmission (5.8 vs. 4%) compared with non-smoking patients [75].

2.5- Comorbidities

Comorbidities such as diabetes, hypertension and cardiovascular diseases are other important risk factors for severity and mortality in COVID-19 infected patients and are targets that must be intensively addressed in the management of COVID-19 [29].

2.5.1- Diabetes

The pancreas and endothelium were found to express angiotensin-converting enzyme 2 (ACE2) receptors, the major binding site for the virus. Clinical data suggest that severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2) can cause metabolic derangement and impaired glucose homeostasis. In addition, overproduction of proinflammatory cytokines, including soluble interleukin-2 receptor (IL-2R), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) during COVID-19, promotes endothelial dysfunction and contributes to pro-coagulability. Thus, people with diabetes have a higher risk of death or health complications related to COVID-19 in ICU compared with people without diabetes [58].
On the other hand, medications often used in the treatment of COVID-19, such as corticosteroids or antiviral agents, can worsen hyperglycemia and lead to lipodystrophy and insulin resistance. A retrospective observational study including 451 patients with diabetes and/or uncontrolled hyperglycemia patients with COVID-19 in 88 U.S. hospitals showed a particularly high mortality rate in these patients compared to patients without diabetes and/or uncontrolled hyperglycemia. Another finding of the same study was that mortality was seven times higher for people without pre-existing diabetes who developed hyperglycemia during hospitalization [76].
Glucotoxicity and its consequences, in conjunction with the inflammatory cytokine storm of COVID-19 infection, and with increased oxidative stress, immune dysfunction, and endothelial damage, lead to other metabolic complications, such as an increased risk of thromboembolism and multi-organ damage in people with diabetes mellitus [58].

2.5.2- Hypertension

Hypertension is the most common comorbidity in patients with COVID-19, followed by diabetes in most studies. In an observational study of a cohort of 12594 patients in New York City, hypertension was reported in 34.6% of cases [77]. Hypertension is also frequently reported in association with diabetes, particularly in patients with more severe disease progression, admission to an intensive care unit and mechanical ventilation, and even death. In several observational studies, hypertension is often associated with other cardiovascular risk factors and advanced age, with these conditions often coexisting worldwide. Interestingly, in a large cohort study of 20133 COVID-19 patients in the United Kingdom, the hazard ratio for death compared with younger subjects increased from 2.63 (95% confidence interval [CI] 2.06-3.35, P<0.001) in patients aged 50 to 59 years and to 11.09 (95% CI 8.93-13.77; P<0.001) in patients aged 80 years or older, and the influence of hypertension on mortality risk was less significant after adjustment for age and sex, with the hazard ratio decreasing from 1.09 (95% CI: 1.05-1.14) to 0.89 (95% CI: 0.85-0.93) [74]. These significant results suggest that hypertension may not play an independent role in SARS-Cov-2 and COVID-19 infection, but rather that the effect of hypertension on COVID-19 progression is influenced by advanced age and its interaction with other cardiovascular risk factors [59].

2.5.3- Cardiovascular disease (CVD)

Cardiovascular damage is mainly caused by systemic inflammation (secretion of the antiviral cytokine INF-γ and proinflammatory cytokines, including IL-1, IL-6, and tumor necrosis factor-α (TNF-α)) after SARS-CoV-2 infection [78].
Cardiovascular manifestations are diverse in patients with COVID-19. For example, some patients presented with cardiovascular system symptoms such as palpitations and chest distress as early symptoms. Myocardial damage was also detected in COVID-19 patients and is confirmed to be associated with poor outcome. The mortality rate in patients with underlying cardiovascular disease and myocardial lesions, which have been shown to be one of the risk factors for severe cases, is much higher than in the general population. Other cardiovascular manifestations of COVID-19 are arrhythmias (ventricular tachycardia and fibrillation) in which elevated troponin T levels were likely to indicate the potential development of malignant arrhythmias. Heart failure is also a common manifestation. Reduced diastolic function, preexisting CVD comorbidities, and cardiac dysfunction associated with sepsis are all potential causes of heart failure in COVID-19. We also have

coagulation abnormalities in which disseminated intravascular coagulation (DIC) and thromboembolic events are highly prevalent in COVID-19 patients. During these thromboembolic events, alteration of the endothelium plays a key role [60].
The prevalence of preexisting disease, particularly cardiovascular disease, was significantly higher in severe cases and deaths due to COVID-19, indicating that preexisting cardiovascular disease could predict the adverse effects of SARS-CoV-2 infection. In a retrospective case study of 1590 patients hospitalized with COVID-19 at the start of the pandemic in China, severe cases of COVID-19 were more likely to develop cardiovascular disease (33.9%) than non-severe cases (15.3%) [79].
Cardiovascular complications have been reported with other respiratory infections. Hospitalization for pneumonia is associated with short- and long-term CVD risk. Consequently, patients with a history of cardiovascular disease develop severe conditions during infection and have a higher mortality rate. Cardiomyocytes express receptors for SARS-CoV-2 (ACE2), so this virus could infect the human heart, potentially even worsening heart failure.
There is a high rate of cardiovascular disease in patients with COVID-19. It is therefore important to know the impact of cardiovascular disease in patients with COVID-19. The results of a systematic review and meta-analysis including 159,698 COVID-19 patients shows that acute cardiac injury, (OR: 13.29, 95% CI 7.35-24.03), heart Failure (OR: 6.72, 95% CI 3.34-13.52), arrhythmia (OR: 2.75, 95% CI 1.43-5.25), coronary artery disease (OR: 3.78, 95% CI 2.42-5.90), and cardiovascular disease (OR: 2.61, 95% CI 1.89-3.62) were significantly associated with mortality [67].
Early in the pandemic, chronic heart failure (CHF) was found to be a significant risk factor for an adverse outcome. It was associated with increased length of stay and mortality. In a prospective international multicenter study examining the role of preexisting chronic heart failure on clinical outcomes in 3917 critically ill elderly (≥70 years) ICU patients with COVID-19, elderly patients with a high prevalence of chronic heart failure (566 of 3917 patients (14%) patients) were particularly vulnerable and were disproportionately affected by the pandemic, with an increased need for intensive care. However, in multivariable analysis, after adjustment for other risk factors, chronic heart failure was not independently associated with 30-day mortality [35].

2.5.4- Acute kidney injury (AKI)

Acute kidney injury (AKI) is also associated with a high mortality rate among hospitalized patients with COVID-19. It is defined according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines as the increase in serum creatinine by ≥0.3 mg/dL (≥26.5 micromol/L) within 48 hours or increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior seven days [30].
Several hypotheses may explain the potential pathophysiological mechanisms responsible for COVID-19-related AKI. These generally involve damage to the tubular epithelium and podocytes due to the high expression of angiotensin 2-converting enzyme (ACE2) in proximal tubular epithelial cells and podocytes, which serves as a portal of entry for SARS-CoV-2, causing acute tubular necrosis (ATN); direct infection of the glomerular endothelium, causing focal segmental glomerulosclerosis (FSGS), a type of glomerular kidney disease; COVID-19-related hypovolemia, leading to prerenal AKI, complement activation, cytokine storm hypercoagulability and microangiopathy, which can lead to multi-organ damage, particularly acute cardiac and pulmonary injury and subsequent AKI due to hypoxia and hypotension; nephrotoxic drugs and co-morbidities such as hypertension and diabetes mellitus, which confer renal vulnerability to AKI [30].
In a systematic review of 44 studies involving a total number of 114 COVID-19 patients with AKI with a mean age of 53.6 years, the results show us that acute renal failure frequently complicates the course of hospitalizations for COVID-19 and is associated with increased severity of illness, prolonged length of hospital stay, and poor prognosis. Thus, early detection of comorbidities and renal complications is essential to improve outcomes for COVID-19 patients [30].

2.5.5- Chronic Kidney Diseases (CKD)

CKD affects approximately 10% of the world's population. The main etiologies are diabetes mellitus and hypertension. Patients with prior CKD undergoing dialysis therapy are a more vulnerable group of patients because of their comorbidities and difficulty in social distancing. SARS-CoV-2 infection in patients with CKD on dialysis is also associated with complications and prolonged hospitalization. A meta-analysis including 73 studies evaluating the association between multi-organ dysfunction and the development of COVID-19 found that patients with CKD were more likely to develop severe SARS-CoV-2 infection (OR 1.84 [95%CI 1.47-2.30]) [82].
CKD on maintenance dialysis is associated with increased disease severity and higher in-hospital mortality. In addition, renal failure in hospitalized patients with SARS-CoV-2 infection is associated with increased in-hospital mortality and worse clinical course, raising concerns in patients with preexisting comorbidities such as chronic kidney disease (CKD), end-stage renal disease (ESRD), and renal transplant patients on immunosuppressive therapy. Patients with prior CKD undergoing conservative treatment have also an increased risk of critical SARS-CoV-2 infection. Similarly, a review of 90 articles showed that there is an association with worse clinical outcomes, more severe disease, higher mortality, and worse prognosis in patients with COVID-19 [56].

