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IMPACT OF SARS-CoV-2 RESPIRATORY INFECTION ON CLINICAL OUTCOMES AND NEED FOR NON-INVASIVE VENTILATORY SUPPORT IN ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A SINGLE-CENTER, PROSPECTIVE, OBSERVATIONAL STUDY

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ABSTRACT

Viral and bacterial infections are the main cause of COPD exacerbations, accounting for 25% and 26% of cases respectively. To date no conclusive data are available on the risk of COPD exacerbations triggered by SARS-CoV-2. The present study was primarily aimed to identify the risk of acute respiratory failure (ARF) requiring non-invasive respiratory support up to Continuous Positive Airway Pressure (C-PAP) and Non-Invasive Ventilation (NIV) in patients affected by SARS-CoV-2 triggered COPD exacerbation compared to patients with COPD exacerbations without SARS-CoV-2 infection. Major secondary endpoints included the overall risk of ARF and its stratification according to severity and consequent respiratory support needed. Mortality in the SARS-CoV-2 cohort was also compared to the control group.

238 COPD patients admitted to hospital due to an acute exacerbation of COPD were consecutively enrolled: 120 patients (50.4%) tested positive for SARS-CoV-2 infection at nasopharyngeal swab, while 118 (49.6%) were negative. No significant difference could be demonstrated in the risk of ARF between SARS-CoV-2 and control groups (Relative Risk (RR) 0.89 ($p = 0.303$), 95% Confidence Interval (CI): 0.73 – 1.06). However, the risk of ARF with the need of ventilatory support up to C-PAP was significantly higher in the SARS-CoV-2 group (RR 4.42 ($p = 0.009$), 95% CI 1.37 – 14.35). On the contrary, the risk of ARF needing NIV was 39% lower in the SARS-CoV-2 group (RR 0.61 ($p = 0.003$), 95% CI 0.44 – 0.84). This result combined with blood gas analysis values reflected a predominant hypoxemic ARF among SARS-CoV-2, differently from hypercapnic ARF in the control group. A significantly higher mortality rate was detected among SARS-CoV-2 patients at Kaplan-Meier survival analysis (1 year mortality: 33.33% in SARS-CoV-2 group vs 3.06% in controls, $p < 0.0001$). Hospitalization was longer in SARS-CoV-2 group than controls (12 days, IQR 7.5–24.5 vs 9 days, IQR 7–14.25, $p < 0.01$). In conclusion, our study demonstrated that SARS-CoV-2 infection can be considered a potent trigger of COPD exacerbation, able to induce severe hypoxic ARF, which significantly increased the risk of needing positive pressure respiratory support. SARS-CoV-2

profoundly impacted on the mortality, meanwhile prolonging the length of hospital stay. Screening for the presence of viral triggers, particularly of SARS-CoV-2, in case of acute exacerbation of COPD is key, to influence clinical outcomes treatment approach and long-term survival.

INTRODUCTION

1. Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is a pathological condition of the respiratory system characterized by chronic airflow obstruction, associated with changes in the lung parenchyma (pulmonary emphysema), bronchi (chronic bronchitis) and bronchioles (small airways disease) (1). In Italy, COPD affects 5.6% of adults (about 3.5 million people) and is responsible for 55% of deaths for respiratory diseases. COPD exacerbations are associated with a worsening of the respiratory function and a decline in the quality of life. Moreover, an increase in the risk of mortality in the 3 years following hospital admission for COPD exacerbation has been described (2). Viral (25% of cases) and bacterial (26% of cases) infections are the main cause of COPD exacerbations, while in 22% of cases no germs are found in culture (3). Several series have shown that, among the viral etiological agents, Rhinovirus (HRV) represents the infectious agent most involved in COPD exacerbations (35-60% of cases), followed by Syncytial Respiratory Virus (10-30%), Influenza Virus (5-30%) and to a much lesser extent Parainfluenza Virus, Adenovirus and Coronavirus (4–6). More recently, the SARS-CoV-2 pandemic might have influenced the prevalence of virus induced COPD exacerbations, although no conclusive data are so far available on the risk of COPD exacerbations triggered by SARS-CoV-2 nor on the possible role SARS-CoV-2 can have on the ecology of respiratory viruses.

2. COPD exacerbations

According to the Anthonisen's definition, a COPD exacerbation is characterized by the worsening of respiratory symptoms, in particular of dyspnea, with cough and sputum production, associated with an increase in purulence of the same (1). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) document defines COPD exacerbation as an acute worsening of respiratory symptoms (dyspnea and/or cough and sputum), that worsened in less than 14 days, which may be accompanied

by tachypnea and/or tachycardia, and which requires increased therapy. COPD exacerbations are stratified into mild, moderate, and severe according to specific characteristics (5). More in details, mild exacerbations are characterized by a slight increase in symptoms (i.e. cough, sputum production, or dyspnea) that patients can manage at home by increasing their dosage of bronchodilators, without requiring systemic steroids or antibiotics. In moderate exacerbations typically symptoms cannot be managed with bronchodilators only, but systemic corticosteroids and/or antibiotics are needed, sometimes requiring the patient hospitalization. Severe exacerbations are life-threatening or significantly debilitating, often associated to acute respiratory failure, thus emergency room admission and hospitalization are required for supplemental oxygen with non-invasive ventilation or intensive care treatment (5). COPD exacerbations have a significant impact on patients, health and social system, with high costs, not only during the acute phase but also in the subsequent period (4). Also in Italy, COPD causes a significant economic impact and a considerable commitment on the National Health System, both linked to chronic home inhalation therapies, and to the high number of hospital admissions, about 110,000 per year, with a 30-day mortality rate of 9.8% and a 30-day hospital readmission rate of nearly 14% (7,8). Moreover, the greater is the number of exacerbations, the lower the survival (7). It has been widely demonstrated that the over expression of inflammatory cytokines (i.e. IL-6, TNF-α) during an exacerbation is able to induce cardiovascular accidents (the leading cause of death in the course of acute COPD exacerbations) (9). COPD patients tend to exacerbate more in the cold months, with an average monthly exacerbation rate 2.16 times higher in winter than in summer (10).

2.1. Pathogenesis of airway inflammation in COPD

COPD involves an exaggerated airway epithelial inflammatory response to inhaled noxious agents, most commonly cigarette smoke (11). In non-smokers, biomass fuel combustion, occupational dust, and particulate air pollution are major risk factors (11–13). Evidence implicates protease–antiprotease imbalance and oxidative stress as central pro-inflammatory mechanisms in disease pathogenesis

(14,15). Only a subset of smokers develops COPD, indicating the contribution of host factors (16,17). Neutrophils accumulate in the airway mucosa, and sustained innate immune activation drives recurrent neutrophilic inflammation (18,19). Dysregulated adaptive immunity underlies the chronic inflammation and irreversible airway remodeling characteristic of COPD (11,20,21). Increased CD8+ T lymphocytes, often organized into lymphoid follicles, are strongly correlated with airflow limitation (11). While these cells mediate antiviral defense, they can also promote tissue damage through cytotoxicity, pro-inflammatory signaling, and recruitment of other immune cells (22–24).

The persistence of abundant CD8+ T cells and B-cell follicles within COPD airways suggests heightened immune surveillance (11). This has led to the hypothesis that, in addition to noxious inhalants, chronic viral infection may contribute to disease initiation or progression.

2.2. Therapy of COPD exacerbations

The therapeutic management of COPD exacerbations is intended to minimize the negative impact of the exacerbation on the global health of the patient, and to reduce the risk of a subsequent event. COPD exacerbations are mainly treated in an outpatient setting; however, up to 20% of exacerbations require the patient to be hospitalized (25). Drugs which are commonly used to treat COPD exacerbations are glucocorticoids, bronchodilators, and antibiotics (26).

COPD patients should be hospitalized in case of severe, potentially life-threatening exacerbation. Particularly, intensive care unit might be needed if an acute respiratory failure requires high flow oxygen supplementation or the adoption of Non Invasive Ventilation (NIV) to correct impaired gas exchange and/or reduce the work of breathing. In less severe cases, when low flow oxygen levels are sufficient to properly correct the respiratory failure, COPD patients can be adequately treated in low intensity hospital wards. The severity of COPD exacerbations can be assessed as per the Rome proposal criteria (5).

2.2.1 The pharmacological therapy

The pharmacological treatment of COPD is based on the use of the following drugs:

- Bronchodilators: the initial treatment of acute exacerbations includes the administration of inhaled short acting beta$_2$-agonists, together with short acting anticholinergics, although there is lack of robust evidence from Randomized Clinical Trials (RCTs). No strong evidence supports the use of metered dose inhalers or nebulizers, although these ones might be more easily used in sick patients. No studies have evaluated the use of long acting beta$_2$-agonists or anticholinergics in combination with ICS. Nonetheless, according to international recommendations this therapy should be continued or should be rapidly introduced if not chronically adopted by the patient. Whenever possible, air-driven nebulizers should be preferred to oxygen-driven nebulizers during a COPD exacerbation due to the increase in the risk of hypercapnia when aerosols are generated by oxygen flow (27,28).
- Glucocorticoids: a dose of 40 mg prednisone equivalent per day for 5 days is recommended in COPD exacerbations (29). The use of systemic glucocorticoids has been associated to reduce the time of recovery and the length of hospitalization, together with the improvement of lung function, oxygenation, risk of relapse (30). Courses of steroids longer than 5 days are instead associated with an increased risk of pneumonia, sepsis and mortality (31). Oral or intravenous administration of steroids is equally effective (32).
- Antibiotics: the use of antibiotics during COPD exacerbations remains controversial, since the available studies on the topic usually lack of enough specificity (29). The evaluation of sputum purulence can be adopted to drive the choice to start an antibiotic, since it has a sensitivity of 94.4% and a specificity of 52% for high bacterial load (33). No conclusive data are available on the effectiveness of antibiotics use according to levels of C Reactive Protein or Procalcitonin. GOLD recommends to use antibiotics if the patient has three cardinal symptoms: increased dyspnea, sputum volume and sputum purulence; or has two of the cardinal symptoms and one of them is the increased purulence; or there is the need for either

invasive or non-invasive mechanical ventilation (3). The duration of antibiotic course should be < 5 days for outpatients and between 5 and 7 days for inpatients. Aminopenicillins with clavulanic acid, macrolides or tetracyclines should be preferred as empirical therapy, although the choice should be targeted as per sputum culture when this is available (34,35).

Moreover, adjunct therapies have been described as useful during COPD exacerbations. In particular, prophylactic therapy for pulmonary embolism should be introduced, an appropriate fluid balance with the use of diuretics can be useful (36,37).

2.2.2 Oxygen therapy and respiratory support

During an acute exacerbation of COPD requiring hospital admission, respiratory support plays a fundamental role:

- Oxygen therapy: supplemental oxygen should be provided to patients, targeting a SpO2 of 88-92%. Whenever possible, Venturi mask has to be preferred to oxygen cannula so to obtain a higher FiO2 precision. Arterial blood gas analysis should be preferred to pulse oximetry to assess the patient response to oxygen delivery, meanwhile allowing an accurate check for hypercapnia and metabolic status (38).
- High flow nasal therapy (HFNT): humidified and heated air-oxygen blends can be delivered through dedicated devices via nasal cannula, or tracheostomy, at rates from 40 to 60 L/min in adults (39). HFNT has been linked to reduced respiratory rate and effort, improved gas exchange and ventilation, decreased work of breathing. This can be helpful both in acute hypoxemic respiratory failure and hypercapnic COPD exacerbations (39,40). HFNT can be used also in the chronic management of stable COPD patients (41).
- Ventilatory support: severe exacerbations might necessitate to be treated with ventilatory support, through Non-Invasive Ventilation (NIV) or Invasive Mechanical Ventilation (IMV). NIV can be provided by nasal or facial mask, while IMV via oro-tracheal tube or

tracheostomy. NIV should be preferred to IMV to treat acute respiratory failure in hospitalized patients, it helps in the correction of acidosis, reduces CO2 levels, work of breathing and respiratory rate, and consequently the mortality rate (42,43). Moreover, NIV does not require a period of weaning, and can be discontinued if the patient can tolerate at least 4 hours of unassisted breathing (44). The main indications for the use of NIV are: 1) respiratory acidosis; 2) severe dyspnea with respiratory muscle fatigue or increased work of breathing; 3) hypoxemia despite oxygen support.

IMV should be considered in case of failure of a NIV trial. The main indication for the step up to IMV are: 1) Intolerance to NIV or failure of a NIV trial; 2) massive aspiration or vomiting; 3) post respiratory or cardiac arrest; 4) in case of diminished consciousness, psychomotor agitation inadequately controlled by sedation; 5) Inability to remove respiratory secretions; 6) Hemodynamic instability with scarce response to fluids or vasoactive drugs; 7) ventricular or supraventricular arrhythmias; 8) life-threatening hypoxemia. Before to initiate an IMV, risks of ventilator acquired pneumonia, ventilator induced lung injury, barotrauma and tracheostomy for prolonged ventilation might be considered and carefully evaluated. Anyway, when compared to ventilation for causes other than COPD, IMV related mortality is generally lower among COPD ventilated patients (45).

2.3 Strategies to prevent the risk of COPD exacerbations

Vaccination against common respiratory pathogens is recommended in every COPD patient, as this can reduce the risk of exacerbations. More in details, yearly influenza vaccine, one dose of anti-pneumococcal vaccine and SARS-CoV-2 vaccine (timing as per WHO indication) are recommended. Vaccine against Respiratory Syncytial Virus, pertussis and Herpes Zoster are also suggested (4). Use of shielding measures (i.e. wearing facial masks, hand washing) are always recommended in COPD patients. An increase in the adoption of these preventive measures was noted during COVID-19 pandemic (4).

