Respiratory Burst Factors in Nigerian Patients with COVID-19

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Abstract: Respiratory burst function resulting in the release of reactive oxygen species from leucocytes is one of the key mechanisms of innate immune system to prevent the establishment of intracellular pathogens in the host cells. Previous studies on COVID-19 patients concentrated on adaptive immunity while study on respiratory burst functions is lacking. Respiratory burst mediators levels [nitric oxide (NO) and hydrogen peroxide (H2O2)] and respiratory burst enzymes activities [Catalase (CAT), Myeloperoxidase (MPO) and Superoxide dismutase (SOD)] were quantitated in the plasma. Mean plasma NO level, MPO activity and H2O2 level were significantly increased while SOD activity was significantly increased in COVID-19 patients at admission compared with control. Mean plasma NO level significantly decreased while MPO activity was significantly increased in COVID-19 patients at discharge compared with control. Plasma NO level, H2O2 level and MPO activity were significantly increased in COVID-19 patients at discharge compared with COVID-19 patients at admission. In COVID-19 patients that spent ≥10days in admission, the levels of NO and H2O2 were significantly increased compared with the levels of NO and H2O2 in COVID-19 patients that spent <10days in admission. In male COVID-19 patients, NO level and MPO activity were significantly increased compared with MPO activity in female patients. In COVID-19 patients ≥40years of age, NO level was significantly decreased while MPO activity was significantly increased compared with COVID-19 patients <40yrs of age. In male COVID-19 patients, NO level and MPO activity was significantly increased compared with MPO activity in female patients. It could be concluded from this study that factors of respiratory burst which are components of the innate immune system are altered in COVID-19 patients and could be involved in the immune-pathogenicity of SARS-CoV-2; and that MPO coupled with NO may explain differential severities of COVID-19 among genders and age groups.

INTRODUCTION

Studies to understand SARS-CoV-2-host interaction to reduce COVID-19 disease burden are continuous (WHO, 2020; Li et al., 2020). Adaptive immune responses to prevent the spread and pathophysiology of SARS-CoV-2 have been extensively studied (Arinola et al., 2020 and 2021). Adaptive immunity is next to innate immunity in the sequences of natural sequelae of immunity (Arinola, 2003). Therefore, assessment of innate immune response such as respiratory burst functions, which is the first immune response to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is important. The outcome may be lead to recommendation that will improve the management of COVID-19 patients. In a mini-review (McKechnie and Blish, 2020), the importance of innate immune factors during SARS-CoV infection was extensively discussed but studies therein and in other literatures (Qin et al., 2020; Lin et al., 2020) concentrated on cytokine levels and leucocyte numbers neglecting respiratory burst functions. Innate immune factors are chemical, cellular and mechanical/physical barriers that prevent entry and establishment of foreign materials, determine the course of adaptive immunity, secrete proinflammatory cytokines and recruit other immune cells to the site of infection (Arinola, 2003).

The first step in SARS-CoV-2 infection is binding to a host airway epithelial cells through angiotensin-convverting enzyme 2 (ACE 2) (Lipsitch et al., 2020; Xu et al., 2020) leading to destruction of lung cells which triggers recruitment of macrophages and monocytes, release of cytokines, and priming of adaptive T and B cell immune responses (Pung and Liu, 2019). In most individuals, recruited cells clear the infection in the lung and patients recover. However, in some patients, a dysfunctional immune response occurs trigger a cytokine storm that mediates widespread lung and systemic inflammation (Ruan et al., 2020), excessive secretion of proteases and reactive oxygen species (Xu et al., 2020, Tian et al., 2020, Zhou et al., 2020). Resultant alveolar damage including desquamation of alveolar cells, hyaline membrane formation and pulmonary oedema may lead to leakage of host lung substances and viral proteins into blood circulation (Liao et al., 2020; Zhou et al., 2020). To combat infection and degrade internalized particles such as SARS-CoV-2, phagocytes use NADPH oxidase to reduce O2− to an oxygen free radical and H2O2 (Buckley et al., 2014). Neutrophils and monocytes use myeloperoxidase to produce hypochlorite from reaction of H2O2 with Cl−, which plays a role in destroying phagocytosed microbes (Aratani et al., 2012). Reactive oxygen species were reported to play a role in mitogenic activation, and the early phase of lytic and non-lytic virus infection (Peterhans, 1997).