2.5.6- Chronic Airway Diseases (CAD)

Patients with chronic lung disease are at higher risk of developing more severe COVID-19, with poor outcomes and a higher risk of mortality. In addition to being more susceptible to infection, these chronic lung disease patients have altered expression profiles of antiviral and immune response genes, altering their ability to fight infection. This would reduce antiviral defense, promote increased viral replication and, ultimately, predispose to severe lung damage [66].
The mortality rate of COVID-19 may be higher in patients with asthma and COPD than in patients without chronic obstructive airway disease. This is indeed the case in a study of 5625 hospitalized patients with COVID-19 were divided into 3 groups. The mortality rates of the asthma and COPD groups were approximately 2.3 and 4.8 times higher than those of the control group, respectively [33]. However, the prevalence of COPD patients with confirmed COVID-19 is low because these patients are so afraid of COVID-19 infection that they might reduce social activity and wear masks more than other people. In a retrospective study in South Korea, although the mortality of the COPD group was higher than that of the non-COPD group (22.9% versus 3.2%, $p<0.001$), only 35 out of 6520 (0.5%) patients with COVID-19 were diagnosed with COPD [34].
Patients with a history of, or suffering from, bronchiectasis, cystic fibrosis, interstitial lung disease, pulmonary hypertension and pulmonary interstitial diseases are also at increased risk of severe COVID-19 and its complications. The risk of mortality is also higher [66].

2.5.7- Chronic Neurologic Diseases (CND)

Neurologic diseases such as Alzheimer disease (AD) also increase the COVID-19 mortality risk. Patients with Alzheimer's disease are associated with the greatest risk of hospitalization and mortality from COVID-19. The link between COVID-19 and AD is mediated by the neuro-immune system. Systemic immune abnormality in AD may promote pro-inflammatory cytokine release and tissue damage in SARS-CoV-2 infection, contributing to poor outcomes [32, 80]. In a retrospective case-control study including 40993 veterans diagnosed as positive for COVID-19 in the USA, subjects with AD had a significantly higher risk of mortality (OR = 1.695, 95% CI [1.383, 2.078] and OR = 1.653, 95% CI [1.219, 2.242]; $p=0.001$) compared to subjects without AD [80].
The link between SARS-CoV-2 and Parkinson's disease can be explained both directly and indirectly. Directly, SARS-CoV-2 could bind to ACE2 receptors on dopaminergic neurons, altering the rate of accumulation of misfolded α-synuclein, inducing mitochondrial stress, affecting

autophagy, and promoting apoptosis. Through indirect pathways, SARS-CoV-2 could lead to neurodegeneration through systemic inflammation via the blood-brain barrier, promoting a hypercoagulable response to form clots in cerebral vessels, and cytokine storms could lead to hyperinflammation and neuroinflammation [32].

Epilepsy is also one of the most common chronic neurological diseases, characterized by the spontaneous recurrence of unprovoked seizures. It is therefore important to know the association and different effects of COVID-19 on epilepsy. COVID-19 patients with a history of epilepsy may experience worsening of their seizures. Some studies have reported risk factors for seizure exacerbation, and similar factors such as the number of antiepileptic drugs (AEDs), seizure frequency at baseline, sleep-related problems, and mental stress. Similarly, other studies show that increased stress and lack of access to physicians or medication refills, particularly during the first months of withdrawal from service, would likely have worsened seizure control during COVID-19 and exposed epilepsy patients to a higher risk of mortality [64]. In contrast, in a study involving three epilepsy centers in Spain and Italy, no significant change in seizure frequency was reported during COVID-19 [81]. This may be explained by the fact that quarantine due to COVID-19 would have enabled epilepsy patients to lead a normal life, thus improving compliance with treatment, and that regular sleep could have led to better seizure control.

Several studies have demonstrated a possible link between COVID-19 mortality risk and other neurological disease histories, such as dystonia, amyotrophic lateral sclerosis, Huntington's disease, neuromuscular diseases, cerebrovascular diseases, and multiple sclerosis. In a monocentric retrospective study of 709 COVID-19 patients in Germany, patients with pre-existing chronic neurological diseases (CND) (35%), including multiple sclerosis, cerebrovascular disease, myasthenia gravis, dementia (defined and undefined) and cognitive impairment, were associated with poor functional outcomes at hospital discharge and had a significantly higher mortality rate than COVID-19 patients without CND [65].

2.5.8- Chronic Liver Disease (CLD)

During the COVID-19 pandemic, cases of chronic liver injury have been reported and are associated with higher mortality. COVID-19 can also worsen underlying chronic liver disease (CLD), leading to hepatic decompensation and severe chronic liver failure, with higher mortality. Liver dysfunction was significantly higher in critically ill patients and was associated with poor outcomes [57].

In an international study of 130 centers in 29 countries, including 745 COVID-19 patients with CLD, disease stage was strongly associated with mortality in COVID-19. The rate of hepatic decompensation and mortality in COVID-19 patients with cirrhosis was particularly high [83].

Among COVID-19 patients with CLD, the coexistence of predictors such as age (>60 years), renal failure, comorbidities (obesity and diabetes), would further worsen the prognosis [84].

2.5.9- Immunosuppression

Before the COVID-19 pandemic, immunocompromised patients for example patients with immunosuppressive or immunomodulatory medication use, chronic systemic steroid use, history of bone marrow transplant or solid organ transplantation, solid tumor, or hematologic malignancies on active treatment and advanced or untreated human immunodeficiency virus (HIV) had more severe organ failure than non-immunocompromised patients. This population of immunocompromised patients, including active cancer, organ transplant, the use of immunosuppressive agents and chemotherapy, and HIV infections are growing. Generally, immunosuppression status is strongly associated with mortality but not with intubation in patients with the novo acute hypoxemic respiratory failure after adjustment, nor after matching on respiratory disease severity markers [36].

During the pandemic, immunocompromised patients were vulnerable to the worse outcomes of the disease [63]. Most of them respond poorly to vaccines in terms of antibody production. Alternatives

using oral antiviral drugs such as Paxlovid and convalescent sera have been proposed to effectively reduce the risk of severe COVID-19 and mortality [37].
However, immunocompromised patients requiring invasive mechanical ventilators for acute respiratory failure in the ICU usually have high morbidity and mortality. In these patients with acute respiratory failure, the use of HFOT in association with conventional oxygenation therapy and non-invasive supports may also decrease the intubation rate [38].
In a Japanese observational study including 14760 COVID-19 patients, immunosuppression patients particularly those with metastatic cancers and hematologic malignancies were older and had bad outcomes during hospitalization compared to non-immunosuppressed patients [39].
In another systematic review of 4942 pre-existing cancer, hematopoietic cell and solid organ transplant patients with COVID-19 had poor outcomes and higher mortality than the general population with COVID-19 [85].

2.5.10- D-dimer level

D-dimers are products of fibrin degradation by the fibrinolytic system, which is activated as soon as a thrombus forms. They are soluble biomarkers of coagulation and fibrinolysis activation. They can be measured in whole blood or plasma. D-dimer assays are used in decision-making algorithms for the diagnosis of pulmonary embolism [40].
D-dimer elevation is a significant marker of prognostic worsening by coagulopathy and incident pulmonary embolism. In the context of the COVID-19, coagulopathy is a key feature of SARS-CoV-2 infection, and D-dimer has been reported as a predictor of severity of the disease. Elevated D-dimer levels at admission were associated with a higher risk of in-hospital mortality in COVID-19 patients. In a retrospective, observational study of 2377 hospitalized COVID-19 patients, patients with elevated D-dimers had an increased risk of severe disease (43.9% vs. 18.5%; P<0.001), thrombotic events (19. 4% vs. 10.2%, P<0.001), acute kidney injury (42.4% vs. 19.0%, P<0.001) and death (548 [29.9%] vs. 60 [10.8%]; OR, 3.5 [95% CI, 2.7-4.7]; P<0.001) compared to those with normal D-dimers at baseline [41].
In a multicenter retrospective observational study including patients hospitalized with a diagnosis of COVID-19 and having been recruited in 32 hospitals of the national health system in 9 autonomous communities of Spain, patients with a harmonized D-dimer ≥ 0.945 mg/L FEU (Fibrinogen Equivalent Units) had a higher mortality rate [42].

3- DO NOT INTUBATE (DNI) STATUS

Supportive treatments for patients with acute respiratory failure include supplemental oxygen, high-flow nasal cannula oxygen, non-invasive ventilation, invasive mechanical ventilation via endotracheal tube or tracheostomy, extracorporeal membrane oxygenation (ECMO), and palliative treatments such as opioids. Do Not Intubate (DNI) order reflects a decision not to proceed to invasive mechanical ventilation when the clinical situation would require such escalation in therapy.
This decision can occur at any point in a patient's medical care pathway in the outpatient department or emergency department, or when the patient has respiratory failure in the intensive care unit [3].
In a systematic review of 26 observational studies to assess the rates and variability of no-intubation orders in patients with acute respiratory failure in groups that included 10755 adult patients with acute respiratory failure in general who required non-invasive ventilation or high-flow nasal cannula oxygenation, rates of “no-intubation” were higher in studies with older patients and in studies in which no-intubation decisions were made without patient or family input. There were no significant differences in orders not to intubate based on severity of illness, observed mortality, malignancy comorbidity, or methodological quality [3].
During the COVID-19 pandemic, severe forms with acute respiratory distress syndrome (ARDS) leading to death are more common in the elderly, frail patients, and those with multi-morbid

conditions. In these patients, appropriate palliative care is essential when the prognosis is poor. An immediate implementation of the DNI order to COVID-19 infected patients, especially elderly patients or those deemed associated with poor prognosis according to the physician's judgment is crucial [43].