3. Viral induced COPD exacerbations

A recent systematic review of 19 studies employing sputum PCR during acute exacerbations of COPD (AECOPD) (n=1972) identified human rhinovirus (HRV; 16.39%), respiratory syncytial virus (RSV; 9.9%), and influenza virus (7.83%) as the most frequently detected pathogens (46). Adenovirus (2.07%), coronavirus (4.08%), and human metapneumovirus (2.78%) were detected less frequently (46). The predominance of HRV, RSV, and influenza likely reflects the increased probability of infection due to co-circulation of multiple HRV genotypes and the annual community-wide epidemics of RSV and influenza. These epidemiological data implicate respiratory viruses in a substantial proportion of COPD exacerbations; however, they do not always establish a causal relationship. Viral detection has indeed also been reported in stable COPD. McManus et al. (47) identified respiratory viruses in 12% of subjects, whereas Rohde et al. (48) reported detection in 19% of stable COPD patients.

However, these data derive from studies conducted prior to the SARS-CoV-2 pandemic, and to date, it has not yet been clarified how SARS-CoV-2 has impacted acute COPD exacerbations and whether this respiratory virus may have altered the viral ecology of COPD exacerbations.

3.1 Molecular mechanisms of viral induced COPD exacerbations

COPD exacerbations are frequently burdened by viral infections, which can magnify small airways inflammation and manipulate host immune response, leading to deterioration of airways obstruction (49,50). Respiratory viruses target airway epithelial cells inducing the deterioration of epithelial barrier and dilatation of the microvasculature, thus inducing oedema, immune cell infiltration and bacterial co-infection (51,52).

3.1.1 The NF-κB pathway

Viral and bacterial infections activate the NF-κB pathway in macrophages and airway epithelium through the pro-inflammatory cytokines (TNF-α and IL-1) and toll like receptors (TLRs) (53). Consequently, activated RelA containing NF-κB complexes stimulates RelA (p65)/p50 to translocate

in the nucleus of the cells, with transcription of pro-inflammatory genes (53,54). This can contribute to the pathogenesis of COPD exacerbation through the amplification of the inflammatory response via the transcription of inhibitors of apoptosis, proteases, cell adhesion molecules (CAMs), pro-inflammatory cytokines and chemokines (55).

3.1.2 The Virus Recognition Receptors Pathways

Respiratory viruses can release their genomes into airway epithelium cells. Viral DNA or RNA is consequently detected by cytoplasmic virus recognition receptors which activate a pro inflammatory cascade leading to the production of antiviral Interferons (IFN) type I and type III, to the release of pro-inflammatory cytokines and to the NF-κB nuclear translocation (56–58). In COPD patients, however, an attenuated IFN response has been observed, and this might result in defective antiviral activity, enhanced viral replication and uncontrolled inflammatory response. Particularly, the combination of weak IFN response and over expression of ICAM-1 on the surface of COPD airway epithelium plays a dominant role in HRV induced COPD exacerbation (59). Indeed, ICAM-1 is one of the major HRV cellular receptor adopted by the virus to infect airways epithelial cells (60). In this sense, targeting ICAM-1 might represent a potential therapeutic strategy against HRV-induced COPD exacerbations.

3.1.3 The CD8+ T cells exhaustion

Viral induced COPD exacerbations are characterized by an enhanced activation of the Programmed Cell Death Protein (PD-1) pathway, with a concomitant depletion of PD-L1 ligand on COPD macrophages and increase in release of IFN-γ. All together this induces an initial increased CD8+ activation, an excessive T cells inflammatory response but a subsequent T cells exhaustion (61,62).

3.2. Mechanisms Underlying Increased Viral Susceptibility in COPD

COPD is associated with impaired antiviral defenses, as evidenced by higher viral loads following human rhinovirus (HRV) infection compared to controls (63,64). Deficient interferon signalling, a key component of innate immunity, has been demonstrated in COPD (64), and is further

compromised by concurrent cigarette smoke exposure, which suppresses interferon-stimulated gene expression and interferon production (65). Increased airway expression of intracellular adhesion molecule-1 (ICAM-1) in smokers with chronic airflow limitation may also facilitate HRV infection (66). Adaptive immunity is similarly impaired. Ex vivo studies show that CD8+ T cells from COPD patients exhibit reduced cytotoxic responses to influenza virus, linked to upregulated programmed cell death protein-1 (PD-1) expression (67). Cigarette smoke further disrupts antiviral immunity by impairing viral recognition, dampening cytokine responses (e.g., IL-6, IL-8), and reducing antiviral signaling pathways, including interferon-β and RIG-1 expression (68).

Therapeutic factors may exacerbate this vulnerability. Inhaled corticosteroids (ICS), particularly fluticasone propionate, have been shown to impair both innate and adaptive antiviral responses, increase mucus production, elevate bacterial load, and reduce antimicrobial peptide secretion (69). Notably, herpes simplex virus-1 (HSV-1) detection is more common in COPD patients on high-dose ICS and is associated with increased mortality risk (70).

3.3. Rhinovirus infection in COPD exacerbations

In the literature, several groups have focused on the causal role of HRV infection and on the pathological-biological responses of the infected organism. HRV is indeed the most common respiratory virus detected during COPD exacerbation (46). Rhinoviruses are single stranded RNA viruses belonging to the *Picornaviridae* family and include three different species (RV-A, RV-B and RV-C). HRV is capable of infecting human cells via specific receptors (ICAM1, LDLR and CDHR3). Once the cells are infected with Rhinovirus they release numerous pro-inflammatory cytokines (IFN-α, INF-γ, TNF- α, IL-6, IL-8). HRV is frequently detected in the airways of COPD patients during acute exacerbations (AE-COPD) and is itself capable of inducing an AE-COPD, as demonstrated in experimental models (71). Although HRV seems less capable of inducing direct cell damage to respiratory epithelial cells, unlike other respiratory viruses (i.e. Influenza), this virus exerts a strong pro-inflammatory action (72). HRV binds to airway epithelial cellular receptor ICAM-1 (CD54),

which is overexpressed in COPD patients, to infect cells (66). Unfortunately, COPD patients have blunted protective immune responses, with reduction in the activity of dendritic cells, alveolar macrophages, T and B cells, mucociliary clearance and mucosal antibody production. Moreover, anti-viral cytokines such as IFN-α and IFN-β are significantly compromised in the lungs of active smokers. This contributes to the susceptibility to viral infections and to worse outcome. Some groups have developed experimental Rhinovirus infection, demonstrating a causal role in the COPD exacerbations, through impaired IFN production and neutrophilic inflammation (64).

3.3.1 Antiviral therapy with a focus on Rhinovirus and future perspectives (aptamers)

AE-COPD is a well-recognized negative prognostic factor in the natural history of COPD patients, thus prevention or efficacious treatment of AE-COPD still represents a fundamental goal. Nonetheless, the actual treatment of COPD exacerbations is mainly based on the administration of systemic corticosteroids, antibiotics and bronchodilators, while no targeted therapy against the majority of viral agents is available, despite the majority of AE-COPD are triggered by viral infections (73,74).

- Inhaled therapy: large clinical trials have demonstrated that inhaled therapy with combinations of inhaled corticosteroids (ICS), long-acting anti-muscarinics (LAMA) and long-acting β2-agonists (LABA) is associated with a reduction in the number of AE-COPD, however this therapy is also linked with an increased risk of pneumonia, though preventive beneficial effects are considered to outweigh this risk (75,76). ICS/LABA/LAMA might exert antiviral effect through the reduction of virus induced inflammation of the airways. Nonetheless, it has also been demonstrated that ICS could someway impair antiviral immunity against viruses (69). Overall, the specific effects of ICS on COPD immunity remains quite unclear, but their overall effect of reducing exacerbations is internationally recognized and this is the basis of their safe use in the daily clinical practice.

- Antiviral therapy: in recent years, numerous antiviral therapies have been investigated, although none have transitioned into routine clinical practice. The majority of these pharmacological agents function as either protease inhibitors or capsid-binding inhibitors. Rupintrivir is a potent inhibitor of the human rhinovirus (HRV) 3C protease. Although phase II randomized, double-blind, placebo-controlled studies demonstrated that its intranasal administration effectively impairs HRV replication with a favorable safety profile, its clinical development was ultimately discontinued, with no further trials published since the initial 2003 findings (77,78). Capsid-Function Inhibitors, including Pleconaril, Vapendavir, and Pirodavir, target the viral capsid to inhibit uncoating and attachment. While these agents have shown efficacy in reducing viral loads during clinical trials, regulatory approval has been withheld for two primary reasons: a marginal Clinical Benefit in term of reduction in the severity and duration of exacerbations and safety concerns, regarding potential risks of hepatic adverse effects (79,80).
- ***Anti ICAM-1:*** an alternative strategy focuses on neutralizing HRV attachment by targeting its cellular receptors, the intercellular adhesion molecule 1 (ICAM-1). Hayden (81) firstly demonstrated that murine monoclonal antibodies directed at ICAM-1 receptor yielded modest reductions in viral titers and consequent clinical symptoms. Some years later, Tremacamra, a recombinant soluble ICAM-1, exhibited limited efficacy in attenuating symptomatic scores when administered peri-inoculation (82). More recently, with the development of 14C11, a mouse anti-human ICAM-1 antibody, the interest in receptor blockade resumed. 14C11 targets the D1 domain, the primary binding site for the majority of HRV serotypes and it seems also effective in modulating the immune response by reducing TH2 cytokine production (83).
- ***Exogenous Interferon:*** patients with COPD may exhibit impaired interferon (IFN) responses, thus exogenous IFN administration might enhance the immune response against virus agents. IFN-beta efficacy against viral infections (such as influenza) is significantly higher when administered prophylactically rather than post-infection (84).

- ***Novel Host and Enzymatic Targets:*** recent research has identified human N-myristoyltransferase (NMT) as a promising target. During HRV polyprotein synthesis, the VP0 region undergoes N-myristoylation by host NMT1 and NMT2, a requisite step for protomer assembly and the maturation of infectious virions (85). Other emerging targets include glutathione inhibitors and the inhaled innate immune stimulator PUL-042, the latter of which is currently progressing through Phase II clinical trials.
- ***Vaccination:*** preventative vaccination is the most desirable strategy, however more than 160 HRV serotypes exist, thus concerns remain on vaccine development. Targeting highly conserved regions of the capsid protein, might be an effective strategy. murine models have shown that immunization with the VP0 protein and an adjuvant can induce T-cell responses, enhance neutralizing antibody production and accelerate viral clearance in the lungs (86).
- ***Aptamers:*** the great push for research following the spread of SARS-CoV-2 has made it possible to discover new possible therapeutic approaches in addition to those already in use (vaccines, antivirals). In particular, some groups have demonstrated in vitro the possible positive effect derived from the use of specific aptamers towards SARS-CoV-2 (87). In these studies, a bulk macromolecule designed to act as a steric hindrance on the cellular receptor adopted by the virus to infect the cells has been effective in the prevention of viral spreading. More precisely, the bulk macromolecule was constituted by two single strand DNA molecules, namely aptamers. These aptamers can bind to specific key sites of the cellular receptors for the virus, efficiently preventing the SARS-CoV-2/human ACE2 interaction and the viral infection in the nanomolar range, suggesting a future clinical development as SARS-CoV-2 infection inhibitors, especially as aptamers have the potential capability to prevent infection also from viral mutants (87). This approach could be of significant interest if applied to Rhinovirus viral infection in COPD patients, in order to prevent and treat one of the leading causes of exacerbations, with considerable benefit for the health of patients and with a possible significant reduction in the social costs of the disease.

3.4 SARS-CoV-2 Infection in COPD exacerbations

SARS-CoV-2 infection and the consequent Coronavirus Disease 2019 (COVID-19) shares clinical features with daily manifestations of COPD, including dyspnea, cough, and sputum production (88). For this reason, when COPD patients present with symptom worsening, laboratory confirmation of SARS-CoV-2 infection is essential to avoid misdiagnosis (89). Moreover, COVID-19 can itself precipitate COPD exacerbations. Although no data on the efficacy of COVID-19 treatments on the subgroup of COPD patients are available, GOLD recommends to manage these patients in accordance with established COPD protocols meanwhile addressing the underlying viral infection. Maintenance inhaled pharmacological therapy should not be interrupted during COVID-19 as withdrawal of therapy may increase the risk of destabilization and exacerbations (90). The use of nebulized therapy, while associated with an increased risk of viral aerosolization, remains appropriate in selected cases, provided that strict infection-control measures are necessary (i.e. adequate room ventilation and the use of personal protective equipment (PPE) by healthcare personnel) (91).

Management of COPD patients who develop COVID-19 should integrate standard SARS-CoV-2 treatment protocols with tailored attention to the underlying chronic respiratory disease. Systemic corticosteroids are useful in COPD exacerbations, especially in patients requiring supplemental oxygen (92). Antibiotics should be prescribed only in case a bacterial superinfection is suspected (93). Furthermore, COVID-19 might enhance the prothrombotic state so prophylactic or standard anticoagulation therapy is recommended, especially in hospitalized COPD patients (94).

In case of respiratory failure requiring ventilatory support, this must be started, balancing efficacy with infection-control. Non Invasive Ventilation (NIV) and high-flow nasal oxygen can be employed in selected patients; however, in case of failure, the escalation to Invasive Mechanical Ventilation (IMV) should not be delayed, always adopting infection-control protocols, since these interventions are aerosol-generating (95,96). COPD patients recovering from COVID-19 might experience prolonged respiratory and systemic sequelae. For these reasons, follow-up is particularly indicated (97).

AIMS AND SCOPE OF THE STUDY

Viral and bacterial infections are the main cause of acute COPD exacerbations, accounting respectively for 25% and 26% of cases (98). In 22% of cases no pathogens can be found on culture tests (99). Among viral etiologic agents, several studies have highlighted how Human Rhinovirus (HRV) is the infectious agent most involved in COPD exacerbations (35-60% of cases), followed by Respiratory Syncytial Virus (RSV) (10-30%), Influenza Virus (5-30%), and, to a much lesser extent, Parainfluenza virus, Adenovirus and Human Coronavirus (98,100,101).

However, these epidemiological data derive from studies conducted prior to the SARS-CoV-2 pandemic, and to date, it has not yet been clarified to what extent the spread of SARS-CoV-2 has impacted on the clinical outcomes of acute COPD exacerbations and whether this respiratory virus may have altered the viral ecology of COPD exacerbations.

Consequently, there is the need to clarify whether acute COPD exacerbations caused by SARS-CoV-2 have peculiar characteristics that distinguish them (i.e. in terms of severity) from those in which no infection or other common infective agents can be found.

The aim of the study was to assess the clinical impact and long-term outcomes of SARS-CoV-2 triggered acute exacerbations of COPD.

More in details, the primary endpoint of the study was to identify the risk of moderate-severe acute respiratory failure requiring non-invasive respiratory support up to Continuous Positive Airway Pressure (C-PAP) and Non-Invasive Ventilation (NIV) in patients affected by COPD exacerbation caused by SARS-CoV-2, compared to a control group of patients with COPD exacerbations without SARS-CoV-2 infection.

Secondary endpoints of the study were to identify the overall risk of acute respiratory failure in the SARS-CoV-2 cohort compared to the control group, and to stratify the risk according to the severity of respiratory failure and the consequent need of respiratory support (i.e. low oxygen flow by nasal cannula, Venturi Mask, Reservoir Mask, High Flow Nasal Cannula). Mortality in the SARS-CoV-2

cohort was also analysed and compared to the control group. Other secondary outcomes included the comparison of the SARS-CoV-2 and control groups for the frequency of COPD exacerbations and hospitalization; frequency of emphysema and impact on severity of COPD exacerbation; length of hospitalization; changes in white blood cells count and blood gas analysis parameters from admission to hospital discharge; association between heart failure and COPD exacerbations. Moreover, in the control group, the frequency of COPD exacerbations secondary to an infection by other than SARS-CoV-2 respiratory viruses was described.

MATERIALS AND METHODS

1. Study design

This is a prospective, observational, single center study which recruited adult COPD patients consecutively admitted for an acute exacerbation of COPD in the Pulmonology and Infectious Diseases Departments of ASST Santi Paolo e Carlo (Milan, Lombardia - Italy) in the period 01/01/2021 – 31/05/2023 (SARS-CoV-2 cohort) and 01/06/2023 – 31/12/2024 (COPD control group).

SARS-CoV-2 patients could be admitted to Pulmonology or Infectious Diseases wards, while patients without SARS-CoV-2 infections were exclusively admitted to Pulmonology unit.

This study was conducted and funded under an Italian Government project by the "Piano Nazionale di Ripresa e Resilienza" (PNRR): Work Project 5.2 - Innovative strategies to counteract novel antimicrobial resistant bacteria and viral infections, Task 2.3 RNA/DNA Aptamers (Leaders: Prof. Stefano Centanni, Prof. Paolo Ciana, Department of Health Sciences, Università degli Studi di Milano). Moreover, the data of the present study contributed to the EuCARE (European cohorts of patients and schools to advance response to epidemics) project, a European registry funded by the European Commission under an Horizon Grant dedicated to projects to fight Coronavirus pandemic (under the supervision of Prof. Camilla Tincati, Department of Health Sciences, Università degli Studi di Milano).

2. Study population and inclusion criteria

Consecutive patients with acute exacerbation of COPD secondary to SARS-CoV-2 infection who required hospitalization for adequate management were prospectively enrolled. The control group consisted of consecutive patients hospitalized for COPD exacerbation and without evidence of SARS-CoV-2 infection at nasopharyngeal swab.

Patients belonging to the control group could be without evidence of infection or with infection by other than SARS-CoV-2 respiratory viruses.

Eligible patients should have met the inclusion criteria: age >18 years; COPD diagnosis; ability to sign the informed consent form; acute COPD exacerbation requiring hospital admission; SARS-CoV-2 infection at nasopharyngeal swab (SARS-CoV-2 group); negative SARS-CoV-2 infection at nasopharyngeal swab (COPD control group); no signs of pneumonia at admission.

Exclusion criteria were: pregnancy; breastfeeding; psychiatric disorders which might impair the ability to sign the informed consent; refuse to take nasopharyngeal swab.

The decision to start a non-invasive ventilatory support and to escalate/de-escalate it was exclusively decided by the doctor to whom the patient was in charge, as per international recommendations and on the basis of the severity of acute respiratory failure.

All patients signed informed consent forms approved by the Ethics Committee, in accordance with current Italian legislation (Privacy Code, Legislative Decree 30 June 2003, no. 196). The study was conducted according to the Declaration of Helsinki. Data were collected in a dedicated institutional database.

3. Variables collected

Clinical, functional, serological, radiological data of the enrolled patients were prospectively collected and analyzed.

More in details, for every enrolled patient, the following data were obtained:

- Demographic characteristics;
- Relevant respiratory and extra-pulmonary comorbidities;
- Blood tests results (at admission and at discharge);
- Pulmonary Function Tests (when available at COPD diagnosis and after discharge);
- Hospitalization details (including the outcome, type and duration of oxygen support);
- Mortality;

- Treatment (COPD therapy);
- Radiology patterns at High Resolution Computed Tomography (HRCT);
- Nasopharyngeal swab results (SARS-CoV-2; other respiratory viruses)

Data were obtained from Electronical Medical Records both recorded during hospital admission for the exacerbation and from anamnestic documents as needed.

Clinical, laboratory, and imaging investigations were performed according to standard clinical practice and international guidelines (1,5).

Chest HRCT were performed using the high resolution protocol (1 mm scans).

4. Statistics

Quantitative and qualitative variables were collected. Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), according to the presence or absence of a normal distribution. Categorical variables were reported as absolute and relative frequencies. Appropriate statistical tests were adopted. Chi-square test of independence of variables and Fisher's exact test were used to compare frequencies of categorical variables. Student's T test, and ANOVA (Analysis of variance) were adopted for comparison on continuous variables with normal distribution, Mann-Whitney U rank test and Kruskal-Wallis test in case of absence of a normal distribution or for independent variables. The nonparametric Aligned Rank Transform (ART) was used to analyze data with complex factorial designs. Survival analysis was performed through Kaplan-Meier methods. A p-value < 0.05 was considered statistically significant. Confidence Interval at 95% were calculated when appropriate. Statistical analysis was performed with the STATA 14 software (Stata Corp LP, College Station, TX, USA).

RESULTS

1. Descriptive characteristics of the population and comorbidities

238 COPD patients admitted to hospital due to an acute exacerbation of COPD were consecutively enrolled (Table 1). 120 patients (50.4%) tested positive for SARS-CoV-2 infection at nasopharyngeal swab performed at admission (SARS-CoV-2 group), while 118 (49.6%) were negative (Control group). Mean age at admission for COPD exacerbation was 77.6 (± 9.1) years among the SARS-CoV-2 positive and 72.6 (± 11.4) years in the negative group ($p < 0.001$). The mean age at COPD diagnosis was 75.3 (± 9.6) years in the SARS-CoV-2 infection group and 68.86 (± 11.9) years in those without infection ($p < 0.001$). The groups did not significantly differ for other demographic characteristic (Table 1). Among smoking categories, only current smokers were significantly less frequent in the SARS-CoV-2 group ($p = 0.048$) (Figure 1). The history of smoke exposure, as expressed by the pack-years index, was higher in the infection group ($p = 0.047$). No difference was noted for the family history of respiratory diseases, while a significantly higher work exposure was registered in the control group ($p = 0.001$).

Although the groups were balanced for the presence of the main comorbidities, pulmonary hypertension ($p = 0.031$) and depression ($p = 0.045$) were more common in the control group, while arterial hypertension was more frequent in the SARS-CoV-2 group ($p = 0.0001$) (Table 2).

Variable		SARS-CoV-2	Control	p-value
Age at COPD Exacerbation, Mean (SD)		77.62 (9.17)	72.69 (11.46)	**<0.001**
Age at COPD Diagnosis, Mean (SD)		75.36 (9.63)	68.86 (11.99)	**<0.001**
Gender, n (%)	Female	50 (41.67)	65 (55.08)	0.052
	Male	70 (58.33)	53 (44.92)	0.052
Ethnicity, n (%)	Caucasian	117 (97.50)	115 (98.29)	1.000
	Asian	3 (2.50)	0 (0.0)	0.247
	African American	0 (0.0)	1 (0.85)	0.493
	Hispanic	0 (0.0)	1 (0.85)	0.493
	Other	0 (0.0)	1 (0.85)	0.493
BMI, Mean (SD)		28.62 (8.87)	26.65 (8.58)	0.083
Performance Status, Mean (SD)		1.56 (1.30)	1.49 (1.21)	0.668
Smoking history, n (%)	Never smoker	6 (5.94)	1 (0.88)	0.067
	Former smoker	66 (65.35)	67 (59.29)	0.369
	Smoker	29 (28.71)	45 (39.82)	**0.048**
Pack-Years, mean (SD)		56.70 (24.70)	49.28 (29.56)	**0.047**
Work exposure, n (%)		3 (2.5)	18 (15.2)	**0.001**
Family History of Respiratory Diseases, n (%)		1 (0.8)	6 (5.0)	0.119

Table 1: Demographic and clinical characteristics of patients in the SARS-CoV-2 and control groups.

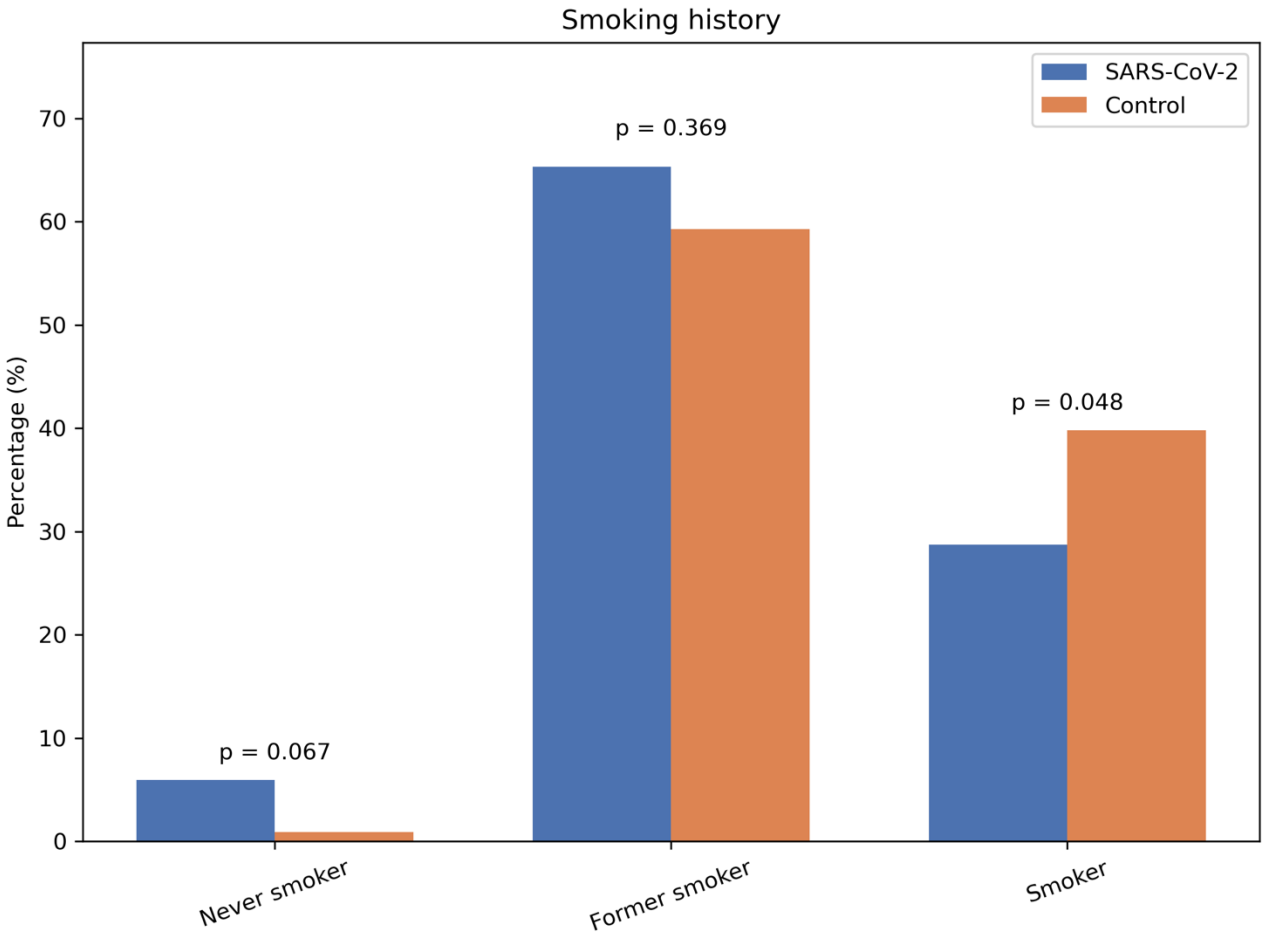

Figure 1: Distribution of smoking history categories in COPD patients with and without SARS-CoV-2 infection. A significantly lower proportion of current smokers was observed in the SARS-CoV-2 group (p = 0.048).

Comorbidity, n (%)	**SARS-CoV-2**	**Control**	**p-value**
Interstitial Lung Disease	3 (2.5)	3 (2.5)	1.000
Obstructive Sleep Apnea	22 (18.3)	21 (17.8)	1.000
Pulmonary Hypertension	5 (4.1)	15 (12.8)	**0.031**
Arterial Hypertension	101 (84.1)	71 (60.1)	**0.0001**
Diabetes	36 (30.0)	23 (19.4)	0.084
Anxiety	15 (12.5)	24 (20.3)	0.145
Depression	7 (5.8)	17 (14.5)	**0.045**
Obesity	30 (26.7)	23 (21.1)	0.405
Osteoporosis	11 (9.1)	21 (17.8)	0.078
Coronary Artery Disease	32 (26.6)	32 (27.1)	1.000
Cardiac Failure	48 (40)	48 (40.6)	1.000
Gastro-esophageal Reflux Disease	46 (38.3)	40 (33.9)	0.564
Immunedepression	9 (7.5)	13 (11.0)	0.476
Lung Cancer	9 (7.5)	4 (3.3)	0.267
Other Solid Organ Cancer	19 (15.8)	15 (12.7)	0.615
Hematologic Neoplasm	3 (2.5)	7 (5.9)	0.319

Table 2: Comparison of the frequency of comorbidities in the SARS-CoV-2 and control groups.

2. Risk of respiratory failure

The absolute risk of respiratory failure was calculated for the two groups of COPD patients with and without SARS-CoV-2 infection.

234 patients were included in the final analysis: 119 patients in the SARS-CoV-2 group and 115 in the control group. The absolute risks of respiratory failure were 60.5% (SARS-CoV-2 group) and 67.82% (control group) (Figure 2).

The consequent relative risk was 0.89 ($p = 0.303$) with a 95% Confidence Interval (CI) of 0.73 – 1.06 (Figure 3, Table 3). Thus, no significant difference could be demonstrated in the risk of respiratory failure between the two groups.

The risk of respiratory failure was then stratified according to the maximum ventilatory support needed in the two groups.

The absolute risk of respiratory failure requiring up to Non-invasive ventilation (NIV) was calculated for the two groups of COPD patients with and without SARS-CoV-2 infection. 235 patients were included in the analysis, since the detailed information on the ventilatory support was missing for three (1.26%) patients (1 patient in the SARS-CoV-2 group and 2 patients in the control group). 36 patients in the SARS-CoV-2 group were treated with NIV, while 58 needed NIV in the control group. The absolute risk of developing a severe acute respiratory failure with the need of ventilatory support up to NIV was thus 30.25% in the SARS-CoV-2 group vs 50.00% in the control group (Figure 2). The consequent relative risk was 0.61 ($p = 0.003$) with a 95% Confidence Interval (CI) of 0.44 – 0.84 (Figure 3, Table 3). The risk of acute respiratory failure needing NIV in the SARS-CoV-2 group was 39% lower than in the control group (Relative Risk Reduction (RRR) = 0.39).

The absolute risk of respiratory failure requiring up to Helmet Continuous Positive Airway Pressure (CPAP) was calculated for the two groups of COPD patients with and without SARS-CoV-2 infection. 141 patients (83 with SARS-CoV-2 infection, 58 in the control group) were included in the analysis, after the exclusion of the 94 patients who needed ventilatory support up to NIV. 19 patients in the SARS-CoV-2 group needed support up to C-PAP versus 3 in the control group. The risk of

developing an acute respiratory failure with the need of ventilatory support up to C-PAP was thus 22.89% in the SARS-CoV-2 group vs 5.17% in the control group (Figure 2). The consequent relative risk was 4.42 (p = 0.009) with a 95% CI of 1.37 – 14.35 (Figure 3, Table 3). Thus, SARS-CoV-2 patients had a Relative Risk Increase (RRI) of 3.42, which corresponds to a 342% higher risk of requiring C-PAP compared with controls.

The absolute risk of respiratory failure requiring up to High Flow Nasal Cannula (HFNC) was calculated for the two groups of COPD patients with and without SARS-CoV-2 infection. Patients requiring C-PAP or NIV (116) were excluded. 119 patients (64 with SARS-CoV-2 infection, 55 in the control group) were thus included in the analysis. 5 patients in the SARS-CoV-2 group needed support up to HFNC versus 12 in the control group. The absolute risks in the groups were thus 7.81% in the SARS-CoV-2 group vs 21.82% in the control group (Figure 2). The consequent relative risk was 0.36 (p = 0.05) with a 95% CI of 0.14 – 0.94 and a RRR of 0.64 (Figure 3, Table 3). Thus, the use of HFNC as the maximum ventilatory support was 64% lower probable in the SARS-CoV-2 group when compared to the control group.

The absolute risk of respiratory failure requiring up to oxygen support with a Venturi Mask at FiO2 (Fraction of inspired oxygen) 60% was calculated for the two groups of COPD patients with and without SARS-CoV-2 infection. After excluding for patients with missing values (4) and for patients which required up to higher support (NIV, C-PAP, HFNC), 102 patients (59 with SARS-CoV-2 infection, 43 in the control group) were considered in this analysis. 12 patients in the SARS-CoV-2 group needed oxygen support up to MV FiO2 60% versus 6 in the control group. The absolute risks in the groups were thus 20.34% in the SARS-CoV-2 group vs 13.95% in the control group (Figure 2). The consequent relative risk was 1.46 (p = 0.567) with a 95% CI of 0.60 – 3.58 (Figure 3, Table 3). Thus, no significant difference could be demonstrated in the need of oxygen support up to MV FiO2 60% between the two groups.

No episodes of pneumothorax were reported independently from the ventilation used. No patients were escalated to full mechanical ventilation.

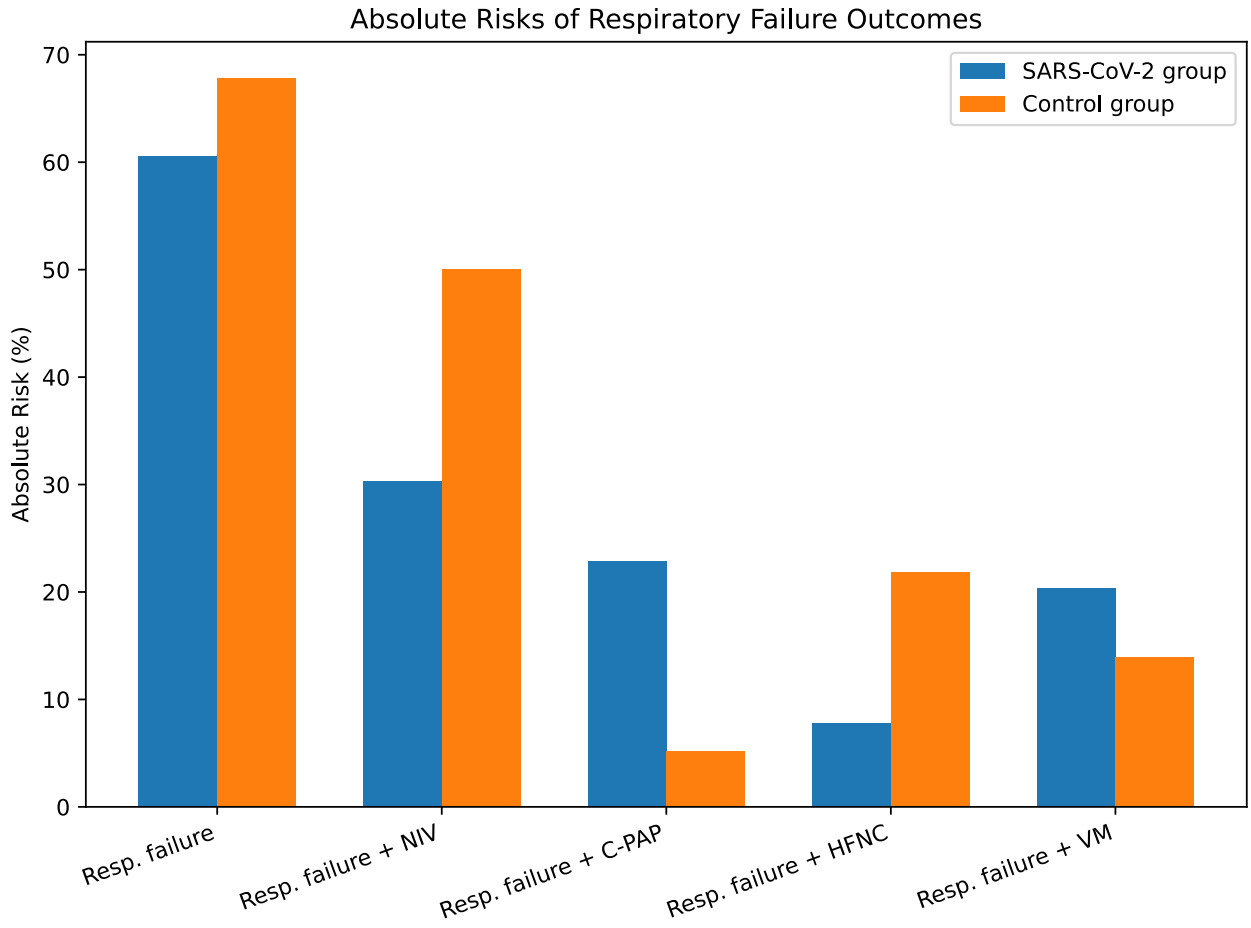

Figure 2: Bar graph showing absolute risks of respiratory failure and escalating ventilatory support modalities in SARS-CoV-2 patients compared to controls. NIV: Non Invasive Ventilation; C-PAP: continuous positive airway pressure; HFNC: high flow nasal cannula; VM: Venturi mask.

Outcome	RR	95% CI	p-value
Respiratory failure	0.89	0.73 - 1.06	0.303
Respiratory failure up to NIV	0.61	0.44 - 0.84	**0.003**
Respiratory failure up to C-PAP	4.42	1.37 - 14.35	**0.009**
Respiratory failure up to HFNC	0.36	0.14 - 0.94	**0.050**
Respiratory failure up to VM	1.46	0.60 - 3.58	0.567

Table 3: Relative risks and 95% confidence intervals for respiratory failure and escalating ventilatory support modalities in SARS-CoV-2 patients compared with controls. RR: relative risks; CI: confidence interval; NIV: Non-invasive Ventilation; C-PAP: continuous positive airway pressure; HFNC: high flow nasal cannula; VM: Venturi mask.

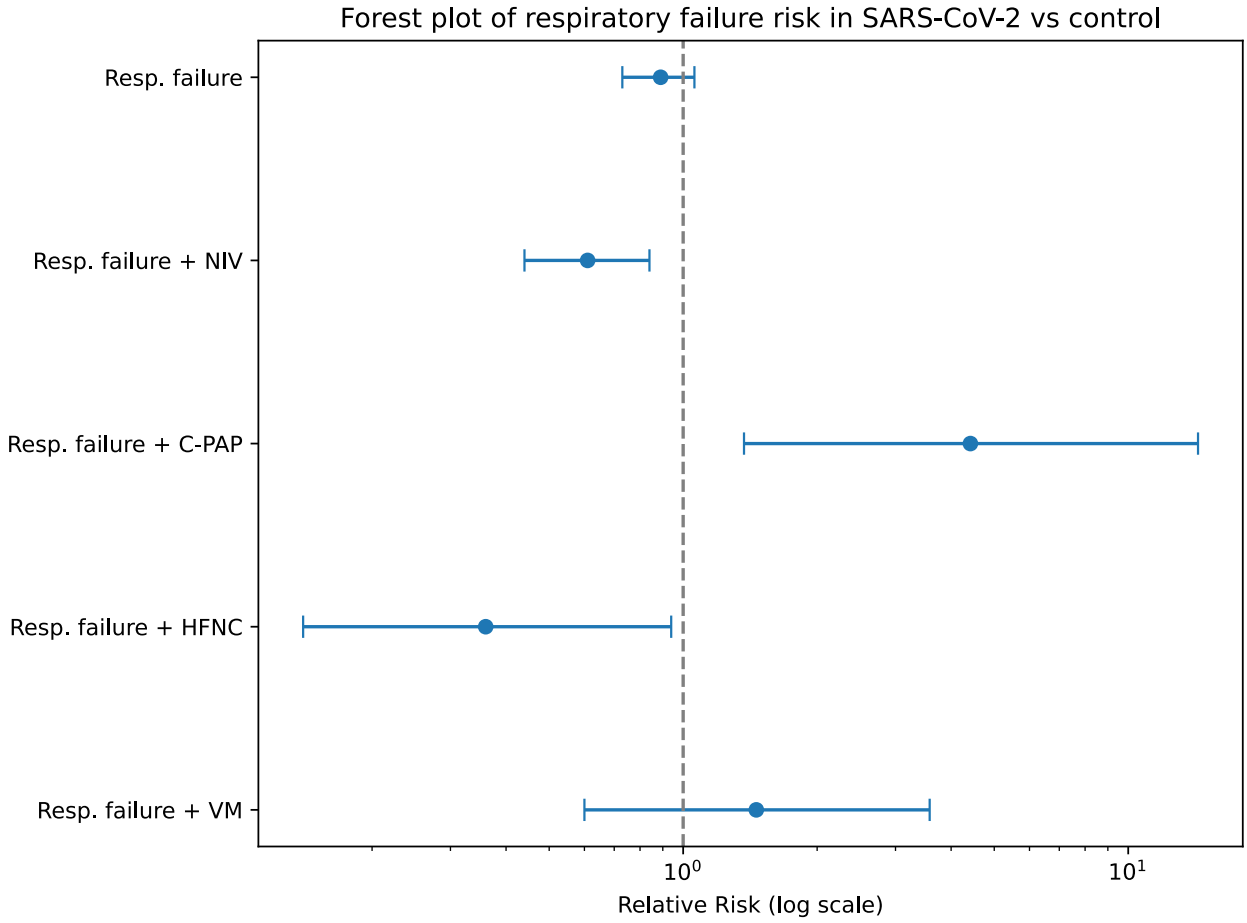

Figure 3: Forest plot showing relative risks and 95% confidence intervals for respiratory failure and escalating ventilatory support modalities in SARS-CoV-2 patients compared with controls. The vertical line represents no effect (Relative Risk = 1), logarithmic scale was adopted. RR: relative risks; CI: confidence interval; NIV: Non-Invasive Ventilation; C-PAP: continuous positive airway pressure; HFNC: high flow nasal cannula; VM: Venturi mask.