From above literatures, humoral respiratory burst factors are essential in the control and elimination of SARS-CoV-2, however, imbalance between these factors may result in immunopathology. Gaining a deeper understanding of respiratory burst factors in the hosts during SARS-CoV-2 infection may shed more light on the innate aspect of immunity in COVID-19 patients. In this study, we provided information on the plasma levels of respiratory burst factors [nitric oxide (NO) and hydrogen peroxide (H2O2)] and respiratory burst enzymes activities [Catalase (CAT), Myeloperoxidase (MPO) and Superoxide dismutase (SOD)] in COVID-19 patients at admission and at discharge in relation to gender and age.

MATERIALS AND METHODS

Participants

This study comprised of 35 SARS-CoV-2 infected- and 20 healthy- Nigerian adults. The COVID-19 cases were confirmed by detection of SARS-CoV-2 nucleic acid using real-time reverse-transcriptase polymerase-chain reaction (RT-PCR) assay
in nasal and pharyngeal swab specimens following the World Health Organization (WHO) recommended guidelines apart from clinical signs of dry cough, high fever, sore throat and shortness of breath. The participants did not have hypertension, diabetes mellitus, cardiovascular disease, cerebrovascular disease, cancer, sickle cell disease, chronic renal disease or parasitic infections. Also excluded were those that drink alcoholic beverages or cigarette smokers.

**Plasma Isolation**
Plasma was obtained from 10ml whole blood collected in a test tube containing lithium heparin anticoagulant by centrifuging at 1500 g for 10 minutes.

**Superoxide Dismutase (SOD) activity determination**
The SOD activity was determined as previously described (Edem and Arinola 2015). This method is based on the principle that SOD inhibits the autoxidation of epinephrine at pH 10.2.

**Catalase (CAT) activity determination**
Catalase activity was determined using the method as previously described (Edem and Arinola, 2015). This method is based on the principle that dichromate in acetic acid is reduced to chromic acetate when heated in the presence of H2O2. The principle that dichromate in acetic acid is reduced to chromic acetate then produced is measured at 570 nm.

**Myeloperoxidase (MPO) activity determination**
MPO activity was determined as previously described (Edem and Arinola, 2015). The rate of decomposition of H2O2 by peroxidase, with guaiacol as hydrogen donor, produced tetraguaiacol which was measured at 436 nm.

**Hydrogen peroxide determination**
Hydrogen peroxide concentration was determined as previously described (Edem and Arinola, 2015). The assay is based on peroxide-mediated oxidation of Fe3+, followed by the reaction of Fe3+ with xylanol orange to form Fe2+ xylanol orange complex with an absorbance maximum of 560 nm. Plasma H2O2 was determined by comparing absorbance with standard solutions of H2O2.

**Nitrile oxide (NO) determination**
Plasma nitric oxide concentration was determined using Griess reagent (Sulphanilamide and N-1-naphthylethylene-diamine dihydrocholoride) as previously carried out (Edem and Arinola, 2015). The assay is based on a reaction that utilizes sulphanilamide and N-1-naphthylethylene-diamine dichlorohydrolide (NED) under acidic (phosphoric acid) conditions. Nitric forces formed chromophore with reagent, with an absorbance maximum at 540nm.

**Statistical Analysis**
Data obtained were presented as Mean ± S.D. The Student t-test was used to compare the mean values of age, SOD, MPO, CAT, NO and H2O2. Values were considered statistically significant at p ≤ 0.05.