At Mont-Godinne Hospital, COVID-19 patients who required HFOT were admitted to the ICU, except for those with a "do not intubate" order. The latter received HFOT in a conventional ward.

Several studies have shown that patients with a Do Not Resuscitate (DNR) or Do Not Intubate (DNI) status are significantly associated with an increased risk of death from COVID-19.

In a retrospective single-center study including 178 COVID-19 patients in Denmark, the mortality rate among patients with a DNI order was high (80.95%) compared with patients requiring intubation (24.34%). This rate was particularly high (98%), particularly in patients with oxygen requirements ≥ 30 l/min [86].

In addition to the condition of the patient, other factors may influence the decision that a patient will not go to intensive care. Particularly, problems of availability of intensive care beds are important in this respect. As the availability of ICU beds fluctuate, choices made at a certain time points in the pandemic may not be the same as at others time points, depending on the overcrowding of intensive care units.

The use of non-invasive respiratory supports especially the high flow oxygen therapy (HFOT) is a good therapeutic alternative or compromise for patients with severe COVID-19 and a DNI order because intubation with invasive mechanical ventilation has some potential harmful effects on the pulmonary system. The prolonged use of this support is associated with severe muscle weakness in all patients and a high mortality rate especially for elderly, frail patients and those with comorbidities who represent a considerable proportion of patients with severe COVID-19 infection admitted to hospital. However, the number of HFOT is also limited in hospitals, so it is interesting to know whether this treatment is effective, not futile for DNI patients, especially those with severe respiratory failure [(4, 44)].

The use of these supports in COVID-19 patients with a DNI order refers us to an ethical or bioethical problem due to the triage of patients. Therefore, the DNI decision has an impact and requires reflection, making consensus difficult due to religions, cultural or lack of knowledge about current legislation and the evolution of bioethics. It drives people in general to rethink bioethical and ethical values. For example, in the Netherlands, advance care planning such as a DNI order are required to be discussed with the patient and/or relatives upon admission [8].

SPECIFIC AIMS

The aim of the study is to assess the vital prognosis of patients admitted in a tertiary care hospital for acute respiratory failure due to SARS-CoV-2 pneumonia who were offered HFOT as the highest therapeutic level, i.e., patients with a DNI order. The primary outcome is in-hospital mortality.
Moreover, other aims are to assess characteristics or comorbidities of these patients associated with mortality and to compare the vital prognosis of these patients to that of patients who were offered HFOT for a SARS-CoV-2 pneumonia but without a “DNI order”

METHODS

TYPE OF STUDY

A retrospective and monocentric cohort study was conducted.

ELIGIBILITY CRITERIA

Adult patients (age>18 years old) hospitalized with a diagnosis of SARS-CoV-2 pneumonia at the CHU-UCL-Namur-Site Godinne hospital and offered HFOT were identify based on the institutional COVID-19 database. Only patients who received HFOT were included.

EXCLUSION CRITERIA

Patients transferred to another hospital while still under HFOT.

OBSERVATION PERIOD

Individuals hospitalized at the CHU-UCL-Namur-Site Godinne with laboratory-confirmed SARS-CoV-2 infection from March 1, 2020, to February 28, 2022, were assessed for eligibility criteria. A laboratory confirmation of SARS-CoV-2 infection was defined as a positive result on a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal swabs.

DATA SOURCE

Data of patients on HFOT were extracted from the institutional electronic health record, anonymized, and stored in an Excel sheet for further statistical analysis. The data were retrieved by the thesis student (Anani TAKPAH, Master student in Biomedical Sciences, UNamur).

DATA COLLECTION

The DNI order was easily identified since patients put on HFOT and a DNI order were not admitted to the ICU whilst those with a “do intubate” order was always treated by HFOT in the ICU, not on a conventional ward.
For each patient we collected demographic data:
- Age
- Body Mass Index (BMI)
- Smoking status: smoker, ex-smoker, non-smoker
- Gender
- Living in a healthcare facility prior to diagnosis
- COVID-19 vaccination status

We also collected comorbidities with history of:
- Chronic airway disease: Asthma, chronic pulmonary disease (COPD), pulmonary infiltrative disease, bronchiectasis, cystic fibrosis, interstitial lung disease and pulmonary hypertension
- Diabetes
- Hypertension
- Cardiovascular disease defined as presence or history of
    - Cardiomyopathy,
    - Coronary artery disease (CAD), or
    - Chronic heart failure (CHF)
- Immunosuppression, i.e.:

- Immunosuppressive or immunomodulatory medication use,
- Chronic systemic steroid use,
- History of bone marrow transplant or solid organ transplantation
- Solid tumor or hematologic malignancies on active treatment
- Advanced or untreated human immunodeficiency virus (HIV)

- Chronic neurologic diseases as Alzheimer's disease, Parkinson's disease, dystonia, amyotrophic lateral sclerosis, Huntington's disease, neuromuscular disease, multiple sclerosis, and epilepsy.
- Chronic kidney disease.
- Chronic liver disease.

and characteristics at admission:
- D-dimer dosage at admission (or diagnosis for nosocomial cases)
- Acute Kidney injuries (AKI) defined as an abrupt (within 48 hours) deterioration in kidney function, manifested by an increase in serum creatinine level with or without reduced urine output. Here AKI is positive if this level of creatinine level is up to 1,25mg/dL.
- Date of diagnosis (positive RT-PCR)

The following data were retrieved for assessment of prognosis.
- Date of admission
- Date of oxygen therapy initiation and weaning (if weaning possible)
- Date of high flow oxygen initiation and weaning (if weaning possible)
- Date of non-invasive ventilation initiation and weaning (if weaning possible)
- Date of intubation and weaning (if weaning possible)
- Date of ECMO initiation and weaning (if weaning possible)
- Treatment with oral corticosteroid therapy (dexamethasone)
- Date of discharge or death
- Type of discharge facility

DATA PROTECTION

The protection of patient's personal data is ensured in accordance with the requirements of the General Data Protection Regulation (GDPR), the Belgian law of July 30, 2018, and the law on the protection of patients (2002). The Ethics Committee of the CHU UCL Namur, Godinne site, has confirmed that it is composed and carries out its activities in compliance with the applicable laws and regulations and according to the ICH/GCP guidelines.

PATIENTS GROUPS

For statistical analysis, we defined several groups for comparisons: DNI vs not DNI, DNI vs not DNI with HFOT as the highest treatment level, DNI survivors vs. DNI non-survivors.
We compared two groups: with and without a DNI order. At Mont-Godinne, the decision to consider a patient as DNI was taken based on a collegial decision between the doctors caring for the patient and between the intensive care unit, the patient himself and his family. This decision is always taken with a view to avoiding treatment deemed futile on the one hand, and on the other, at certain points during the pandemic, there were also choices dictated by the number of available ICU beds. Most often, however, the decision was based on the conviction that intubation would be futile, given the patient's poor prognosis.
Similarly, we compared the group of DNI patients with the group of patients eligible for intubation but who did not require intubation or ECMO. The aim is to compare the mortality of two groups who had access to the same intensity of treatment.
Finally, we compared two groups of patients with a DNI order based on their survival status and we performed an ROC analysis of the significant predictors of mortality in DNI patients

STATISTICAL ANALYSIS

Groups were compared by using the Chi-square test for qualitative variables and unpaired Student's t-test or Mann-Whitney test for quantitative variables. Demographic characteristics were described as median and interquartile ranges (IQR) for continuous variables, or frequencies and proportions (%) for categorical variables.
Numeric variables were expressed as mean (±SD) and discrete outcomes as absolute and relative (%) frequencies. Group comparison was assessed by comparing baseline demographic data, comorbidities, and characteristics at admission between groups. Continuous outcomes were compared with unpaired Student t-test or Mann-Whitney U test according to data distribution. Discrete outcomes were compared with chi-squared or Fisher's exact test accordingly.
For the age, Body Mass Index (BMI) and D-dimer dosage (ng/mL), normality of data was assessed with the Shapiro-Wilk test and the Levene's test.
Discrete outcomes were compared with chi-squared or Fisher's exact test accordingly.
We created 2 groups according to the values of "patients offered HFOT with do not intubate order (Yes=1; No= 0)".
To compare the mortality of two groups who had access to the same intensity of treatment, we created 2 groups according to the values of "patients in ICU without intubation and ECMO (Yes=1; No= 0)". Similarly, these groups comparison was assessed by comparing baseline demographic data, comorbidities, respiratory supports, and other parameters. Data on intubation and ECMO were not used for this analysis. As well as data on 20 patients since these represent patients eligible for intubation and who received ECMO and/or invasive mechanical ventilation. Continuous outcomes were compared with unpaired Student t-test or Mann-Whitney U test according to data distribution. Discrete outcomes were compared with chi-squared or Fisher's exact test.
We created 2 groups of patients with a DNI order based on their deceased status (Yes=1; No=0) to compare demographic data, comorbidities, respiratory supports, and characteristics at admission between groups. Similarly, in this analysis, a lot of data disappeared, namely data on ECMO, intubation and 69 patients that represent those eligible for intubation were not included. Continuous outcomes were compared with unpaired Student t-test or Mann-Whitney U test according to data distribution. Discrete outcomes were compared with chi-squared or Fisher's exact test.
The alpha risk was set to 5% ($\alpha = 0.05$) for all comparison analysis and two-tailed tests were used.