3. Survival analysis after COPD exacerbation in SARS-CoV-2 and control groups

A Kaplan-Meier survival analysis was performed to assess mortality rates in the SARS-CoV-2 and control groups from the day of hospitalization for acute exacerbation of COPD to 12 months from hospital discharge (Figure 4). Data from 237 patients were available for inclusion in the analysis (1 missing value due to lost at follow up visits). Comparison of the mortality curves clearly showed a significantly higher mortality rate among SARS-CoV-2 patients ($p < 0.00001$). Moreover, a secondary exploratory analysis was performed to punctually assess and compare the outcome all-cause mortality at specific time points: during the hospitalization for COPD exacerbation, at 30 days, 6 months and 12 months from hospital discharge. When mortality was analyzed by time intervals among patients at risk, SARS-CoV-2 infection was associated with significantly higher mortality during hospitalization ($p < 0.0001$) and between 6 and 12 months ($p < 0.0001$). Mortality differences between discharge and 30 days and between 30 days and 6 months were not statistically significant (Fisher's exact test) (Table 4 and Figure 5).

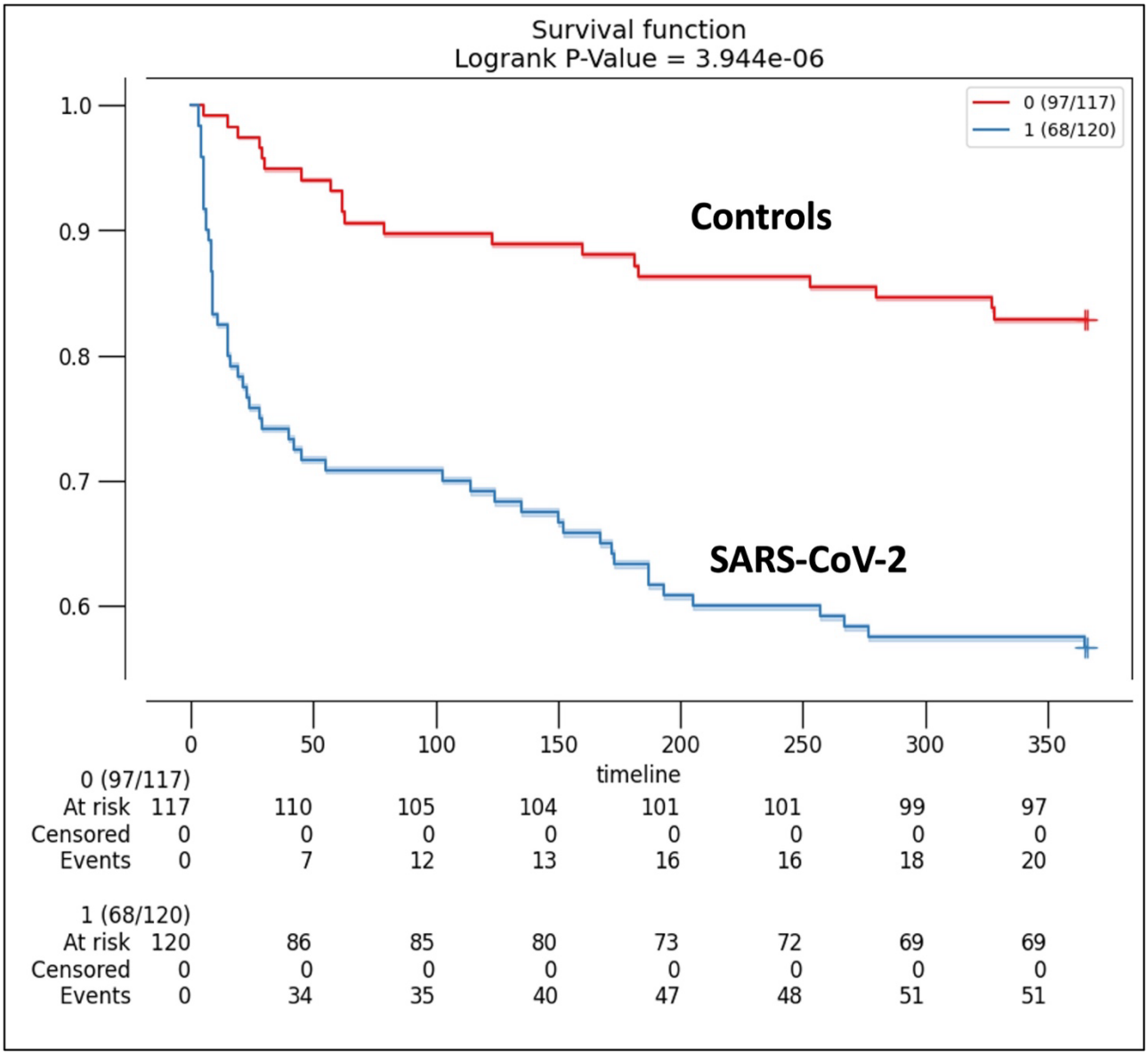

Figure 4: Kaplan-Meier survival analysis comparing mortality from the time of hospital admission for acute exacerbation of COPD to 12 months after in the two groups of patients with and without SARS-CoV-2 infection (respectively blue and red line).

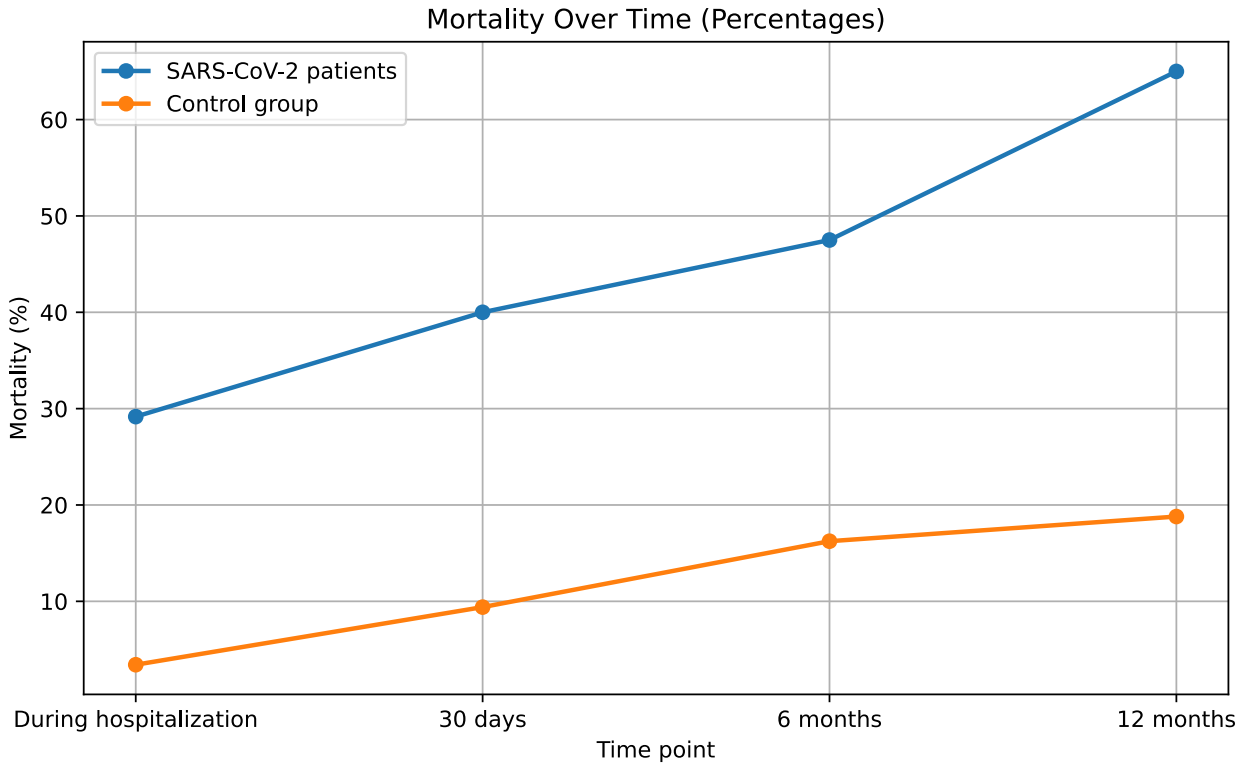

Figure 5: cumulative mortality rate for acute exacerbation of COPD during hospitalization, at 30 days, 6 months and 12 months in the two groups of patients with and without SARS-CoV-2 infection.

Time interval	**SARS-CoV-2 (n = 120)**	**Control (n = 117)**	**p-value**
During hospitalization	35/120 (29.17%)	4/117 (3.42%)	**< 0.0001**
At 30 days	13/85 (15.29%)	7/113 (6.19%)	0.06
At 6 months	9/72 (12.50%)	8/106 (7.55%)	0.33
At 12 months	21/63 (33.33%)	3/98 (3.06%)	**< 0.0001**

Table 4: mortality rate at different time points from the hospitalization for acute exacerbation of COPD (during hospitalization, at 30 days, 6 months and 12 months) in the two groups of patients with and without SARS-CoV-2 infection.

4. Number of COPD exacerbations and hospitalizations

The total number of COPD exacerbations and hospitalizations for COPD exacerbations were compared between COPD patients with and without SARS-CoV-2 infection. On average, COPD patients in the SARS-CoV-2 group had 1.96 exacerbations in the period of follow up with 1.85 hospitalizations, which were significantly lower than the control group (respectively 3.15 and 2.80). When limiting the analysis in the last 24 months preceding the end of the last follow-up visit, these differences were still evident, with a mean number of exacerbations in the SARS-CoV-2 group of 1.51 and 1.46 hospitalizations, while in the control group, there were 2.18 exacerbations with 1.96 hospitalizations (Table 5).

Event number, mean (SD)	**SARS-CoV-2**	**Control**	**p-value**
Total number of COPD exacerbations	1.96 (1.79)	3.15 (2.71)	**0.0001**
COPD exacerbations in the last 24 months	1.51 (1.04)	2.18 (1.61)	**0.0001**
Total number of hospitalizations for COPD exacerbation	1.85 (1.73)	2.80 (2.46)	**0.0007**
Hospitalizations in the last 24 months for COPD exacerbation	1.46 (0.98)	1.96 (1.43)	**0.002**

Table 5: comparison of number of COPD exacerbations and hospitalizations in the SARS-CoV-2 and control patients. SD: standard deviation.

5. Frequency of emphysema and impact on severity of exacerbation

The presence of emphysema was assessed in 177 patients (78 in the SARS-CoV-2 group, 99 in the control group) who had at least one chest HRCT performed during hospitalization or in the past five years. No significant difference (p = 0.866) was observed in the frequency of emphysema across the groups (58.97% in SARS-CoV-2 group vs 56.57% in control group).

Independently from the presence or absence of SARS-CoV-2 infection, patients were then stratified for the severity of the acute COPD exacerbation, according to an empiric scale based on the maximum ventilatory support required. 176 patients (1 missing value) were thus categorized according to these 6 strata: no respiratory support was required; O2 low-flow nasal cannula; O2 MV; HFNC; C-PAP; NIV. Results are reported in table 6. The distribution of COPD exacerbation severity did not differ significantly between patients with and without emphysema (Pearson chi-square test, p = 0.90).

COPD exacerbation severity group	Frequency (n, %)	Emphysema (n, %)	No Emphysema (n, %)
No oxygen support	3 (1.70)	1 (33.33)	2 (66.67)
LFNC	50 (28.41)	30 (60.00)	20 (40.00)
VM	11 (6.25)	5 (45.45)	6 (54.55)
HFNC	14 (7.95)	8 (57.14)	6 (42.86)
C-PAP	19 (10.80)	10 (52.63)	9 (47.37)
NIV	79 (44.89)	48 (60.76)	31 (39.24)

Table 6: Distribution of emphysema according to the adopted scale for the severity of COPD exacerbation. LFNC: low flow nasal cannula; VM: Venturi mask; HFNC: high flow nasal cannula; C-PAP: continuous positive airway pressure; NIV: Non-Invasive Ventilation

6. Length of hospitalization according to the presence of SARS-CoV-2 infection and COPD exacerbation severity

Median length of hospitalization in the SARS-CoV-2 group (12 days, IQR 7.5–24.5) was significantly longer ($p < 0.01$) than in the control group (9 days, IQR 7–14.25), as displayed in figure 6.

The length of hospitalization (i.e. the number of in-hospital days) was then compared between patients stratified by the presence of SARS-CoV-2 infection (factor 1) and COPD exacerbation severity (factor 2), according to the already adopted empiric scale based on the maximum ventilatory support required. Data from 233 patients were available for the analysis, once excluding those with missing values. Aligned Rank Transform (ART), followed by ANOVA test were applied to evaluate the effect of each factor and the combined effect. Both the presence of SARS-CoV-2 and the severity of exacerbation independently had a significant impact on the length of hospitalization (expressed as number of days), respectively $p = 0.0076$ (factor 1) and $p = 0.0021$ (factor 2). However, the interaction between factors was not statistically significant ($p = 0.568$), suggesting that their effects do not depend on one another.

Moreover, among patients requiring LFNC and NIV, SARS-CoV-2 infection was associated with a significantly longer length of hospital stay, with moderate effect sizes ($p = 0.02$, Cohen's $d = 0.56$ and $p = 0.03$, Cohen's $d = 0.48$, respectively) (Table 7 and Figure 7-8). In the remaining subgroups, effect sizes ranged from negligible to moderate but did not reach statistical significance, partly likely due to limited sample size. Indeed, as per bars and whiskers plot, among patients whose exacerbation required up to LFNC and NIV, hospitalizations were significantly longer in the SARS-CoV-2 groups. Effect size was moderately high in the C-PAP group, but with wide CI and low power. Among VM and HFNC groups the effect sizes were restricted and with wide CI meaning low power. Due to limited sample size, no conclusive effect could be determined for the group who did not require oxygen support (Figure 8).

	SARS-CoV-2		Control		
COPD exacerbation severity group	**Frequency (%)**	**Hospitalization - Days, Mean (SD)**	**Frequency (%)**	**Hospitalization - Days, Mean (SD)**	**p-value**
No oxygen support	5/118 (4.24%)	6.0 (2.61)	5/115 (4.35%)	8.2 (4.53)	0.38
LFNC	42/118 (35.59%)	14.48 (11.76)	32/115 (27.83%)	9.25 (5.39)	**0.02**
VM	12/118 (10.17%)	22.42 (14.27)	6/115 (5.22%)	23.33 (28.23)	0.93
HFNC	5/118 (4.24%)	20.2 (10.59)	12/115 (10.43%)	16.42 (15.7)	0.55
C-PAP	19/118 (16.1%)	20.37 (12.84)	3/115 (2.61%)	12.33 (5.44)	0.14
NIV	35/118 (29.66%)	17.94 (12.89)	57/115 (49.57%)	12.75 (8.72)	**0.03**

Table 7: Length of hospital stay (expressed as number of days) according to the adopted scale for the severity of COPD exacerbation. LFNC: low flow nasal cannula; VM: Venturi mask; HFNC: high flow nasal cannula; C-PAP: continuous positive airway pressure; NIV: Non-invasive Ventilation

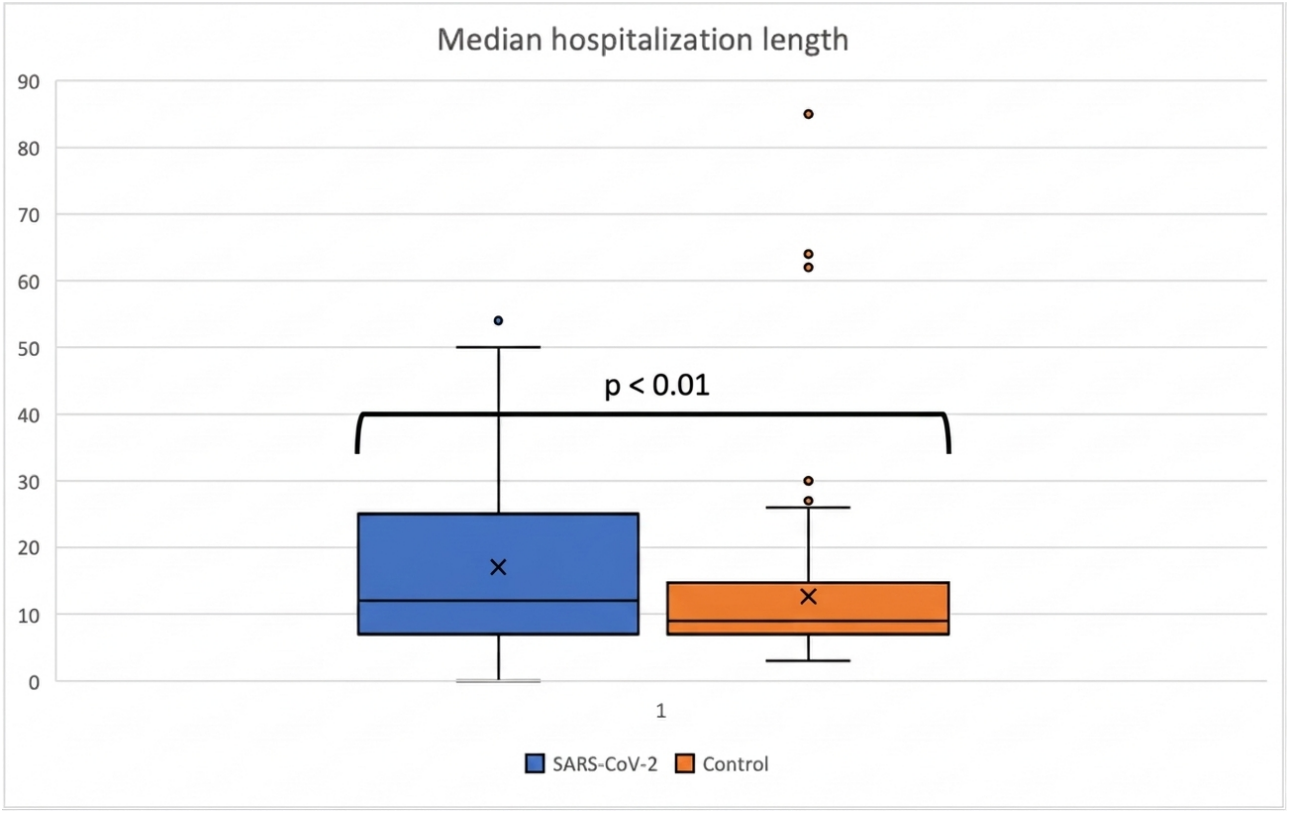

Figure 6: Bars and whiskers plot of the median length of hospital stay (expressed as number of days) in the SARS-CoV-2 and control groups. X represents the mean value.

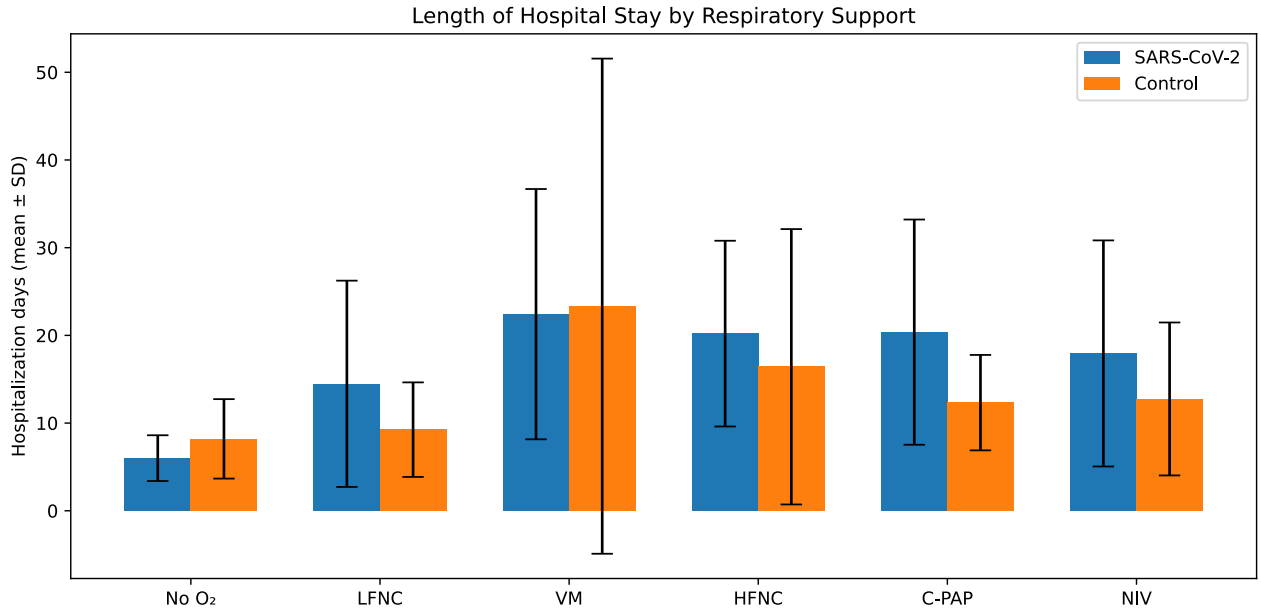

Figure 7: Length of hospital stay (expressed as number of days) according to the adopted scale for the severity of COPD exacerbation. Bars represent mean ± SD. SARS-CoV-2 patients showed longer hospitalization particularly in LFNC and NIV groups. LFNC: low flow nasal cannula; VM: Venturi mask; HFNC: high flow nasal cannula; C-PAP: continuous positive airway pressure; NIV: Non-Invasive Ventilation.

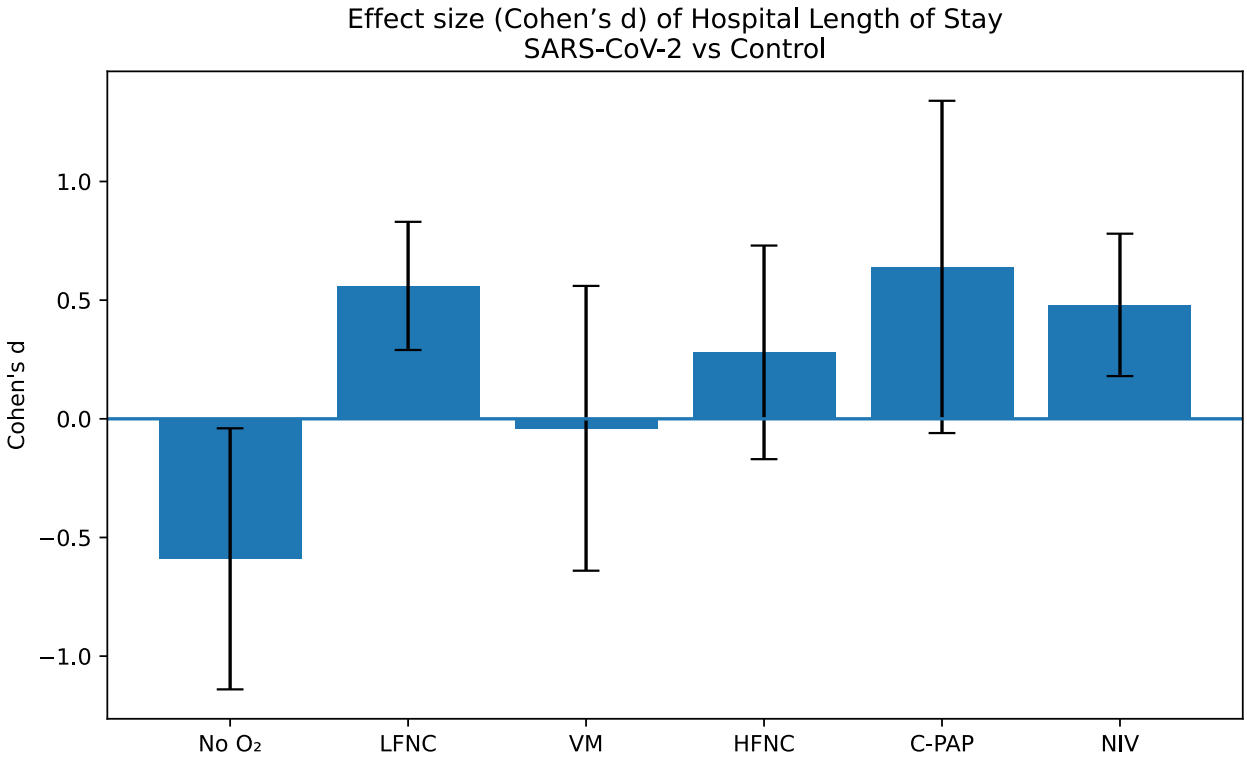

Figure 8: Effect size of hospital length of stay according to the adopted scale for the severity of COPD exacerbation. Bars represent the effect size (Cohen's d) of the difference in the length of hospital stay in SARS-CoV-2 patients when compared to controls. Whiskers represent the approximate 95% CI. Values > 0 stand for longer hospital stay in the SARS-CoV-2 group, while values < 0 for longer hospital stay in the control group. LFNC: low flow nasal cannula; VM: Venturi mask; HFNC: high flow nasal cannula; C-PAP: continuous positive airway pressure; NIV: Non-Invasive Ventilation.

7. Blood gas analysis changes from admission to discharge in patients with and without SARS-CoV-2 infection

Values of the main blood gas analysis (BGA) parameters (pH, PaO_2, $PaCO_2$, HCO3-) were compared between hospital admission and discharge in the two groups (SARS-CoV-2 infection and control patients). A two-way ANOVA with repeated measures was adopted to compare BGA data from multiple measurements on the same individuals (values at admission and discharge) across different groups (SARS-CoV-2 and control), testing the effects of both within-subjects (Time) and between-subjects (SARS-CoV-2 infection) factors, as well as their interaction effect.

At discharge, both groups had a normal pH. A clear reduction in $PaCO_2$ (median $PaCO_2$ at admission 48.7 mmHg, median $PaCO_2$ at discharge 43.0 mmHg) was observed in the control group only, in line with the classic hypercapnic COPD exacerbation responding to treatment. SARS-CoV-2 patients did not show meaningful CO_2 washout, supporting a different pathophysiological profile. Oxygenation (PaO_2) remains largely unchanged in both groups, albeit values at hospital admission were partly influenced by the oxygen support which was promptly started in the Emergency Department. Overall, the within-group analysis showed a significant increase in pH in both SARS-CoV-2 and control patients. A significant reduction in $PaCO_2$ was observed only in the control group, whereas no relevant changes in PaO_2 and HCO3- were detected in either group (Table 8).