**RESULTS**
Mean plasma NO level, MPO activity and H2O2 level were significantly decreased while SOD activity was significantly increased in COVID-19 patients at admission compared with control (p=0.000 in each case)(Table 1). In Table 2, mean plasma NO level significantly decreased (p=0.040) while MPO activity (p=0.010) was significantly increased in COVID-19 patients at discharge compared with control. Plasma NO level, H2O2 level and MPO activity were significantly increased in COVID-19 patients at discharge compared with COVID-19 patients at admission (p=0.013, p=0.010 and p=0.000 respectively)Table 3). In COVID-19 patients that spent ≥10days in admission, the levels of NO and H2O2 were significantly increased compared with the levels of NO and H2O2 in COVID-19 patients that spent <10days in admission (p=0.005 and p=0.006 respectively) (Table 4). In COVID-19 patients ≥24years of age, NO level was significantly decreased (p=0.015) while MPO activity was significantly increased (p=0.008) compared with COVID-19 patients <40yrs of age (table 5). In male COVID-19 patients, NO level (p=0.000) and MPO activity (p=0.050) were significantly increased compared with MPO activity in female patients (Table 6).

**Table 1:** Mean Plasma Levels of Nitric oxide and Hydrogen peroxide, and activities of Myeloperoxidase, Catalase and Superoxide dismutase in COVID-19 patients admitted with control

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n=20)</th>
<th>COVID-19 patients (n=35)</th>
<th>t-values</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO (μmol/L)</td>
<td>1.22±0.01</td>
<td>1.99±0.17</td>
<td>2.809</td>
<td>0.013*</td>
</tr>
<tr>
<td>MPO (U/mg protein)</td>
<td>1.90±0.01</td>
<td>2.06±0.09</td>
<td>0.849</td>
<td>0.402</td>
</tr>
<tr>
<td>MPO (U/mg protein)</td>
<td>1.16±0.15</td>
<td>0.83±0.07</td>
<td>3.688</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

*Significant at p ≤ 0.05.

**Table 2:** Mean Plasma Levels of Nitric oxide and Hydrogen peroxide, and activities of Myeloperoxidase, Catalase and Superoxide dismutase in COVID-19 patients at discharge compared with control

<table>
<thead>
<tr>
<th>Variables</th>
<th>COVID-19 patients (At Discharge) (n=35)</th>
<th>Control (n=20)</th>
<th>t-values</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO (μmol/L)</td>
<td>1.24±0.15</td>
<td>1.22±0.15</td>
<td>0.234</td>
<td>0.817</td>
</tr>
<tr>
<td>MPO (U/mg protein)</td>
<td>1.13±0.39</td>
<td>1.12±0.21</td>
<td>0.258</td>
<td>0.800</td>
</tr>
<tr>
<td>MPO (U/mg protein)</td>
<td>0.96±0.09</td>
<td>0.94±0.09</td>
<td>0.285</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

*Significant at p ≤ 0.05.

**Table 3:** Mean Plasma Levels of Nitric oxide and Hydrogen peroxide, and activities of Myeloperoxidase, Catalase and Superoxide dismutase in COVID-19 patients admitted with control

<table>
<thead>
<tr>
<th>Variables</th>
<th>COVID-19 patients (At Admission) (n=35)</th>
<th>COVID-19 patients (At Discharge) (n=35)</th>
<th>t-values</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO (μmol/L)</td>
<td>1.38±0.23</td>
<td>1.74±0.20</td>
<td>3.754</td>
<td>0.005*</td>
</tr>
<tr>
<td>MPO (U/mg protein)</td>
<td>1.22±0.24</td>
<td>7.85±2.24</td>
<td>3.555</td>
<td>0.006*</td>
</tr>
<tr>
<td>MPO (U/mg protein)</td>
<td>1.98±0.01</td>
<td>1.98±0.01</td>
<td>0.485</td>
<td>0.632</td>
</tr>
<tr>
<td>MPO (U/mg protein)</td>
<td>1.13±0.39</td>
<td>1.22±0.21</td>
<td>0.254</td>
<td>0.817</td>
</tr>
</tbody>
</table>

*Significant at p ≤ 0.05.