We used survival analysis with Kaplan Meier curves to compare survival between patients with a DNI order and those without. To perform the Kaplan Meier analysis, we considered as time data, the length of stay after high flow oxygen therapy initiation. Survivors were censored at the time of hospital discharge. In other words, the starting date of this analysis was the initiation date of the HFOT and the last follow-up date, the date of death or discharge. The Logrank non-parametric test for comparison of survival distributions was used to compare survival differences between groups.
A multivariate analysis was useful for identifying variables which can be risk factors for death. The linear regression allowed to study numeric response variables and the logistic regression which allowed to study binary variables.
The interpretation of the OR (Odds Ratio) depends on whether the predictor is categorical or continuous. For continuous variables, if the OR is greater than 1, it indicates that the event (death), is more likely to occur as the predictor increases. Less than 1, it indicates the event (death) is less likely to occur as the predictor increases. For categorical variables, the OR compares the odds of the event (death) occurring at 2 different levels of the predictor (Yes and No). Level "No" is the reference level for the factor. If the OR is greater than 1, it indicates that the event "death" is more likely at level "Yes". OR less than 1 indicates that the event "death" is less likely at level "Yes".
We compared survival according to variable such as patient demographics, comorbidities variable, characteristics at patients' admission, do-not intubate order, COVID-19 treatment with dexamethasone and the other therapies or ventilatory supports used during the patient's hospitalization. The alpha risk was also set to 5 %.

A ROC analysis was performed to determine a threshold of age associated with the highest level of mortality.

STATISTICAL SOFTWARE

The data management and statistical analyses were performed using EasyMedStat (version 3.22; www.easymedstat.com) and XLSTAT for Kaplan Meier analysis.

MISSING VALUES

We need to remove variables with too much missing data to perform a multivariate analysis. So, we need to have full data for our patients

RESULTS

From March 1, 2020, to February 28, 2022, 669 patients were hospitalized at Mont-Godinne due to severe COVID-19 infection, either in the ICU or conventional care units. Of these, 537 patients did not receive HFOT and were excluded (see fig 1).
A total of 132 treated with HFOT were included in the analysis. 63 (47.73%) received a DNI order and 69 patients were classified as eligible for intubation and invasive mechanical ventilation (52.27%).
In the DNI group, 48 patients (76.19%) died, and 15 patients (23.81%) were alive at the time of discharge. In the patients eligible for intubation, 9 patients (13.04%) died, and 60 patients (86.96%) were alive at the time of discharge.

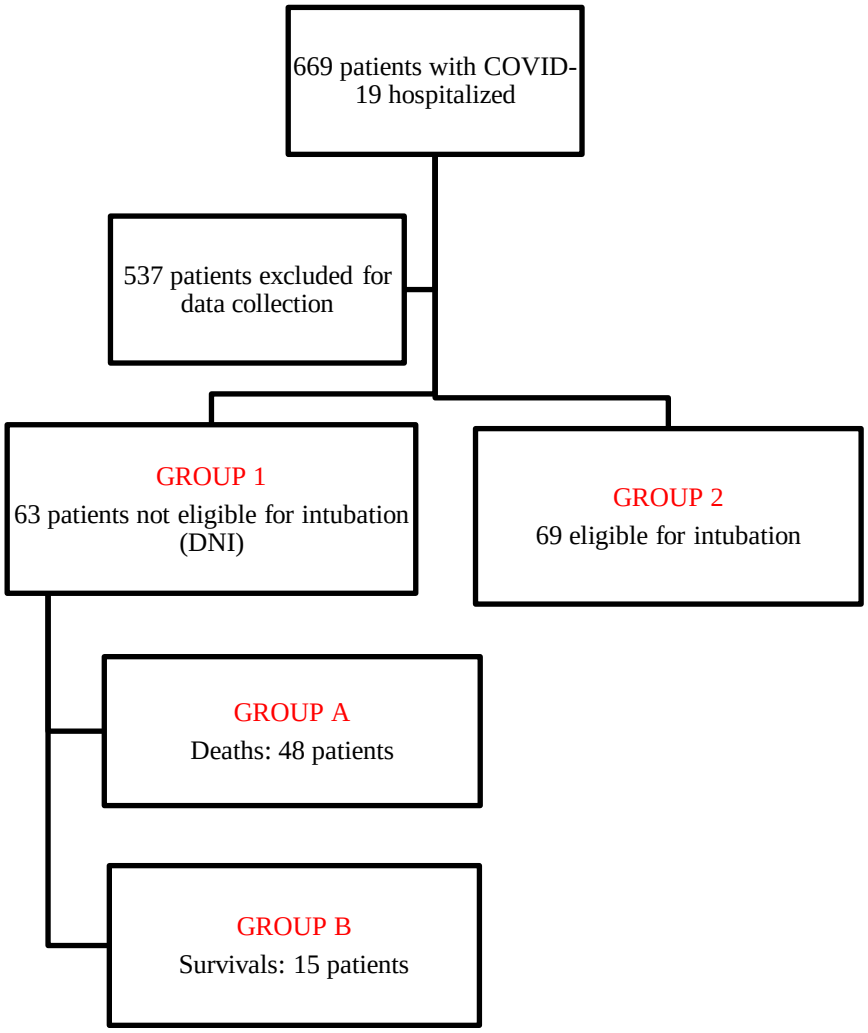


Figure 2: Flow chart

1- Survival in DNI patient

Table 1 summarizes the comparison analysis of group A and B. Groups A, and B are subgroups of group 1, depending on whether the patient has died or not. Group A represents patients who died with DNI status (Yes=1) and group B, patients who did not die with DNI status (No=0).
This comparison concerns patient characteristics and other parameters, notably length of hospitalization and, more pertinently, length of hospitalization after initiation of high-flow oxygen therapy, which are associated with mortality in DNI patients.

The only predictive factor for mortality is age. DNI patients were younger in group B (69 (51-85) vs. 79 (56-93) years; p < 0.001) than in group A. There was no statistical difference between the two groups regarding smoking, BMI, diabetes, hypertension, cardiovascular disease, acute kidney injury, chronic neurological disease, chronic respiratory disease, chronic kidney disease, chronic liver disease, immunosuppression, and D-dimer dosage.
There was also no significant difference between the two groups regarding the mean duration and the rate of the treatments use such as dexamethasone, HFOT and non-invasive ventilation.
The mean length of hospital stays and after HFOT initiation were significantly longer for patients in survivors (respectively, 18 (1-56) vs. 11 (2-51) days; p = 0.008 and 16 (0-45) vs. 7 (0-45) days; p = 0.001).

Characteristics and outcomes	**Group A (n= 48)**	**Group B (n= 15)**	**p-Value**
Population characteristics			
Male, n (%)	28/n (58.3%)	8/n (53.3%)	0.772
Female, n (%)	20/n (41.7%)	7/n (46.7%)	0.772
Age (years); x	79.4 (56 – 93) 48	69 (51 – 85) 15	0.001
BMI (Kg/m^2); x	26 (16.6 – 37.8) 25	29.1 (23.7 – 57.8) 14	0.178
Smoking status, n (%)	1*= 2/x (5.3%) 2*= 19/x (50%) 3*= 17/x (44.7%)	1*= 1/x (6.7%) 2*= 7/x (46.7%) 3*= 7/x (46.7%)	>0.999
Living in a health facility, n (%)	3/x (6.2%)	1/x (6.7%)	>0.999
COVID-19 vaccination status, n (%)	6/x (22.2%)	1/x (20%)	>0.999
Comorbidities			
Chronic airway disease, n (%)	17/x (35.4%)	4/x (26.7%)	0.755
Diabetes, n (%)	14/x (29.2%)	6/x (40%)	0.528
Hypertension, n (%)	35/x (72.9%)	9/x (60%)	0.353
Cardiovascular disease, n (%)	23/x (47.9%)	3/x (20%)	0.074
Immunosuppression, n (%)	5/x (10.4%)	3/x (20%)	0.382
Chronic neurologic disease, n (%)	13/x (27.1%)	3/x (20%)	0.74
Chronic kidney disease, n (%)	10/x (20.8%)	4/x (26.7%)	0.725
Chronic liver disease, n (%)	5/x (10.4%)	3/x (20%)	0.382
Acute Kidney Injury, n (%)	13/x (27.1%)	4/x (26.7%)	>0.999
At admission			
D-dimer dosage (ng/mL) ; x	2579.3 (290 – 20000) 45	1338.6 (500 – 2220) 14	0.254
Respiratory Support			
HFOT duration, (days); x	5.7 (1 - 30) 33	7.33 (0 - 24) 15	0.075
NIV, n (%)	5/x (10.4%)	1/x (6.7%)	>0.999
NIV duration (days); x	1.1 (0 - 26) 47	0.2 (0 - 3) 15	0.781
Medication			
Dexamethasone, n (%)	45/x (93.7%)	14/x (93.3%)	>0.999
Other parameters			
Length of hospital stay (days); x	10.7 (2 - 51) 48	17.7 (1 - 56) 15	0.008

Length of stay after HFOT initiation (days); x	7.1 (0 - 45) 48	15.9 (0 - 45) 15	0.001

Table 1: Patient characteristics and outcomes; 1= Smoker, 2*= Ex-Smoker and 3*= Non-Smoker; x= number of patients with non-missing data.*

As compared to survivors, patients who did not survive were significantly older (median age: 82.5 (IQR 10)) as compared to patients discharged from the hospital (median age: 70 (IQR 15); p = 0.001 for comparison; Figure 3)

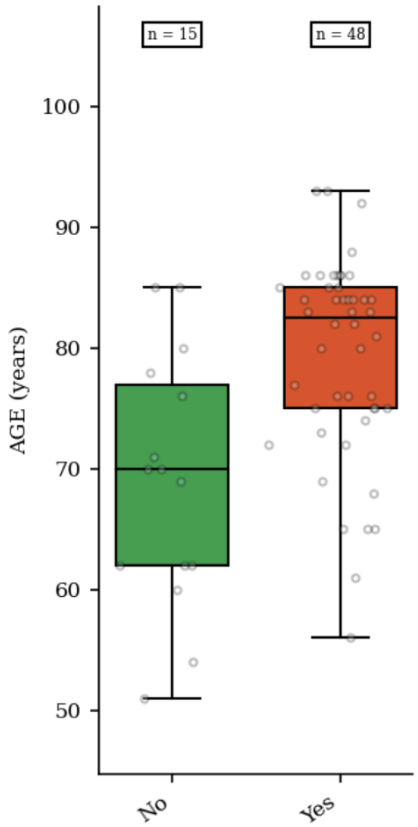
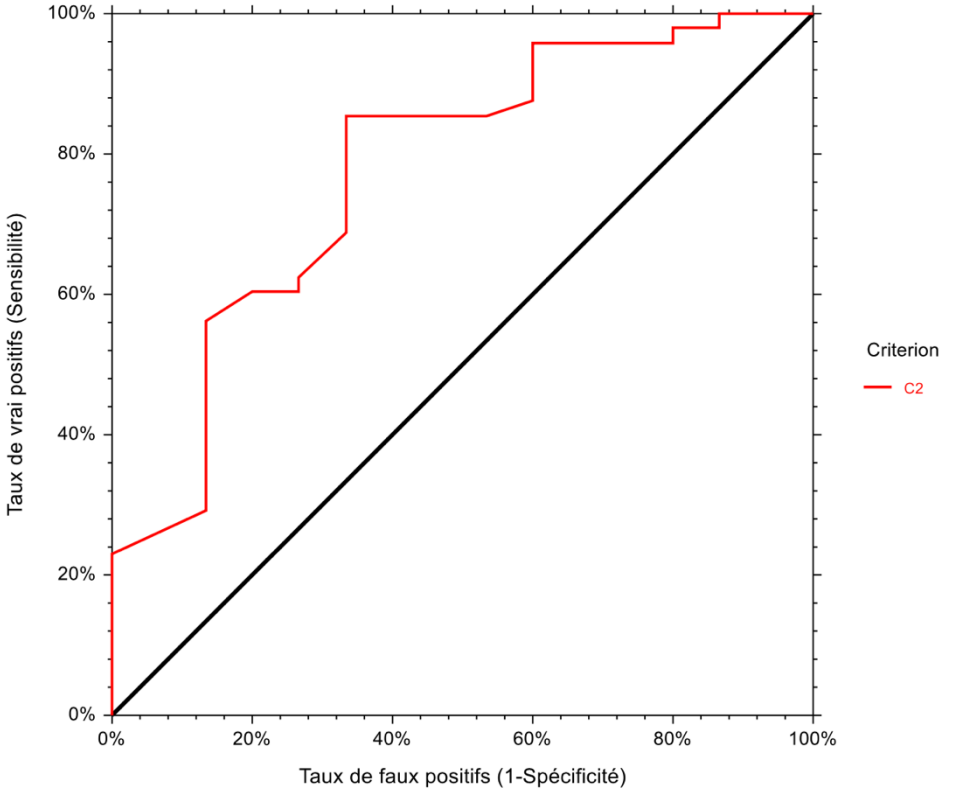


Figure 3: Box plot of the comparison of age according to death status (Yes or No) in patients with a DNI order

A Cox regression analysis showed that only age (p = 0.001; r^2 change: 0.22) and D-dimers levels (p = 0.0015; r^2 change: 0.14) were significantly associated with mortality in DNI patients, with a cumulative r^2 of 0.36, meaning that these 2 parameters only explained 36% of the vital prognosis in this group of patients.

The ROC analysis (Figure 4) confirmed that age (C2) was a significant and discriminant predictor to predict death (AUC of 0.7764 with 95% CI [0.5917 - 0.8836] and a p-value clearly =0.0001). At the threshold of 72, age had a positive predicted value for death of 89% with a negative predicted value of 59. Interestingly, all 11 patients aged over 85 years died.



Criterion	Count	AUC	Standard Error	Z-Value to Test AUC > 0,5	Upper 1-Sided P-Value	95% Confidence Limits Lower	Upper
C2	63	0,7764	0,0721	3,832	0,0001	0,5917	0,8836

Figure 4: ROC curve for age as predictor of mortality in DNI patients

2- Comparison of survival according to DNI status

Table 2 describes the patient's characteristics and other parameters associated to the vital prognosis in patients having received HFOT, divided in group 1 (63 patients with a DNI order) and group 2 (69 patients eligible for intubation and invasive mechanical ventilation).

Characteristics and outcomes	**Group 1 (n = 63)**	**Group 2 (n = 69)**	**p-value**
Population characteristics			
Male, n (%)	36/x (57.1%)	47/x (68.1%)	0.261
Female, n (%)	27/x (42.9%)	22/x (31.9%)	0,261
Age (years); x	76.9 (51 – 93) 63	62.6 (24 - 83) 69	<0.001
BMI (Kg/m^2); x	27.1 (16.6 – 57.8) 39	29.8 (15.1 -55.8) 55	0.049
Smoking status, n (%)	1*= 3/x (5.7%) 2*= 26/x (49.1%)	1*= 3/x (5.2%) 2*= 22/x (45.8%)	0.465
Living in a health facility, n (%)	4/x (6.3%)	1/n (1.4%)	0.192
COVID-19 vaccination status, n (%)	7/x (21.9%)	16/x (28.1%)	0.618
Comorbidities			
Chronic airway disease, n (%)	21/x (33.3%)	18/x (26.5%)	0.505

Diabetes, n (%)	20/x (31.7%)	22/x (31.9%)	>0.999
Hypertension, n (%)	44/x (69.8%)	35/x (50.7%)	0.039
Cardiovascular disease, n (%)	26/x (41.3%)	22/x (31.9%)	0.348
Immunosuppression, n (%)	8/x (12.7%)	8/x (11.6%)	>0.999
Chronic neurologic disease, n (%)	16/x (25.4%)	14/x (20.3%)	0.623
Chronic kidney disease, n (%)	14/x (22.2%)	9/x (13%)	0.246
Chronic liver disease, n (%)	8/x (12.7%)	4/x (5.8%)	0.228
Acute Kidney Injury, n (%)	17/x (27%)	16/x (23.2%)	0.763
At admission			
D-dimer dosage, (ng/mL) ; x	2284.9 (290 – 20000) 59	3152.6 (290 – 20000) 62	0.878
Respiratory Support			
HFOT duration (days); x	6.2 (0 - 30) 48	6.7 (0 – 90) 68	0.933
NIV, n (%)	6/x (9.5%)	21/x (30.4%)	0.006
NIV duration (days); x	0.9 (0 – 26) 62	3 (0 – 31) 68	0.001
Medication			
Dexamethasone, n (%)	59/x (93.6%)	64/x (92.7%)	>0.999
Other parameters			
Death, n (%)	48/x (76.2%)	9/x (13%)	<0.001
Length of hospital stay (days); x	12.4 (1 – 56) 63	28 (2 – 153) 69	<0.001
Length of stay after HFOT initiation (days); x	9.2 (0 – 45) 63	25.7 (1 – 152) 69	<0.001
Length of stay from HFOT initiation to death (days); x	7.1 (0 – 45) 48	47.9 (1 – 152) 9	0.004
Length of stay from HFOT initiation to discharge (days); x	15.9 (0 – 45) 15	22.9 (2 – 129) 60	0.786

Table 2: Patient characteristics and outcomes; 1= Smoker, 2*= Ex-Smoker; x= number of patients with non-missing data*

The death rate was strikingly higher in group 1 as compared to group 2 (76.2% vs 13%; p<0.001). Comparing survival between group 1 and 2 according to Kaplan-Meier curves (Figure 5) confirmed a significant difference in survival distributions (%; p<0.0001).

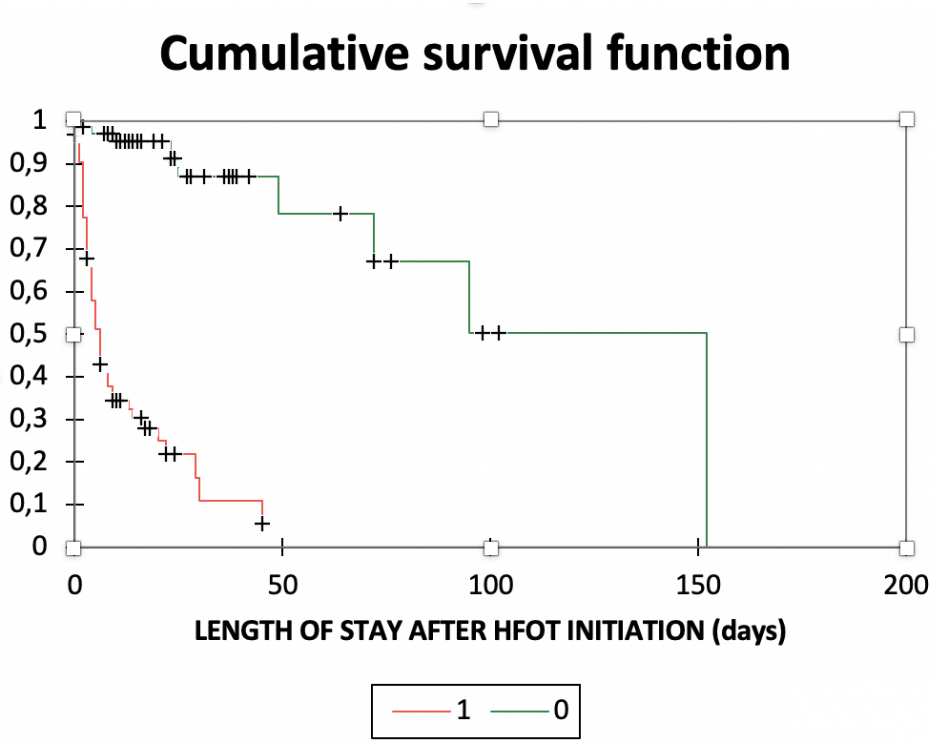


Figure 5: Kaplan-Meier curves comparing survival according to DNI status (Yes=1; No=0)

There was a significant difference between the two groups in terms of age (77 years (group 1) vs. 63 years (group 2); p<0.001), BMI (27.1 (group 1) vs. 29.8 (group 2); p=0.049), prevalence of hypertension (69.8% (group 1) vs. 50.7% (group 2); p=0.039). On the other hand, there was no statistical difference between the two groups in terms of smoking status, diabetes, cardiovascular disease, acute kidney injury, chronic neurologic disease, chronic airway disease, chronic kidney disease, chronic liver disease, immunosuppression, and D-dimer dosage.
There was also a significant difference between the two groups regarding the proportion of patients using non-invasive ventilation (9.5% (group 1) vs. 30.4% (group 2); p=0.006), and it mean duration of use (1 day (group 1) vs. 3 days (group 2); p=0.001). However, there was no significant difference between the two groups regarding the rate of patients using dexamethasone and the mean duration of HFOT use.

We used a full multivariate analysis feature to integrate factor variables in this survival analysis study.
Before performing multivariable analysis, we removed “BMI” and “COVID-19 vaccinal status” variables because there are many patients which missing data for these variables. We also removed variables that have not enough patients: “smoking status” (the smoker group “1” have too small effective (n=6) compared to the other groups), “living in a health facility” (only 5 patients for the group Yes=1) and “dexamethasone treatment” (only 9 patients for the group No=0). We obtain a high methodology quality level of the analysis (88%).

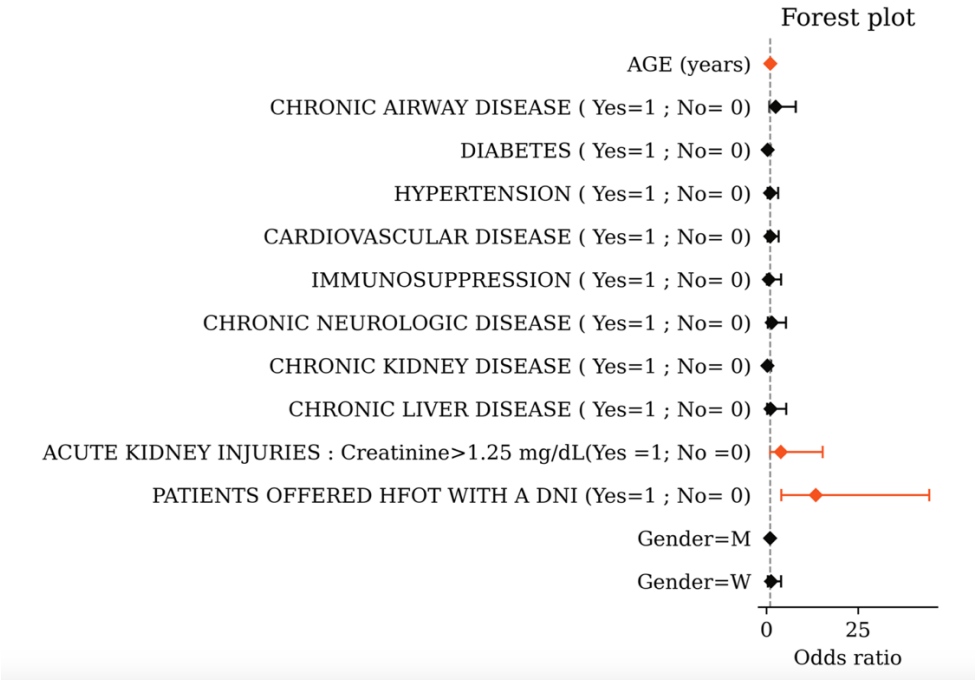


Figure 6: Forest plot of multivariate analysis. M: Men; W: Women. Red caterpillar plot represents OR>1 for a significant factor. Black capterpillar plot represents OR for non-significant factors

	Odds Ratio	**p-value**
AGE (years) Risk for each 1-unit increase	1.09 [1.03; 1.17]	0.0044 **
CHRONIC AIRWAY DISEASE (Yes=1; No= 0)	2.55 [0.809;8.03]	0.11
DIABETES (Yes=1; No= 0)	0.368 [0.117; 1.16]	0.0874
HYPERTENSION (Yes=1; No= 0)	1.01 [0.317; 3.22]	0.985
CARDIOVASCULAR DISEASE (Yes=1; No= 0)	1.05 [0.331; 3.35]	0.931
IMMUNOSUPPRESSION (Yes=1; No= 0)	0.713 [0.126; 4.04]	0.703
CHRONIC NEUROLOGIC DISEASE (Yes=1; No= 0)	1.49 [0.418; 5.35]	0.537
CHRONIC KIDNEY DISEASE (Yes=1; No= 0)	0.311 [0.0747;1.29]	0.108
CHRONIC LIVER DISEASE (Yes=1; No= 0)	1.12 [0.23; 5.44]	0.889
ACUTE KIDNEY INJURIES: Creatinine>1.25 mg/dL (Yes =1; No =0)	3.95 [1.01; 15.37]	0.0476 *
PATIENTS OFFERED HFOT WITH A DNI (Yes=1; No= 0)	13.48 [4.09; 44.43]	<0.0001 ****
Gender Reference: M F	1.31 [0.423; 4.02]	0.643
* p<0.05** p<0.01*** p<0.001**** p<0.0001		

Table 3: Results of the multivariate analysis

As illustrated in table 3, DNI status (OR=13.48, [4.09; 44.43], p< 0.0001), age (OR=1.09, [1.03; 1.17], p=0.0044), and the presence of acute kidney injury (OR=3.95, [1.01; 15.37], p= 0.0476) were all significantly associated with a higher rate of mortality.

Overall, the mean length of hospitalization was lower in group 1 (12 days) than in group 2 (28 days); p<0.001. Relevantly, the mean duration of hospitalization after initiation of high-flow oxygen therapy was also lower in group 1 (9 days) than in group 2 (26 days); p<0.001. In patients who did not survive, the mean length of hospital stay after HFOT initiation was also lower in group 1 (7 days) than in group 2 (48 days); p=0.004. However, there is no significant difference between the two groups regarding the mean length of hospital stay from HFOT initiation to discharge for those who survived.

Finally, we compared patients treated with HFOT and a DNI order with patients without DNI for whom HFOT was the highest level of respiratory support.

Characteristics and outcomes	**Group 1 (n= 63)**	**Group 2bis (n= 49)**	**p-value**
Population characteristics			
Male, n (%)	36/x (57.1%)	37/x (75.5%)	0.068
Female, n (%)	27/x (42.9%)	12/x (24.5%)	0.068
Age (years); x	76.9 (51 – 93) 63	61.6 (30 – 83) 49	<0.001
BMI (Kg/m^2); x	27.1 (16.6 – 57.78) 39	30.1 (21.2 – 55.8) 42	0.031
Smoking status, n (%)	1*= 3/x (5.7%) 2*= 26/x (49.1%)	1*= 2/x (4.6%) 2*=14/x (32.6%)	0.218
Living in a health facility, n (%)	4/x (6.3%)	1/x (2%)	0.384
COVID-19 vaccination status, n (%)	7/x (21.9%)	7/x (18.9%)	0.774
Comorbidities			
Chronic airway disease, n (%)	21/x (33.3%)	10/x (20.8%)	0.215
Diabetes, n (%)	20/x (31.7%)	13/x (26.5%)	0.695
Hypertension, n (%)	44/x (69.8%)	26/x (53.1%)	0.105
Cardiovascular disease, n (%)	26/x (41.3%)	18/x (36.7%)	0.77
Immunosuppression, n (%)	8/x (12.7%)	3/x (6.1%)	0.342
Chronic neurologic disease, n (%)	16/x (25.4%)	8/x (16.3%)	0.353
Chronic kidney disease, n (%)	14/x (22.2%)	6/x (12.2%)	0.217
Chronic liver disease, n (%)	8/x (12.7%)	3/x (6.1%)	0.342
Acute Kidney Injury, n (%)	17/x (27%)	6/x (12.2%)	0.093
At admission			
D-dimer dosage (ng/mL) ; x	2284.9 (290 – 20000) 59	3230.7 (290 – 20000) 45	0.604
Respiratory Support			
HFOT duration (days); x	6.2 (0 - 30) 48	5.3 (1 – 31) 49	0.971
NIV, n (%)	6/x (9.5%)	11/x (22.4%)	0.068
NIV duration (days); x	0.9 (0 – 26) 62	2.7 (0 – 31) 49	0.016
Medication			
Dexamethasone, n (%)	59/x (93.6%)	45/x (91.8%)	0.728
Other parameters			

Death, n (%)	48/x (76.2%)	0/x (0%)	<0.001
Length of hospital stay (days); x	12.4 (1 – 56) 63	17.1 (2 – 65) 49	<0.001
Length of stay after HFOT initiation (days); x	9.2 (0 – 45) 63	15.4 (2 – 64) 49	<0.001
Length of stay from HFOT initiation to death (days); x	7.1 (0 – 45) 48	–	–
Length of stay from HFOT initiation to discharge (days); x	15.9 (0 – 45) 15	14.8 (2 – 64) 49	0.541

Table 4: Patient characteristics and outcomes; 1= Smoker, 2*= Ex-Smoker; x= number of patients with non-missing data*

Table 4 shows the patient characteristics, comorbidities, respiratory supports, medications, and other parameters for 2 groups that have the same intensity of treatment: patients not eligible for intubation or DNI patients (group 1) and ICU patients without intubation and ECMO (group 2 bis). In group 2 bis, all patients (49) were treated with HFOT and 11 (22.4%) with non-invasive ventilation.
In group 2 bis, no patients died, compared with 76.2% in group 1; $p<0.001$. Overall, the mean length of hospital stay was lower in group 1 (12 days) than in group 2 bis (17 days); $p<0.001$.
.
There was a significant difference between the two groups in terms of age (77 years (group 1) vs. 62 years (group 2 bis); $p<0.001$) and BMI (27.1 (group 1) vs. 30.1 (group 2 bis); $p=0.031$). In contrast, there was no statistical difference between the two groups regarding smoking, diabetes, hypertension, cardiovascular disease, acute kidney injury, chronic neurological disease, chronic respiratory disease, chronic kidney disease, chronic liver disease, immunosuppression, and D-dimer dosage.

The mean duration of hospitalization after initiation of high-flow oxygen therapy was also lower in group 1 (9 days) than in group 2 bis (15 days); $p<0.001$. This may suggest that death occurred quite rapidly after HFOT initiation in patients with a DNI order. However, there was no significant difference between the two groups regarding the mean length of hospital stay from HFOT initiation to the discharge for those who survived.

DISCUSSION

This study retrospectively investigates the vital prognosis of patients with severe COVID-19 with a DNI order but offered HFOT. There is little data in the literature that talks about this.
Generally, a poor prognosis is predicted for patients using HFOT in general wards due to their severe respiratory condition. Survival will be very poor, and mortality will be high [88]. In a Japanese study evaluating the efficacy and tolerability of HFOT in 84 patients with interstitial lung disease with DNI order, the 30-day survival rate was 31.5% and in-hospital mortality rate was 79.6% [45]. In the context of COVID-19 pandemic, Delbove et al [19]. reported a 54.5% mortality rate in a small cohort study (n=11) of COVID-19 patients thus considering HFOT as a rescue therapy in DNI order. In a retrospective study including 178 COVID-19 patients, mortality was 24% for patients eligible for intubation and 81% for DNI patients, rising to 98% for DNI patients requiring very high oxygen flow (≥ 30 l/min.) [86]. In our study, in-hospital mortality rate in patients with a DNI order was significantly higher (76.2%) than those without DNI order (13%) and those eligible for intubation but without ECMO and invasive ventilation (0%). Our results are in line with those reported previously [19, 28, 86].
The results of this study therefore shed light on the question of uncertainty regarding the benefits of HFOT in patients with a DNI order. Survival rate was low in these patients, for whom intubation was considered futile. More than 3/4 (76.2%) of DNI patients died when they needed HFOT.
When comparing DNI patients according to their survival status (table 1), only age was significantly higher in DNI patients who died. There was a significant difference between ages in all comparison groups ($p \leq 0.001$). The results of cox regression analysis indicate that only age and D-dimer levels (to a lesser extent than age) were associated with death in DNI patients. On average, D-dimer levels were higher in survivors than in deceased DNI patients. This may be explained by the fact that coagulation abnormalities are increasingly recognized in hospitalized patients with COVID-19. Patients with high D-dimer levels on admission have an increased risk of pulmonary embolism, vasculitis, and alveolar damage, which can lead to death in severe cases [50]. Our results are in line with the results of previous studies [41, 42]. The multivariate analysis showed that age is strongly associated to an increased risk of mortality in COVID-19 patients with a DNI order. Undoubtedly, age is the important factor to consider when assessing the prognosis of patients who received HFOT with a DNI order. This result agreed with those reported in previous studies [4, 43, 86]. On average, deceased DNI patients (80 years) are older than surviving DNI patients (69 years). This could be explained by the impact of more comorbidities and frailty, which is often associated with advanced age (>70 years) [25, 71]. Advanced age was a factor in the decision to opt for HFOT in patients with DNI order. According to the results of the ROC analysis, we were able to identify the age group most at risk of mortality in DNI patients. Interestingly, all 11 DNI patients older than 85 years died. At this age (>85 years), it's not worth instituting high-flow oxygen therapy in patients with COVID-19-related ARDS. During the pandemic, in a context of limited equipment availability due to high patient numbers in hospitals, HFOT might apparently be futile in DNI patients over 85 years. These results were in line with the results of previous studies [4, 14, 43].
We observed a significant difference for the age, BMI, and hypertension when comparing groups according to patients' DNI status (table 2). Comparative analysis of patients who received the same intensity of treatment (table 4) also showed a significant difference only for the age and BMI. Multivariate analysis (table 3) performed on the whole group of patients treated with HFOT whatever the DNI status showed that the increased risk of mortality was significantly associated with age, acute kidney injury (AKI) for a creatinine level > 1.25 mg/dL, and patients receiving HFOT with a DNI order. Patients receiving HFOT with a DNI order was strongly linked to the mortality followed by age and AKI. Patients with DNI order (80 years) were on average older than patients without DNI order (65 years) and patients eligible for intubation but with the same intensity of treatment (i.e., without ECMO and intubation). This may also be explained by the impact of more comorbidities and frailty, which is often associated with advanced age (>70 years). Advanced age was a significant factor in the decision to opt for a DNI order. In this situation, elderly patients would

not benefit much from intubation and therefore invasive ventilation [52]. Our results are in line with several previous studies [7, 19, 86]. In a meta-analysis of 57420 adult COVID-19 patients receiving invasive ventilation, the case-fatality rate in patients over 60 years of age was over 70%, and increased exponentially with age, reaching 84.4% in those over 80 [61]. In a prospective observational cohort study including 554 patients aged 65 and over undergoing mechanical ventilation for the first time over an 18-month period in Israel, in-hospital mortality was 64.1% (61.1% in <85 years and 73.8% in ≥ 85 years, p=0.008), with 48% dying within the first week of hospitalization. All these results suggest that mechanical ventilation at advanced age is associated with poor survival and that advanced age remains an independent predictor of poor prognosis [53].