When considering the combined effect of both the presence/absence of SARS-CoV-2 infection and time (admission/discharge), a statistically significant impact of the interaction could be demonstrated on pH and PaO2 (Table 9).

	SARS-CoV-2		Control	
Parameter	**Admission, Median (25th-75th percentiles)**	**Discharge, Median (25th-75th percentiles)**	**Admission, Median (25th-75th percentiles)**	**Discharge, Median (25th-75th percentiles)**
pH	7.40 (7.36-7.45)	7.43 (7.40-7.46)	7.37 (7.32-7.41)	7.43 (7.41-7.46)
PaO_2, mmHg	68.50 (59.00-81.25)	67.5 (63.00-83.00)	70.0 (57.92-98.25)	68.3 (62.92-74.25)
$PaCO_2$, mmHg	40.00 (35.95-48.75)	42.3 (37.00-49.00)	48.7 (39.88-60.25)	43.0 (38.22-48.25)
HCO3-, mmol/l	26.00 (23.60-28.00)	27.0 (25.00-31.55)	27.0 (24.88-31.00)	28.25 (26.00-32.00)

Table 8: Comparison of blood gas analysis parameters (pH, PaO_2, $PaCO_2$, HCO3-) between hospital admission and discharge in the two groups (SARS-CoV-2 infection and control patients).

Parameter	**Factor**	**p-value**
pH	SARS-CoV-2/Control	0.134
	Time	**<<0.001**
	Interaction	**0.003**
PaO_2	SARS-CoV-2/Control	0.674
	Time	0.075
	Interaction	**0.0018**
$PaCO_2$	SARS-CoV-2/Control	**0.012**
	Time	0.153
	Interaction	0.254
HCO3-	SARS-CoV-2/Control	0.689
	Time	0.727
	Interaction	0.370

Table 9: Combined effect of the presence/absence of SARS-CoV-2 infection and time (admission/discharge) on the BGA parameters.

8. White blood cells values in patients with and without SARS-CoV-2 infection

Baseline at admission values of white blood cells (WBC), Neutrophils (N) and Lymphocytes (L) were compared in the groups of patients with and without SARS-CoV-2 infection (Table 10). Median value of WBC was significantly higher in controls (p = 0.0002), and this was mainly sustained by neutrophilia (p = 0.001). Albeit not reaching statistical significance, Lymphocytes were generally more reduced in SARS-CoV-2, in line with viral induced lymphopenia. Figure 9 summarizes these results.

Blood exam	**SARS-CoV-2, median (IQR)**	**Control, median (IQR)**	**p-value**
White Blood Cells (10^9/L)	8.2 (6.30-10.85)	11.3 (8.30-14.00)	**0.0002**
Neutrophils (10^9/L)	6.4 (4.00-9.15)	8.15 (5.60-11.88)	**0.001**
Lymphocytes (10^9/L)	1.0 (0.50-1.40)	1.35 (0.80-2.00)	0.48

Table 10: Median level of white blood cells (WBC), Neutrophils (N) and Lymphocytes (L) in the groups of patients with and without SARS-CoV-2 infection.

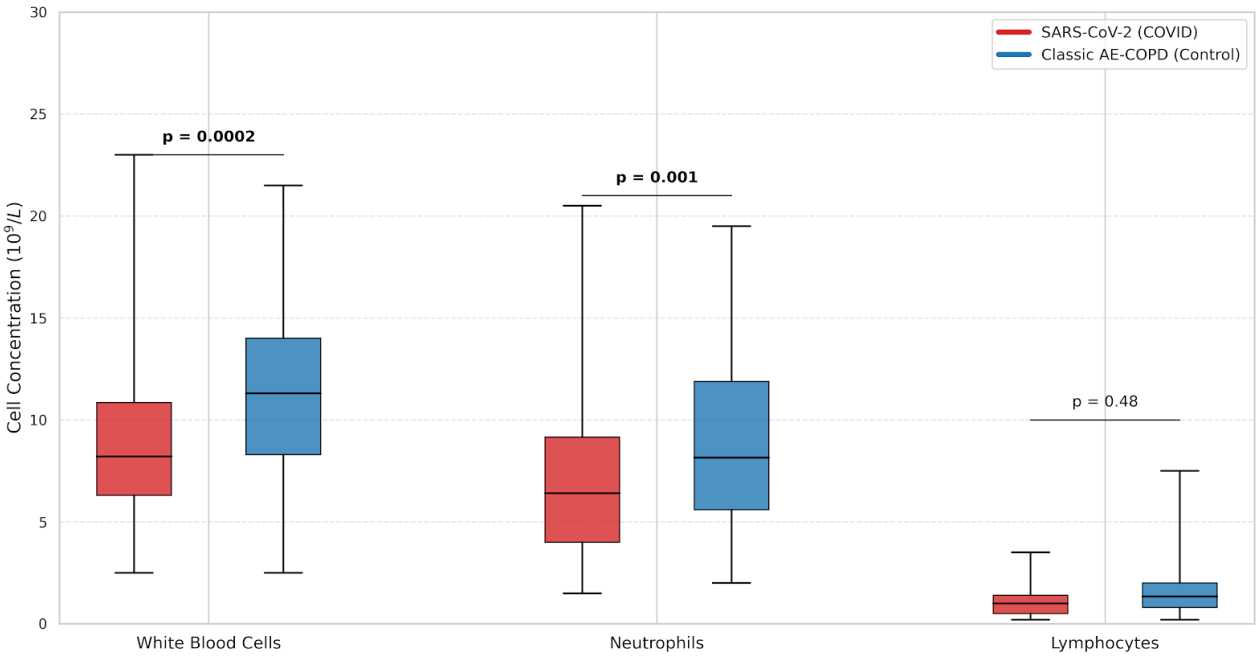

Figure 9: Box and whiskers plots of median levels of white blood cells (WBC), Neutrophils (N) and Lymphocytes (L) in the groups of patients with and without SARS-CoV-2 infection.

9. Association between heart failure and COPD exacerbations

Heart failure (HF) is a common comorbidity in COPD patients. Also in our cohort, as reported above, 40% of patients had HF. Mean values of the severity of COPD exacerbations (as per the previously defined arbitrary scale of severity), total number of exacerbations, total number of exacerbations in the last 24 months, total number of hospitalizations for COPD exacerbation and total number of hospitalizations for COPD exacerbation in the last 24 months were compared between patients with and without HF (Table 11). Only patients with no missing values were included (n = 232). While the severity of COPD exacerbations was comparable between groups, patients with HF had more COPD exacerbations and hospitalizations (both when considering the total number and the last 24 months).

Event number, mean (SD)	**HF**	**No HF**	**p-value**
COPD exacerbation severity group	3.03 (1.81)	3.04 (1.87)	0.97
Total number of COPD exacerbations	3.06 (2.8)	2.32 (2.44)	**0.01**
COPD exacerbations in the last 24 months	2.05 (1.5)	1.78 (1.43)	**0.05**
Total number of hospitalizations for COPD exacerbation	2.89 (2.63)	2.1 (2.28)	**0.01**
Hospitalizations in the last 24 months for COPD exacerbation	1.92 (1.36)	1.65 (1.30)	**0.05**

Table 11: comparison of severity of COPD exacerbations, number of COPD exacerbations and hospitalizations according to the presence or absence of heart failure (HF). SD: standard deviation.

10. Prevalence of viral infections other than SARS-CoV-2 in the control group

The presence of viral infections other than SARS-CoV-2 was tested exclusively in the control group. The first 100 COPD patients admitted to the hospital for acute exacerbation who tested negative for SARS-CoV-2 received a second nasopharyngeal swab (NFS). A specific PCR (Polymerase Chain Reaction) panel for the detection of viral genomes was performed. The test was directed to the identification of the most common viruses which are involved in COPD exacerbations: Human Rhinovirus (HRV), Human coronavirus OC43 (HCV), Influenza A virus (IAV), Human metapneumovirus (MPV), Parainfluenza virus (PIV), Respiratory Syncytial Virus (RSV). Out of 100 NFS, 34 tested positive for the presence of a viral agent, while 66 were negative (Figure 10). The most prevalent virus was Human Rhinovirus, detected in 14 samples (14%), followed by Influenza A virus (8 samples, 8%), Human metapneumovirus (6 samples, 6%), Respiratory Syncytial Virus (3 samples, 3%), Parainfluenza virus (2 samples, 2%), and Human coronavirus OC43 (1 sample, 1%). The limited sample size did not allow for further sub-analysis on the endpoints already covered when considering the whole control group.

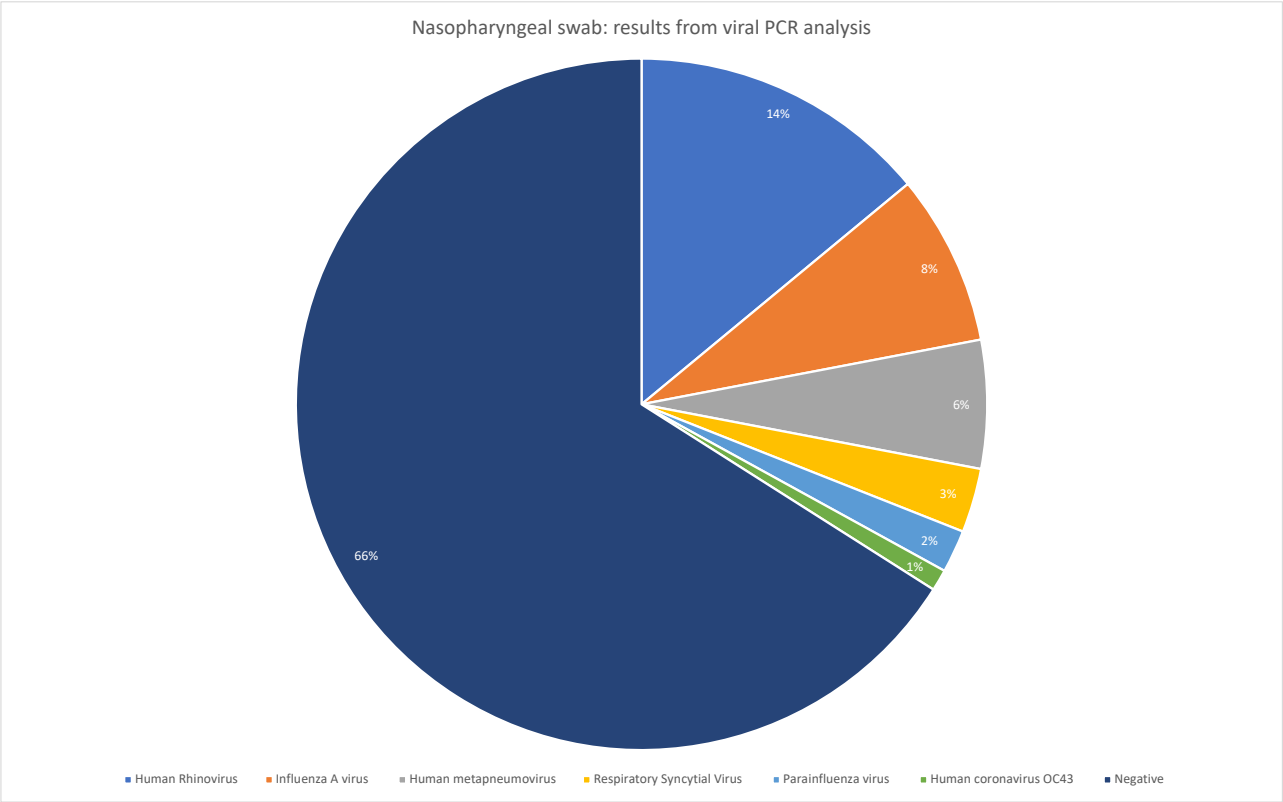

Figure 10: Pie chart of the frequency of viral infections in the group of patients with acute exacerbation of COPD who tested negative for SARS-CoV-2 infections.

DISCUSSION

The present study was primarily aimed to evaluate clinical outcomes and the need for non-invasive respiratory support in COPD patients hospitalized for an acute exacerbation triggered by SARS-CoV-2 infection, compared to a control group of exacerbated COPD patients not related to SARS-CoV-2 infection.

Several studies in the literature have analyzed the impact of COPD as a relevant comorbidity in patients with SARS-CoV-2 infections and pneumonia (102–104). However, until now no studies have focused on the specific role of SARS-CoV-2 infection on patients hospitalized for acute exacerbation of COPD.

In our study, when compared to controls, COPD patients with a SARS-CoV-2 infection received a COPD diagnosis later, were older at the time of the exacerbation for which they entered the study and showed a more severe exacerbation. On the contrary, COPD controls have experienced in their life more episodes of exacerbations and hospitalizations than those in SARS-CoV-2 group, which can be related to the longer history of disease. These results might suggest that SARS-CoV-2 patients had a distinct clinical phenotype than controls, due to a possible "survivor effect": older patients with late-onset COPD might had survived other less noxious infections previous than SARS-CoV-2. Of note, patients in the SARS-CoV-2 cohort were more exposed than controls to smoke, as reflected by the higher number of pack-years smoked. Since control patients had received a COPD diagnosis earlier in life, they might have had a reduced smoke exposure. On the contrary, the high cumulative tobacco exposure might have predisposed older SARS-CoV-2 patients to more severe outcomes when infected. As reported in the literature, cigarette smoke induces chronic inflammatory remodeling of the airways and enhances the susceptibility to SARS-CoV-2 infection by the increase of alveolar macrophages expression of ACE2 (Angiotensin converting enzyme type 2), which is used by the virus to infect respiratory system cells and to induce cytokine storm (105,106).