**Table 4:** Mean Plasma Levels of Nitric oxide and Hydrogen peroxide, and activities of Myeloperoxidase, Catalase and Superoxide dismutase in COVID-19 patients ≥24 years of age compared with COVID-19 patients <40 years of age

<table>
<thead>
<tr>
<th>Variables</th>
<th>COVID-19 patients ≥24yrs of age (n=22)</th>
<th>COVID-19 patients &lt;40 yrs of age (n=7)</th>
<th>t-values</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO (μmol/L)</td>
<td>1.24±0.23</td>
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<td>3.754</td>
<td>0.005*</td>
</tr>
<tr>
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</tr>
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<td>MPO (U/mg protein)</td>
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<td>1.22±0.21</td>
<td>0.254</td>
<td>0.817</td>
</tr>
</tbody>
</table>

*Significant at p ≤ 0.05.

**Table 5:** Mean Plasma Levels of Nitric oxide and Hydrogen peroxide, and activities of Myeloperoxidase, Catalase and Superoxide dismutase in male COVID-19 patients compared with female COVID-19 patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Male COVID-19 patients (n=15)</th>
<th>Female COVID-19 patients (n=14)</th>
<th>t-values</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO (μmol/L)</td>
<td>1.38±0.23</td>
<td>7.85±2.24</td>
<td>3.754</td>
<td>0.005*</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

*Significant at p ≤ 0.05.

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DISCUSSION
Previous researches have largely focused on the role of cytokine storm and adaptive immunity in the pathogenesis and management of SARS-CoV-2 infection (Blanco-Melo et al., 2020; Zhou et al., 2020; Li et al., 2020). Moreno, SARS-CoV-2 is known to evade host adaptive immunity through different mechanisms (Blanco-Melo et al., 2020; Zhou et al., 2020). This therefore suggested the need to exploit the potential benefits of early immune function such as humoral respiratory burst factors rather than late-appearing adaptive immune factors in the control of COVID-19. Our present study seeks basis for more targeted management of patients with COVID-19 based on changes in humoral respiratory burst factors.

Leucocyte respiratory burst function is a series of events triggered by phagocytosis or inflammatory mediators which directly converts molecular oxygen to reactive oxygen species such as superoxide anion (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), hypohalous acid (HOCI), hydroxyl radical (OH$_1$), and singlet oxygen. These reactive oxygen species are essential for the killing of microorganisms but are also associated with damage to neighbouring tissues (Aratani et al., 2012; van der Veen et al., 2009). Because viruses replicate in living cells, leucocyte respiratory burst influences the growth of viruses by serving as a host defense mechanism and induces hypoxia (Yoo et al., 2009).

The mean plasma MPO activity, NO and H$_2$O$_2$ levels were significantly decreased in COVID-19 patients at admission compared with COVID-19 free control. During the intracellular killing of phagocytosed microbes, large amount of oxygen is consumed to generate H$_2$O$_2$ through reaction catalysed by SOD (Aratani et al., 2012; Yoo et al., 2009). H$_2$O$_2$ combines with halide ions (i.e. I$^-$, Cl$^-$, Br$^-$) to form a hypohalous acid (e.g. HOCI/HOBr) in the presence of myeloperoxidase. HOCI/HOBr reacts with O$_2^-$ or Fe$^{2+}$ to produce stronger oxidant (hydroxyl radical, -OH). If this reaction is not controlled, high concentrations of O$_2^-$, -OH, HOCI/HOBr and H$_2$O$_2$ may leak into surrounding cells resulting in increased quantities of free radicals (Aratani et al., 2012; van der Veen et al., 2009). It is thus, likely that decreased H$_2$O$_2$ in newly admitted COVID-19 patients compared with controls was due to consumption of H$_2$O$_2$ in the production of hypohalous acid by infected cells to eliminate SARS-CoV-2. Similarly, reduced MPO in admitted COVID-19 patients compared with control was a result of its utilisation during reaction of H$_2$O$_2$ with halide ions in order to generate highly toxic hypohalous acid (HOCI) innately produced as anti-SARS-CoV-2 agent.