There was a significant difference in BMI values when we compare the two groups according to the DNI status (table 2) and according to patients with the same intensity of treatment (table 4) with p-values close to the range of statistical significance (0.049 and 0.031 respectively). The mean for both groups with the same intensity of treatment was 27.1 for patients with a DNI order and 30.1 for patients eligible for intubation but without ECMO or intubation. Similarly, the BMI value in the group without DNI order was as high as in the group with DNI order. Frailty played a key role in the decision to classify the patient as a DNI. In our study, we did not use an objective scale to assess patients' degree of frailty. We were unable to quantify the degree of frailty using existing tools in the literature, but intuitively, in collegial discussions to determine whether a patient has a DNI status or not, we can observe this aspect of frailty by seeing the patient or asking about his or her lifestyle, for example. Furthermore, doctors intuitively know that frailty is associated with a poor prognosis in intensive care beyond COVID-19 pneumonia. In fact, frailty is often associated with low BMI, sarcopenia (muscle loss) or malnutrition [69, 87]. The results of our study are in line with those reported in the literature [7, 19, 54, 86, 73]. Fat accumulation in the body and alterations in immunity associated with obesity would therefore be linked to a severe course of COVID-19. Mechanically, obesity impairs pulmonary function characterized by a decline in expiratory reserve volume, functional capacity, and respiratory system compliance. So, a high BMI is related to a higher risk of developing respiratory failure and thus the need for mechanical ventilation [62, 73].

If we consider the rate of patients with a history or prevalence of hypertension, we also observe a significant difference (p=0.039) between the two groups according to DNI status (table 2). This rate was higher in patients with a DNI order (69.8%) than in patients without a DNI order (50.7%). Given that advanced age is a risk factor for hypertension, increasing age would interact with the proportion of patients with a history or prevalence of hypertension. The association of advanced age with DNI patients would probably explain the high proportion of DNI patients with a history of hypertension [20, 43].

In our study, AKI, i.e., a creatinine value>1.25 mg/dL on admission, were associated with a higher risk of mortality for all patients on HFOT with or without DNI. This could be explained by the fact that hypertension and elevated D-dimer values are often associated with AKI. Hypercoagulability and microangiopathies associated with elevated D-dimers levels would promote multi-organ damage, particularly acute cardiac and pulmonary injury, and subsequent AKI due to hypoxia and hypotension. Similarly, comorbidity like hypertension is a risk factor for AKI [30]. Given that elevated D-dimer values are significantly associated with mortality in DNI patients, the association of AKI with mortality in DNI patients than in patients without DNI order would be true but to a lesser extent than age. Our results are consistent with those reported in previous studies [30, 41].

The mean duration of hospitalization and, more pertinently, after initiation of HFOT is significantly higher in surviving DNI patients than in those who have died. Death probably occurs rapidly after initiation of HFOT in DNI patients.

Comparison of the two groups according to the mean length of hospital stay and length of hospital stay after the start of HFOT revealed a significant difference (p<0.001). Indeed, this duration of hospitalization and well relevant after initiation of HFOT is low in DNI patients compared to those without DNI and even if the latter received the same intensity of treatment (i.e., DNI patients without ECMO or intubation). This may be due in part to the fact that the majority of DNI patients with advanced age, comorbidities and frailty received palliative care. In addition, the fact that these

patients are not eligible for mechanical ventilation, and that they present severe cases of the disease as well as high mortality, would on average shorten their survival. These results are in line with those of previous studies [19, 28].

Both the mortality rate and the Kaplan-Meier curves analysis (Figure 5) showed that survival of patients without DNI is significantly better than that of patients with DNI. This is obviously not surprising since their estimated chance of survival was a critical element in the decision for choosing a DNI status. These patients also have more comorbidities, more frail and more likely to require comfort care based on the opinion of the patient, family, or physician.

Comparing the groups while considering other comorbidities and parameters such as smoking status, living in a healthcare facility, vaccination status, diabetes, immunosuppression, D-dimer dosage, acute kidney injury, use of dexamethasone as corticosteroid therapy, chronic airway disease, cardiovascular disease, chronic neurological disease, chronic kidney disease, and chronic liver disease, we did not obtain a significant difference ($p>0.05$). This could be explained by the high number of patients with missing data who could not be included in the analysis in some cases, as well as by our small cohort size (n=132 patients).

Apart from HFOT, other non-invasive respiratory supports techniques are available for patients with DNI orders. However, these supports can also be potentially dangerous for patients by generating high tidal volumes and excessive transpulmonary pressure variations that can induce volutrauma, particularly in the case of CPAP which is most often used as a rescue option. This will help to delay intubation [7]. The mean rate and duration of NIV use were significantly lower in DNI patients compared to patients eligible for intubation. We also have the same results when comparing them to patients that have the same intensity of treatment but with no statistical significance for the mean NIV use rate comparison. These results could be explained by the fact that at the Mont-Godinne hospital, HFOT was preferred to CPAP or others non-invasive ventilation supports (e.g., BiPAP) for patients with a DNI order. In most cases, invasive ventilation is rapidly used after HFOT failure in patients eligible for intubation.

Our study has several limitations. Firstly, the monocentric retrospective design and the small sample size limit the performance of multivariate analysis. A multi-center randomized controlled trial involving a large cohort of patients would be more efficient, reliable, and consistent in terms of multivariate analysis results, given that at the time of the pandemic, there were not many articles in the literature, nor a high level of evidence-based knowledge regarding the therapies applied for a DNI order in COVID-19 patients.

Secondly, it can never be said that the choice for a DNI status was made on the same criteria at Mont-Godinne for all patients. Indeed, as the overflow of the ICU varied during the pandemic, this factor might have influenced the choice for DNI status at some time points during the study. Moreover, between institutions, decisions have a certain subjective character. As a result, there were no clearly defined criteria, making it difficult to generalize our findings.

This could also raise ethical questions like how ethical is it to consider unilateral DNI orders for COVID-19 patients in the face of limited resources? To answer these questions, a comprehensive literature review was conducted using PubMed, Medline, Science Direct and online information sites to gather evidence and summarize local, regional, and international recommendations. Curtis et al [46] note that the term "unilateral DNR" was coined to reduce the risk of medically futile cardiopulmonary resuscitation (CPR) for patients, families, and healthcare workers, especially when CPR is unlikely to restore an acceptable quality of life. It also saves intensive care unit resources to accommodate patients with a better chance of recovery. If such protocols are implemented, all patients and family members should be informed of and adhere to the wishes of the care unit [46].

In the context of the COVID-19 pandemic, most patients who are successfully resuscitated will require a respiratory support, contributing to the shortage of resources, and possibly depriving other patients with a higher probability of survival from using these resources. Considering these debatable issues, DNR appears to be a good option in appropriate situations.

Added to this are other questions such as what are the potential consequences for other patients with traffic accidents, acute cardiac conditions, or respiratory conditions requiring elective surgery and

who may be competing with COVID-19 patients for limited resources? These patients might end up infected once admitted to the hospital. For example, to resolve this problem at the beginning of the pandemic in Italy, elective surgeries were canceled, semi-elective procedures were postponed, and operating rooms were turned into makeshift intensive care units [47].

In conclusion, our results suggested a very higher in-hospital mortality rate for COVID-19 patients with a DNI order requiring HFOT as the highest therapeutic scale. An analysis comparing groups of DNI patients based on death status revealed that age was the most important predictive factor predicting mortality. Above the age of 85, HFOT appears highly likely to be futile in patients with a DNI status. However, our multivariate analysis results are not exclusive, given the presence of numerous missing data for certain factors, which is not essential for this analysis. Further studies with larger cohorts and less missing data would therefore be required for a more complete multivariate analysis.

PERSPECTIVES

Apart from its main objective of investigating the vital prognosis of COVID-19 patients on HFOT with a DNI order, this manuscript shows that advanced age should be considered as a discriminating factor in predicting death in DNI patients. This could be useful when triaging COVID-19 patients in intensive care due to problems of overcrowding and ICU bed availability. It will also enable us to manage other pneumonia and lung diseases requiring HFOT at the highest therapeutic level.

A study including a large cohort of patients could therefore reveal the association of other prognostic factors leading to a DNI decision. It would be very instructive to extend our results to another randomized, controlled multicentric study, also based on other treatments and respiratory supports, to investigate other prognostic factors that could not be studied in this single-center study, such as admission parameters like Quick SOFA total score, respiratory rate, Glasgow score, fibrinogen, and C-reactive protein.

It would also be conceivable to carry out studies of combined treatments and non-invasive respiratory supports to optimally study the survival of DNI patients hospitalized with COVID-19.

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