Well documented comorbidities in COPD patients as depression and pulmonary hypertension (107,108) were present in our cohort. Systemic hypertension was prevalent in the SARS-CoV-2 cohort. This can be a consequence of the dysregulated ACE2 pathway. As a matter of fact, COPD patients with chronic hypertension are often treated with drugs like ACE inhibitors and sartans which cause hyper-expression of tissue ACE2. SARS-CoV-2 can more easily infect cells through the hyper-expressed ACE2, thus COPD patients with hypertension might be more susceptible to SARS-CoV-2 infection. Moreover, once the virus has entered the cells, the subsequent viral-induced downregulation of these receptors leads to an accumulation of Angiotensin II and consequent uncontrolled hypertension and pulmonary inflammation (109–111).

A crucial goal of our study was to evaluate the risk of respiratory failure in the two groups of exacerbated COPD patients and to compare the need of non-invasive ventilatory supports. The results clearly showed that the absolute risks of respiratory failure were similar between groups (60.5% for SARS-CoV-2 group and 67.8% for the control group). Noteworthy, the groups significantly differed for the maximal respiratory support needs, a surrogate of the severity of exacerbation. When compared to controls, the relative risk of CPAP as maximal respiratory support was 4.42 in the SARS-CoV-2 group. These patients had consequently a 342% higher risk of requiring C-PAP. On the contrary, the risk of needing NIV or HFNC as maximal respiratory support was respectively 39% and 64% lower in SARS-CoV-2 group than controls. A minority of patients in both groups were maximally treated with VM without significant differences.

When looking at the variations of blood gas analysis from admission to hospital discharge in the two groups, SARS-CoV-2 triggered exacerbations were not characterized by hypercapnia. COPD controls, on the contrary, significantly improved $PaCO_2$ from admission to hospital discharge. These results supported the evidences on hypoxic respiratory failure as hallmark of SARS-CoV-2 induced infection (112-114) and are consistent with the different type of respiratory failure observed in the two groups, i.e. hypoxic respiratory failure in the SARS-CoV-2 group and hypercapnic respiratory failure in COPD exacerbations not related to SARS-CoV-2 infection. According to the literature,

hypercapnic respiratory failure is a strong indication for NIV (115). NIV is considered the "gold standard" ventilatory support therapy for hypercapnic respiratory failure in acute exacerbation of COPD to offload work of breathing and clear CO_2, while it can be less effective in pure hypoxemia where the primary issue is to restore oxygenation (115). SARS-CoV-2-related respiratory failure is more often characterized by hypoxia without hypercapnia, and CPAP may be an appropriate treatment.

While several reports in the literature support the use of CPAP in hypoxemic respiratory failure secondary to SARS-CoV-2 induced pneumonia (116), the lack of data on how to treat respiratory failure in COPD exacerbations triggered by SARS-CoV-2 can find some evidence from the results of the present study. More in details, SARS-CoV-2 seemed to induce intrapulmonary shunting and ventilatory-perfusion mismatch much more than bronchi inflammation and bronchospasm. It has also to be considered that in our study, SARS-CoV-2 patients were heavier smokers than controls with increased endothelial damage and reduction in the efficiency of the alveolar-capillary membrane. As known from the literature, since SARS-CoV-2 can cause micro-thrombosis, alveolar edema and downregulation of ACE2 and subsequent microvascular injury, these patients had reduced reserves, justifying the need for high-pressure PEEP (C-PAP) to recruit remaining alveoli (117,118). While the control group followed the classic hypercapnic model of acute exacerbation of COPD responsive to NIV, the SARS-CoV-2 cohort exhibited a sort of "pneumonic" phenotype which required higher mean airway pressures provided by helmet CPAP to overcome intrapulmonary shunting (119). This could explain the higher risk of C-PAP requirement as primary intervention to maintain oxygenation in the absence of significant hypercapnia.

Our study demonstrated that SARS-CoV-2 infection significantly impacted the survival trajectory of COPD patients hospitalized for an acute exacerbation. While in-hospital mortality in COPD patients without SARS-CoV-2 infection was 3.42%, in line with previous reports in the literature (120–124), SARS-CoV-2 patients mortality reached 29.17%. This finding could partly align with established evidence that viral infections can induce systemic inflammation and accelerate the shift from acute

to chronic respiratory failure (122) and that SARS-CoV-2 infection leads poorer short-term outcomes (123). When all-cause mortality was analyzed by time intervals, SARS-CoV-2 infection was associated with significantly higher mortality, not only during hospitalization but also between 6 and 12 months from the exacerbation. On the contrary, mortality rates did not significantly differ between discharge and 30 days and between 30 days and 6 months. A bimodal mortality risk could thus be identified: early-term (during exacerbation) and between 6 and 12 months. Noteworthy, the late-term divergence in mortality between 6 and 12 months post-discharge, following a period of relative stability between 30 days and 6 months, could suggest that, while survivors of the acute phase might have achieved temporary clinical compensation, they remained at high risk for "late-onset" mortality. This might be linked to the prolonged inflammatory state which is one of the manifestations of the so called "Long COVID", with the consequent increase in cardiovascular risk and lung function decline, especially among respiratory patients (124,125). Furthermore, the Kaplan-Meier survival curves demonstrated a net separation, which is well evident since the first days of hospitalization. This suggests that SARS-CoV-2 did not just induce a transient complication in the acute exacerbation of COPD but led to permanent functional decline. Unlike bacterial exacerbations of COPD, where the risk profile often stabilizes after 90 days from the exacerbation, these data indicate that among survivors of SARS-CoV-2 induced COPD exacerbation a sustained frailty syndrome continued (126). For those with a history of SARS-CoV-2 induced COPD exacerbation, follow-up and multiorgan watchful clinical monitoring should be prolonged at least for the first year after discharge (127,128). The presence of emphysema at CT did not significantly differ between groups in our study. This result could support the balance of the groups for a relevant pathological phenotype of COPD. Interestingly, while emphysema is traditionally associated with poor outcomes in COPD and respiratory infections, its equal distribution in the groups suggests that the higher mortality observed in the SARS-CoV-2 group, even outside the acute phase, was predominantly driven by the systemic viral impact, instead that by structural emphysematous lung destruction (88,128).

In our cohort, SARS-CoV-2 infection significantly extended the hospital stay, with a median difference of 3 days (12 days vs 9 days) when compared to controls. This finding suggests that SARS-CoV-2 effect was more harmful than other viral or bacterial triggers. It aligns to previous studies in the literature (104), which found that patients with COPD and SARS-CoV-2 pneumonia had longer hospital stay (15 vs 5 days) then patients with COPD and non-SARS-CoV-2 community acquired pneumonia. Moreover, length of hospitalization was independently impacted by SARS-CoV-2 infection and the severity of COPD exacerbation. The presence of SARS-CoV-2 infection might have added an independent and fixed effect on the length of hospital stay, regardless of the severity of COPD exacerbation. When the hospital length in the two groups was stratified per required respiratory support, SARS-CoV-2 impact was noticeable among patients requiring NIV and LFNC, though with moderate effect size (Cohen's d values 0.48 and 0.56 respectively). No significant effect was noted in C-PAP, HFNC and VM groups, albeit these results should be interpreted with caution, due to limited power of the study for this exploratory analysis.

Our study demonstrated that, also in the context of COPD, the inflammatory alveolar damage and the microvascular injury secondary to SARS-CoV-2 induced cytokine storm seemed to act as the prevalent mechanism, superseding the more common obstructive ventilatory defect which might be expected during COPD exacerbation (110–114). Moreover, when considering the combined effect of both the presence/absence of SARS-CoV-2 infection and time (admission/discharge) on blood gas analysis variations, a statistically significant impact of the interaction could be demonstrated for pH and PaO2. More in details, while pH values at discharge were normal in each group, acid-base balance followed different compensative roots, namely a correction of the respiratory acidosis in controls, and an improvement in the metabolic component parallel to infection resolution in the SARS-CoV-2 cohort. Similarly, PaO_2 improvement was likely due to resolution of the alveolar and microvascular damage in SARS-CoV-2 group and to enhanced lung parenchyma recruitment after bronchodilation and pressure support in the control group (119,129).

At admission, differences between groups were also evident in the hematological profile, particularly in the median count of WBC. Viral induced COPD exacerbations, as in SARS-CoV-2 classic pneumonia, were characterized by lymphocytes reduction due to cytotoxic effect exerted by the virus and the T-cells sequestration in the lung (130–132).

Finally, we have analysed two aspects frequently investigated in COPD cohorts: the impact of heart failure and the prevalence of respiratory virus infections (apart from SARS-CoV-2).

The study confirmed an appreciable prevalence of heart failure of 40%, in line with the well described cardiovascular damage observed in COPD patients (133). Heart failure was associated with a higher frequency of total and recent (in the last 24 months) COPD exacerbations and hospitalization for COPD exacerbations. In this sense, heart failure has been linked to worse clinical management of COPD patients, whose mortality often depend to cardiovascular events (134,135).

The screening for the presence of respiratory viruses other than SARS-CoV-2 in our control group identified a prevalence of 34%, which is in line with reports from the literature in the pre-SARS-CoV-2 pandemic era (136–138). This can be also considered helpful in further validation of the cohort as a more rigorous control for the SARS-CoV-2 group, since more than 30% of patients were experiencing exacerbation due to viral infection. Human Rhinovirus was the most prevalent virus in the cohort (14%) followed by Influenza A virus (8%), which is consistent with the literature, where Rhinovirus is considered the most common viral trigger, followed by seasonal peaks for Influenza A (64,139,140). Notably, since more than 30% of controls were affected by a viral exacerbation, this result suggests once more that SARS-CoV-2 was able to induce a more severe form of COPD exacerbation, which reflected for example in the longer hospital stay. Human Rhinovirus, Influenza A and the other more common viral triggers tent to induce upper airway and subsequently bronchial epithelial inflammation and bronchospasm, whereas SARS-CoV-2 more likely damaged lung parenchyma (64,141,142). It has also to be considered that our results might partly be influenced by the post pandemic period when the data of controls were collected. During SARS-CoV-2 pandemic the commonly hygienic rules massively adopted by the population, like wearing protective masks,

frequently washing hands and the social distancing, reduced the circulation of common viral agents, and this reflected in a drastic reduction in the admission for COPD exacerbation triggered by viral agents other than SARS-CoV-2. Despite the pandemic effect, in the early post pandemic era, we detected a rate of viral induced exacerbation similar to the pre-SARS-CoV-2 era, though some viral agents, as Respiratory Syncytial Virus, Parainfluenza virus and other coronavirus were rarely present and seemed to reflect a change in the viral ecology, as an effect of the SARS-CoV-2 prevalent circulation.

Since respiratory viral infections are still a major cause of COPD exacerbations, antiviral strategies might play a key preventive role. Vaccinations against SARS-CoV-2, influenza and RSV are recognized as effective in reducing the risk of AE-COPD and consequent mortality (143–145). Moreover, targeting host entry receptors represents a fascinating antiviral strategy because it interferes with the infection process at an early, upstream stage of the viral life cycle. In this sense, innovative therapeutic modalities such as nucleic acid aptamers are under investigation. Aptamers can exert their antiviral activity primarily through steric hindrance, thereby blocking virus–receptor interactions without activating downstream signalling pathways or altering host protein function. Two ACE2-targeting aptamers have been successfully isolated and shown to effectively counteract ACE2-dependent coronavirus infection (87). Notably, the same approach may be extended to other clinically relevant respiratory viruses. Aptamers targeting HRV host receptor, the intercellular adhesion molecule 1 (ICAM-1), which is abundantly expressed on airway epithelial cells, are under investigation as part of the same PNRR Project of the present study. Targeting ICAM-1 with high-affinity, non-activating aptamers may therefore represent a promising strategy to broadly inhibit HRV entry while minimizing host-related adverse effects. Overall, host receptor–targeted aptamer therapeutics may constitute a versatile and broadly applicable antiviral platform, particularly suited to counteract highly variable respiratory viruses for which traditional virus-directed strategies, as vaccination, remain insufficient.

The study has some limitations, which might be carefully considered. Firstly, the two cohorts of patients (SARS-CoV-2 and controls) were sequentially enrolled, due to the limited hospital admission for non-SARS-CoV-2 COPD exacerbations during the peak of the pandemic. Nonetheless, the control group was prospectively enrolled and not taken from historic retrospective datasets. Since the enrolment of controls was performed in the early post-pandemic era, this might have had some influence on the viral ecology, albeit frequencies of the most common virus (i.e. Human Rhinovirus and Influenza A) were comparable to those reported in the literature from pre-pandemic studies.

The groups were well matched for main demographic and clinical characteristics, but SARS-CoV-2 patients showed a more consistent tobacco exposure, as previously discussed. This might have partly influenced the susceptibility to the virus and the mortality, acting as a confounder.

Finally, the evolving knowledge of the pathophysiology of the infection and the availability of medical resources might have partly influenced the use of different ventilatory support strategies during the peak phases of the pandemic.

CONCLUSIONS

Our study pinpointed that SARS-CoV-2 infection can be considered a potent trigger of COPD exacerbation, able to induce severe hypoxic respiratory failure, which significantly increased the risk of needing positive pressure respiratory support.

Moreover, SARS-CoV-2 profoundly impacted on the mortality (both in-hospital and between 6 and 12 months post-discharge), meanwhile prolonging the length of hospital stay.

Screening for the presence of viral triggers, particularly of SARS-CoV-2, in case of acute exacerbation of COPD is key, to influence clinical outcomes, treatment approach and long-term survival.

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