Nitrergic NO is produced during intracellular killing by phagocytes and inflammation (Ignarro, 2020). Burak and Ahmet (2020) related decreased endothelial NO production and NO bioavailability with COVID-19 related deaths. It might be explained that reduced NO in our COVID-19 patients at admission and at discharge compared with controls might be due to its utilisation as host immune response to eliminate SARS-CoV-2. Raised NO, H$_2$O$_2$ and MPO in COVID-19 patients at discharge compared with COVID-19 patients at admission was an indication of persistent non-specific stimulation of phagocytic cells and continuous inflammatory responses in SARS-CoV-2 infected patients till discharged. NO was reported to induce tissue damage especially after conversion into peroxynitrite radical (ONOO$^-$), thus elevated NO in COVID-19 patients at discharge compared with the level at admission might be an indication of tissue repair during patients' stay in the ward before discharged. In addition, NO elevation in COVID-19 patients at discharge compared with the level at admission could also be a physiologic response for the relaxation of smooth muscle as previously reported (Ricciardolo et al., 2004) which might be development of effective inflammation. Therefore, MPO activity and levels of NO or H$_2$O$_2$ may be used to differentiate newly admitted COVID-19 patients from discharged patients.

Binding of NO with heme moiety of its receptor (guanylate cyclise) significantly increases enzymatic conversion of guanosine-5'-triphosphate to cyclic guanosine monophosphate, which subsequently promotes vasorelaxation. Nitric oxide in the blood stream rapidly reacts with intra-erythrocytic haemoglobin and the delivery of NO into well-ventilated lung promotes local vasodilatation, induces mild bronchodilatation and inhibits neutrophil-mediated oxidative burst (Griffiths and Evans, 2004). Both endogenous non-enzymatic NO were shown to inhibit SARS-CoV viral replication (Akerström et al., 2005). Infection with SARS-CoV-2 causes a range of cardiopulmonary and vascular complications, ranging from upper respiratory tract symptoms to severe acute respiratory distress syndrome (ARDS), as well as arterial and thromboembolic complications (Oxley et al., 2020; Ye et al., 2020). Therefore, the consumption of NO for vasorelaxation, vasodilatation and inhibition of SARS-CoV-2 replication might have resulted to low level of NO in blood of the COVID-19 at admission compared with control. In patients with SARS, inducible NO was associated with improvements in oxygenation in a severity-matched observational cohort (Chen et al., 2004).

Our present result supports previous report (Alvarez et al., 2020) which suggested that NO could be used early in the course of COVID-19 infection to reduce the need for invasive mechanical ventilation and SARS-CoV-2 replication.

NO is produced by conversion of an amino acid arginine into citrulline using inducible nitric oxide synthase (iNOS) (Olianji and Arinola, 2011; Rodriguez et al., 2003; Ochoa et al., 2001). Hence, decreased NO in COVID-19 patients at admission compared with controls could be linked with arginine insufficiency or utilisation during infection. NO production from arginine by the inducible NO synthase (iNOS) was shown to be essential for native immune responses in many infections and arginine availability is a critical factor for host resistance to infection (Rodriguez et al., 2007). Arginine is known to improve lymphocyte-based immunity, maturation of CD8$^+$ and the proliferation of CD8$^+$ T lymphocytes, lymphocyte differentiation (Rodriguez et al., 2007; Ochoa et al., 2001; Galban et al., 2000) and the reports of clinical trials showed that arginine shortened hospitalizations and decreased infections (Galban et al., 2000).

Reduced arginine availability, either by nutrient deprivation or by specific pathogens significantly blunts the immune response (Morrison, 2010). In addition, lymphopenia present in a significant number of severe COVID-19 patients was strongly linked to arginine and ascorbate deficiencies (Stancious et al., 2020). Therefore, our present result and previous narrations support arginine supplementation during the management of COVID-19 patients. This suggestion calls for determination of mucronittient status in COVID-19 patients to provide evidence-based recommendations to support various calls for mucronittient supplementation as an adjuvant to standard COVID-19 management strategies to improve clinical outcome in COVID-19 patients.

Significantly raised mean plasma MPO activity, NO and H$_2$O$_2$ levels in COVID-19 patients at discharge compared with COVID-19 at admission could be related to on-going destruction of SARS-CoV-2 and persistence of inflammatory responses in discharged COVID-19 patients. Moreno, increased levels of NO and H$_2$O$_2$ in COVID-19 patients that spent >10days on admission compared with those that spent ≤10days on admission might be linked with slow destruction of virus and persistence of tissue damage leading to longer hospital stay.

In male COVID-19 patients, the level of NO and activity of MPO were significantly increased compared with female COVID-19 patients. COVID-19 showed difference in fatality rate between males (2.8%) and females (1.7%) (Epidemiology Working Group, 2020) and higher prevalence in males than females among COVID-19 patients had been reported (Arinola et al., 2021b). This was attributed to the fact that ACE 2 genes are located on the X chromosomes which might have alleles that confer resistance to COVID-19, therefore lower fatality rate in females. Alternatively, the oestrogen and testosterone sex hormones have different immunoregulatory functions, which could influence immune protection or disease severity (Taneja, 2018). It may also be conjectured that raised NO and MPO in
male COVID-19 patients might also have contributed to higher fatality of COVID-19 in males because of excessive production of free radicals and toxic acids. The activity of enzymes (including respiratory burst enzymes) in the body can be changed either by their rate of synthesis and secretion from the organ of expression, the distribution of enzyme within the extracellular compartments or the rate and routes of elimination as well as inactivation (Logsdon, and Li 2013; Schroder and Kaufman 2005). These factors may be influenced by individual variability, gender, diseases, drugs or physical activities (Addo and Alfred, 2014; Diodata, et al., 2001). Emokpae and Aghohgo (2016) reported that the activity of MPO was significantly higher in apparently healthy females compared with males. However, the present study found decreased activity of MPO in female COVID-19 patients compared with male COVID-19 patients. Another viral infection (HIV) caused reduced MPO activity (Emokpae and Aghohgo (2016). It is thus likely that viral infection impacted negatively on MPO.

Other previous study reported that nitric oxide (NO) production is higher in the systemic vasculature of females than males and that NO is important in the control of renal vascular tone and renal hemodynamics (Jilma et al., 1996). Inhibition of NO synthase results in hypertension, increases in renal vascular resistance, and decreases in renal plasma flow (Lahtera et al., 1991) and that estrogen stimulates NO production (Weiner et al., 1994). Nitric oxide synthase activity and NO release response to acetylcyanine infusion have been shown to be higher in females than males (Kauser and Rubanry, 1995). Our present study shows that SARS-CoV-2 infection reverses this normal steady-state phenomenon of NO production probably due to virus effect on estrogen production causing development of hypertension and renal impairment. It will be of interest to determine reproductive hormone profile and renal function parameters in COVID-19 patients.

Ageing can be associated with immunosenescence, which may be one of the factors that predispose older people to severe COVID-19 (Delgado and Mestaba, 2020). Ageing is also linked with an increase in blood concentrations of many inflammatory mediators (inflammaging) which can lead to impairment of acquired immunity and increased risk of chronic diseases (Delgado-Rochea and Mestaba, 2020; Davies, 2016; Gil del Valle et al., 2015). It is well established that antioxidants decreases with accumulation of oxidative damage occurring with ageing process (Davies, 2016; Gil del Valle et al., 2015). It is suggested that age related accumulated oxidative damage and a weakened antioxidant defense system cause a disturbance in the redox balance, resulting in increased reactive oxygen species. Our present study reported increased MPO in COVID-19 patients ≥40 years of age compared with patients <40 years of age. However, decreased NO in COVID-19 patients ≥40 yrs of age may also support increased severity or susceptibility of this age group to SARS-CoV-2 infection. Therefore, ageing is not only associated with alterations in the adaptive immune response, but also with a proinflammatory state in the host. Among hospitalised patients in Ibadan, Nigeria, COVID-19 was found in 39% of patients belonging to <36 years age group (Arinola et al., 2021b).

Collectively, our results suggested endogenous pathway that establishes involvement of humoral respiratory burst functions in host defense and pathogenicity of SARS-CoV-2. Moreover, MPO coupled with NO may explain differential severities of COVID-19 among genders and age groups

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Conflict of Interest: None

REFERENCES:


