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Review

SARS-CoV-2, hemoglobin and protoporphyrin IX: Interactions and perspectives

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ABSTRACT

Background: SARS-CoV-2 attacks hemoglobin through its structural protein ORF3a, dissociating the iron from the heme, as iron is necessary by cell machinery for virus replication. In this process protoporphyrin (PpIX) is released.
Methods: The decrease in the hemoglobin levels observed in patients with Covid-19 is frequently accompanied by an increase in PpIX levels. This evidence was confirmed by the quantification of PpIX by high-performance liquid chromatography (HPLC). PpIX emission is observed in its two characteristic bands at approximately 635 nm and 705 nm.
Results: This paper searches to understand the role of heme and PpIX inside the cells. Perspectives on the use of PpIX fluorescence as a sensor to monitor the presence of SARS-CoV-2 in the tissue, blood, urine, or feces to map the evolution and severity of the disease or to monitor the response of the Covid-19 treatment modalities were described.
Conclusion: Fluorescence spectroscopy could be adopted as an excellent diagnostic technique for Covid-19, of low cost and high sensitivity. This method can potentially be used as a marker to monitor the response to the treatments. Photodynamic and sonodynamic therapies using the endogenous PpIX increased in the acute phase of the disease, could be employed for Covid-19 treatment.

1. Introduction

Methods based on fluorescence are those in which the excitation of a molecule is obtained through photon absorption. In this case, the molecule is promoted to an electronic state of higher energy, which returns to the fundamental state accompanied by the emission of electromagnetic radiation [1].

We can mention some important properties of fluorescence as high sensitivity and low detection limits. Fluorescent measurements usually present low background signals. Fluorophores show characteristic wavelengths of excitation or emission that guarantee selectivity. The instrumental setup is simple with low maintenance and analysis costs when compared with other analytical methods [1].

Fluorescence spectroscopy is particularly important for disease diagnosis [2–10]. The fluorescence emission from different natural fluorophores in biological tissues is obtained by exciting them with ultraviolet or visible light. Examples of tissue fluorophores' contribution to autofluorescence are nucleotides and polynucleotides, nicotinamide adenine dinucleotide (NADH), flavin dinucleotide (FAD), elastin, collagen, tryptophan, and porphyrins [11].

The two most important forms of diagnostic testing available for SARS-CoV-2 are molecular and serological tests. Among those, the serum neutralization assay stands out as the gold standard for evaluation of the effectiveness of neutralizing antibodies (NAbs) against viral infections. Some publications have mentioned the fluorescence method to detect Covid-19. The RT-PCR (reverse transcriptase-polymerase chain reaction) determination of the SARs-CoV-2 is possible by applying an immunochromatographic fluorescence assay [12]. Froggatt et al. developed a fluorescence assay based on a GFP-derived protein [13]. Nars et al. used L-Serine doped QDs for fast detection of Covid-19 [14]. Guo et al. applied quantum dot nanobeads and magnetic Fe_3O_4 nanospheres as a highly sensitive fluorescence-linked immunosorbent assay for the determination of human IgG in serum [15]. Plasmonic biosensing schemes for virus detection were also described [16]. In contrast, our

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paper is specifically directed to the virus determination via porphyrin fluorescence.

The protoporphyrin IX (PpIX) is composed of four pyrrolic rings linked by methylene bridges. Its absorption spectrum has five bands: the most intense band, the Soret band, is in the region of 400 nm, and four extra bands, known as Q bands, which comprise the region between 450 and 750 nm. The PpIX emission is observed in its two characteristic bands at approximately 635 nm and 705 nm [17]. The PpIX tetrapyrrole structure enables chelation with transition metals, for example, iron and zinc to form metalloporphyrins, which perform a variety of biologic functions. Red blood cell zinc protoporphyrin IX (Zn-PpIX) provides a functional measurement of iron deficiency. When iron supply decreased hemoglobin production is restricted [18]. Incrementing of zinc PpIX formation and its fluorescence peak around 590 nm indicates iron deficiency and the development of anemia [18].

In general, fast proliferating cells may accumulate more porphyrins preferentially. Besides porphyria patients, cancer, and atherosclerosis patients present increased PpIX concentration in tissues and blood, and PpIX fluorescence can be applied for these diseases' diagnosis [2,3,19].

This review is going to describe the role of hemoglobin, heme, iron, and PpIX inside the cells. We will also evaluate if PpIX fluorescence could be used for the diagnosis of Covid-19 since an abnormal phenomenon related to hemoglobin dysfunction was observed in the patients with this disease. According to the best of our knowledge, there are no further published or ongoing studies about the link between SARS-CoV-2 and PpIX fluorescence that could become a biosensor of SARS-CoV-2 infection. Therapy approaches using PpIX are going to be described.

2. Covid-19 and red blood cells

Covid-19 is a highly transmitted acute infectious disease caused by the SARS-CoV-2 coronavirus. The viruses are unable to replicate themselves, and it is, therefore, essential to parasitize a cell to replicate themselves. Covid-19 patients with induced pneumonia present as symptoms: fever, dry cough, dyspnea, fatigue, headache, loss of taste or smell, sore throat, and tomography revealing ground-glass opacity in the lungs [20]. This pneumonia was first discovered in December 2019 in Hubei Province, China [20]. In April 2021 more than 141 million people have been infected worldwide and more than 3,000,000 have died.

Viral infections initiate with local invasion of an epithelial or mucosal barrier. Once the virus overcomes the early mechanical barriers, such as cilia, mucus, or skin integrity, it infects the target cell. A typical viral life cycle involves the 1) entrance of the virus into the host cell; 2) translation of viral proteins; 3) replication of the viral genome; 4) assembly of viral particles, and 5) release of the mature virions into the extracellular environment. Once attached the virus penetrates the cell or it fuses itself with the cell membrane, receptor-mediated endocytosis, or non-clathrin-mediated endocytosis [21]. During uncoating, replication, and assembly, the viruses attach to the host cell and incorporate their genetic material into it inducing the cell machinery to replicate the exogenous nucleic acids. During the maturation, the created viruses are released from the host cell, either by causing the cell to break apart waiting for the cell to die or by budding off through the cell membrane.

The SARS-CoV-2 is an enveloped virus of approximately 60–140 nm in diameter [22]. The nucleic acid of SARS-CoV-2 is a positive-stranded RNA. Its structural proteins include spike protein (S), an envelope protein (E), membrane protein (M), and nucleocapsid phosphoprotein. Transcribed non-structural proteins include orf1ab, ORF3a, ORF6, ORF7a, ORF10, and ORF8. Spike proteins, ORF8 and ORF3a proteins are significantly different from other known SARS-like coronaviruses.

The spike protein consists of an extracellular N-terminal, a transmembrane domain (TM) anchored in the viral membrane, and a short tail intracellular C-terminal [23]. The spicules are coated with polysaccharide molecules producing a camouflage, which aids it to avoid the host immune system surveillance during the invasion [24]. A positively charged area, a polybasic cleavage site, was recently discovered, which is located at 10 nm from the exact point that the spicule uses to connect to cells [25]. This area of protein allows a strong bond between the virus and the cellular receptors, which are negatively charged.

When S protein binds to the receptor a protease serine 2 (TMPRSS2) located on the host cell membrane promotes the virus invasion into the cell. SARS-CoV-2 attaches itself to the receptor ACE2 and viral entry-associated protease TMPRSS2 is highly expressed in the nasal goblet and ciliated cells. High ACE2 expression was identified in type II alveolar cells (AT2) of the lungs, upper esophagus and stratified epithelial cells, absorptive enterocytes from ileum and colon, myocardial cells, kidney proximal tubule cells, and bladder urothelial cells [26]. Once the virus enters the cell the viral RNA is released into the cytoplasm where it will be translated and replicated, or it will reach the cell nucleus [27].

Viruses depend on host cell survival during replication and the cellular metabolism requires iron as a nutrient [28]. Iron is necessary for many fundamental enzymatic and non-enzymatic reactions and diverse physiological processes, such as mitochondrial function including ATP generation, DNA/RNA synthesis, and repair [27].

Several publications report that SARS-CoV-2 attacks hemoglobin and attacks the normal metabolic pathway of heme and tissue iron overload [29–35]. A study with 1210 Covid-19 patients showed significantly low hemoglobin levels (<100 g/L) [36,37]. The values of serum ferritin index, erythrocyte sedimentation rate, C-reactive protein, albumin, and lactate dehydrogenase of many patients have increased significantly [38]. Decreased heme production dampens repression of aminolevulinic acid synthase, and thereby increases the production of heme precursors. Hence, it leads to porphyrin accumulation. Excess porphyrins in red blood cells can precipitate cell lysis and it can be responsible for hemolytic anemia development [30].

Cavezzi et al. reported pathologic metabolic pathways deriving from hemoglobin denaturation, and iron metabolism dysregulation [33]. This interaction resulted in a hemoglobin functioning quantity decrease, elevated serum ferritin levels, free toxic circulating heme, low level of oxygen in the blood, and systemic hypoxia, reduction of nitric oxide, coagulation activation, ferroptosis with oxidative stress and lipoperoxidation, mitochondrial degeneration, and apoptosis.

Cavezzi et al. suggested that SARS-CoV-2 can have a tropism for blood cells [33]. They proposed that the interaction with hemoglobin molecule occurs through CD147, CD26, and other receptors located on erythrocyte and/or blood cell precursors and that hepcidin-mimetic action of a viral spike protein, inducing ferroportin blockage [33]. SARS-CoV-2 could induce hemolysis and/or form a complex with the released heme, generating a quote of dysfunctional hemoglobin, with reduced oxygen and CO_2 transport [33].

Ropa et al. reported that hematopoietic stem cells (HSCs) from cord blood express ACE2 and the exposure to the S protein can reduce their functionality [39]. Recently Cosic et al., found that the red blood cells (RBC) Band3 surface proteins have the same resonant recognition model characteristics as ACE2 receptors. They proposed that hypoxia in severe cases of COVID-19 is caused by SARS-CoV-2 interacting with the RBC Band3 surface protein and hampering RBC oxygen transport function [40]. Bernards et al. reported an aberrant increase of erythroid progenitors in circulation [41]. Erythrocyte lysis may occur in COVID-19 due to the high oxidative environment [42]. Encabo et al. studied hematopoietic stem/progenitor cell (HSPCs) and different erythroid progenitor populations to assess if they can be infected by SARS-CoV-2 [43] (Fig. 1). They show the first evidence of direct infection of specific erythroid progenitors. They reported the high ability of the virus to infect ERP-S2, the most vulnerable erythroid progenitor population and show that the decline in hemoglobin levels coincides with an aberrant increase of nucleated red blood cells in circulation. Shahbaz et al. reported that the nucleated red blood cells correspondent to ERP-S3 cells can be infected by SARS-CoV-2 and that the infection induces the immunosuppressive capacity of these cells [44].

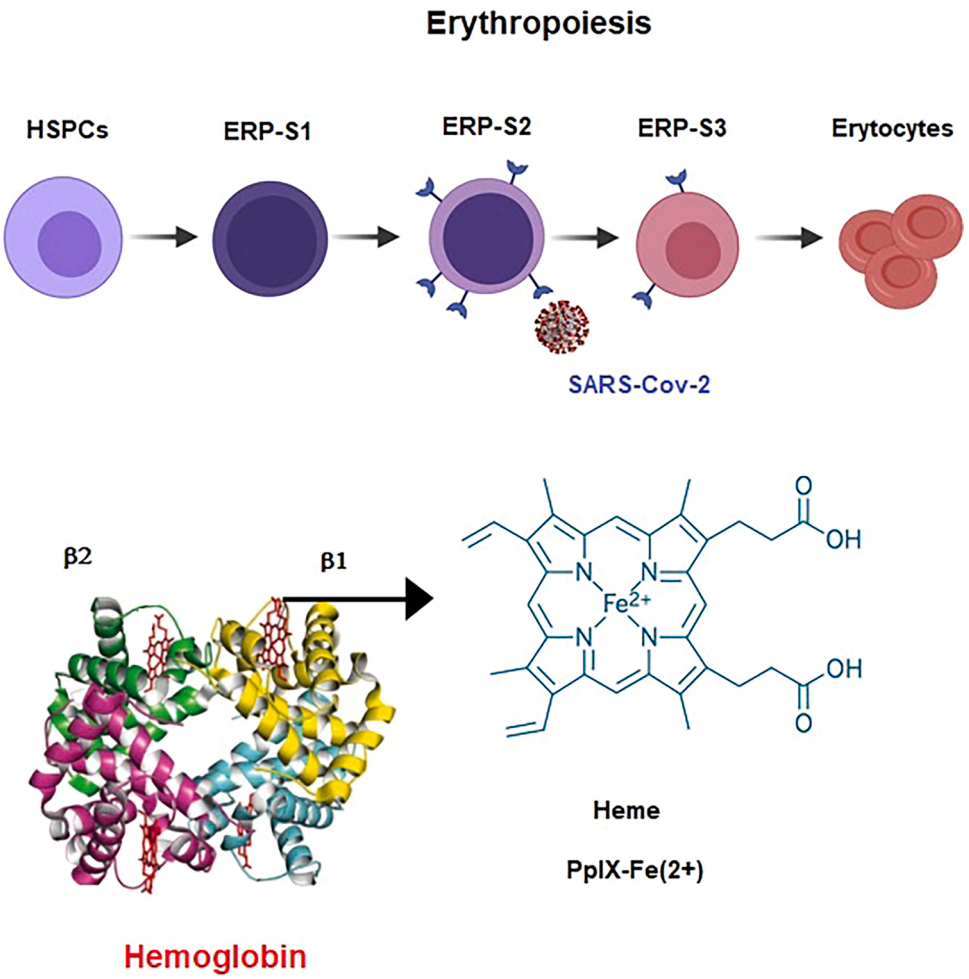

Fig. 1. Direct infection of specific erythroid progenitors, ERP-S2 and ERP-S3 by SARS-CoV-2 [43]. Hemoglobin structure with the alpha chains (α1, α2), the beta chains (β1, β2), and the four heme groups. On the right the structure of the iron protoporphyrin IX subunit of heme B.

3. Hemoglobin and Iron

Cellular processes such as DNA synthesis and the molecules ATP generation require iron [45]. Viruses depend on iron ions to replicate within living host cells [28]. The uptake of iron pathways free iron and from heme are associated with their proliferation and virulence and, consequently, their pathogenicity [46].

In the human body, iron exists in complex forms of hemoproteins as heme compounds such as hemoglobin or myoglobin, heme enzymes, or non-heme compounds as flavin-iron enzymes, iron-sulfur clusters, transferring, and ferritin [47].

More than two-thirds of the human body's iron is localized in the hemoglobin of developing erythroid precursors and mature RBCs. Iron is also stored in liver cells and macrophages bound to ferritin. A smaller fraction is bound to myoglobin in muscle tissue and a variety of enzymes involved in oxidative metabolism and many other cell functions [47].

Iron is important for hemoglobin and myoglobin synthesis, also iron formation depends on enzymes involved in oxidative phosphorylation, which is the metabolic pathway that converts nutrients to energy [47]. Critical enzymes in the DNA metabolism, including multiple DNA repair enzymes and ribonucleotide reductase, take iron as an indispensable cofactor to function [48].

A balance between iron uptake, transport, storage, and utilization is required to maintain iron homeostasis. Non-heme iron compounds are transported across the apical membrane of the intestinal enterocyte by divalent metal transporter 1 (DMT1) and are exported into circulation via ferroportin 1 (FPN1). The iron homeostasis regulator is the liver-derived peptide hepcidin [49]. Fe-transferrin (Tf) complex transports iron to other cells and tissues through the blood circulation in the body. Tf binds to transferrin receptor 1 (TfR1) on the cell membrane, and the TfR1-TfFe complex is then endocytosed by the cell, where the iron content is released. Free iron ion enters the mitochondria for its utilization in metabolic processes, such as the synthesis of hemoglobin. Excess iron is transported out of the cell by iron efflux protein ferroportin 1 (FPN1) located at the cell membrane [50]. When cellular iron concentrations are low the iron regulatory proteins (IRPs) are in their mRNA-binding conformations. The binding of IRPs to the untranslated ferritin mRNA regions (UTRs) blocks the translation ensuring that ferritin is produced when iron storage is not required.

Hemoglobin consists of four subunits, 2-α and 2-β, and each subunit presents a heme as observed in Fig. 1. Heme synthesis occurs in both the cytosol and the mitochondria with the formation of δ- aminolevulinic acid (ALA) [51]. It begins with glycine and succinyl coenzyme A and ends with the production of a PpIX ring. The insertion of Fe^{2+} into PpIX catalyzed by ferrochelatase in the mitochondria determines the final step of the heme biosynthetic pathway. Heme regulates a wide spectrum of gene expression, cell differentiation, proliferation, and immune stimulation [52]. In non-erythroid cells, the heme synthesis depends on the ALA production, and in erythroid cells, it depends on the availability of iron for ferrochelatase.

Hemoglobin (Hb) is expressed by both erythroid and non-erythroid cells [53]. Hb expression has been observed in different cells including macrophages, alveolar, lungs, hepatocytes, mesangial, retinocytes, endometrium, cervix, vaginal, and neuronal cells [53–55]. In erythroid

cells in the blood, Hb carries oxygen from the lungs throughout the body where it is used in aerobic metabolism pathways. In some non-erythroid cells, Hb expression is upregulated in response to hypoxia as compensation for the increased oxygen demand [54]. Hb can recognize pathogens thereby reducing the risk and/or severity of infections, and this is the possible mechanism by which Hb exhibits antimicrobial and antioxidative functions.

Grek et al. discovered that hemoglobin RNA and protein are expressed in several alveolar cell lines. Including A549 and MLE-15 as well as in primary AT2 cells purified from murine and rat lungs. They demonstrated that hemoglobin mRNA is up-regulated during hypoxic exposure in the murine AT2 and MLE-15 cell lines [54].

Heme is a hydrophobic molecule and is insoluble in the aqueous cellular milieu. Free heme is toxic to biological macromolecules. High levels of free heme result in pro-inflammatory and proliferative effects [56]. Free heme causes inflammation and acute lung injury [57]. In pathologies such as hemolytic diseases, sepsis, renal injuries, malaria, and atherosclerosis, large quantities of hemoproteins are released into the plasma.

Hemoglobin is degraded into globin and heme molecules, which occurs when the tetrapyrrole ring of porphyrin is opened by the action of the enzyme heme oxygenase breaking the methine bridge between pyrroles I and II. This reaction releases Fe^{2+}, which is quickly sequestered by ferritin, carbon monoxide (CO), and biliverdin (BV), and further converted into bilirubin (BR) through the enzyme biliverdin reductase (BVR) [52]. CO, BV/BR exert important cytoprotective and anti-inflammatory effects during oxidative stress and inflammation. CO binds to hemoglobin and interferes in the oxygen-carrying capacity of the blood leading to tissue hypoxia [58]. When BR production is increased it accumulates in the blood. BR plays a crucial role in innate immunity affecting the immune system depending on the complement cascade it interrupts the C1 complex to antibodies [59]. The BV function relies on the increasing level of heme oxygenase (HO-1) by BVR in the lungs. The blockage of HO-1 activity results in loss of BV inhibitory effects on lipopolysaccharide LPS-induced lung injury [60].

4. Covid-19 and PpIX

San Juan et al. quantified the total porphyrin content in the serum of 134 Covid-19 patients in the acute phase of the disease (confirmed by positive rt-PCR testing) through high-performance liquid chromatography (HPLC). They reported an abnormal accumulation of porphyrins in association with severe Covid-19 [61]. Porphyrins possessing free iron, and other ROS/oxidants generated from the ensuing inflammation create a toxic milieu that causes protein aggregation [62]. Therefore, protein aggregation provides a potential mechanism for cell and tissue damages. Thus, this could be causing neurological problems attributed to Covid-19.

The virus's invasion mechanism via non-structural proteins predicted by Wenzhong et al. could occur via erythroid cells as well as non-erythroid cells. They made a computational analysis to compare the biological roles of specific proteins belonging to the novel coronavirus [63]. The conserved domain analysis showed that the envelope protein (E), nucleocapsid phosphoprotein (N) and ORF3a had heme linked sites, which is Arg134 of ORF3a, Cys44 of E, Ile304 of N were the heme-iron linked site, respectively. ORF3a's role would be the iron heme dissociation to form porphyrin. The docking results showed that orf1ab, ORF10, and ORF3a proteins coordinate the attack of the hemoglobin's β1 chain and some structural and non-structural viral proteins bind to the porphyrins. According to them, the binding part of the orf1ab protein acts as a clip, that is bounded to the α chain and attacks the β chain. This attack causes configurational changes in their α and β chains. The ORF3 attacks the β chain and exposes heme. ORF10 attaches to the β chain and directly impacts the iron atoms on the heme of the β chain. The heme is dissociated into porphyrin, and orf1ab finally captures the porphyrin. ORF8 and surface glycoproteins could combine themselves with the porphyrin to become a complex. Facilitating the entrance of the virus into the cell.

We hypothesize that SARS-CoV-2, that depends on iron to replicate within living host cells, obtains this iron at the expense of hemoglobin and heme, which once disrupted, release PpIX.

The porphyrin is degraded into bilirubin and excreted from the bile duct. Porphyrins that leave the cells and appear in blood, urine, and feces are mostly oxidized and are fluorescent. To date, there seem to be no further published or ongoing studies about the link between SARS-CoV-2 and PpIX fluorescence.

PpIX could represent not only a sensitive indirect biosensor of SARS-CoV-2 infection but also a specific and low-cost diagnostic test.

5. Covid-19: PpIX diagnostic marker

COVID-19 does lead to increased porphyrin release. Thus, the PpIX fluorescence analysis from blood, urine, and feces samples can yield information about the presence of SARS-CoV-2 in the body. Through the PpIX spectroscopic properties, it is possible to monitor and quantify its concentration [2].

A variety of porphyrins are presented in urine or feces, which could be easily collected at home. In ordinary light, normal urine is amber, or it shows a pinkish amber tinge if concentrated. Normal urine excited with UV light around 400 nm shows a greenish-blue or greenish-yellow or pinkish-yellow fluorescence if concentrated. Urine containing an increased concentration of porphyrins may be pink, red, or brown. When excited around 400 nm, urine containing porphyrins presents red fluorescence [64]. So, patients with Covid-19 must present urine with red fluorescence.

Hennig et al. measured the red blood cell zinc protoporphyrin at ~589 nm in the microcirculation of the lower lip to established an iron status indicator [18]. The iron deficiency detection sensitivity and specificity were 97 % and 90 %, respectively. They concluded that the fluorescence method potentially provided a rapid, easy-to-use means for point-of-care screening for iron deficiency in resource-limited settings lacking laboratory infrastructure. A similar method could be employed to detect Covid-19.

In Fig. 2a it is shown a calibration curve obtained with synthetic PpIX fluorescence (Sigma). This figure shows that fluorescence spectroscopy can distinguish low PpIX concentrations, and this method should present good sensitivity. For quantitative analysis, to monitor the progression of Covid-19, PpIX could be easily extracted from blood, or feces using acetone (3 parts of acetone/1 part of the analyte), centrifugation, and discarding the cell pellet formed in the bottom of the tube [65,66].

Fig. 2b shows the average fluorescence spectra of PpIX extracted with acetone from blood samples from 30 people without Covid-19 (Reference values for blood protoporphyrin of healthy people: 0.16 to 0.60 μg/mL or 0.28–1.07 μmol/L). In this spectrum, it is possible to see Zn-PpIX (~590 nm) and PpIX (~633 nm) peaks. As an abnormal accumulation of porphyrins is expected in a patient with Covid-19 [62], increased blood PpIX concentration is predictable for contaminated people. The fluorescence method could contribute to monitoring and evaluating the severity or evolution of the disease. Even asymptomatic patients should present abnormal PpIX levels. Covid-19 patients with anemia, more susceptible to death should present an increment in Zn-PpIX/PpIX rate [67].

Mobile platforms allow online and on-site diagnostic transitioning from laboratory-based trials. Since the introduction of smartphones, hundreds of millions of devices possessing high pixel count images operating under low light conditions have been sold. Such cameras can be employed as a sensor to perform functions equivalent to much larger and more expensive laboratory instruments. The smartphone fluorimeter can perform tests with a good detection limit which could be applicable in medical clinics [68–70].

Studies are necessary to determine the method specificity because other diseases as porphyria, cancer, or atherosclerosis can lead to an

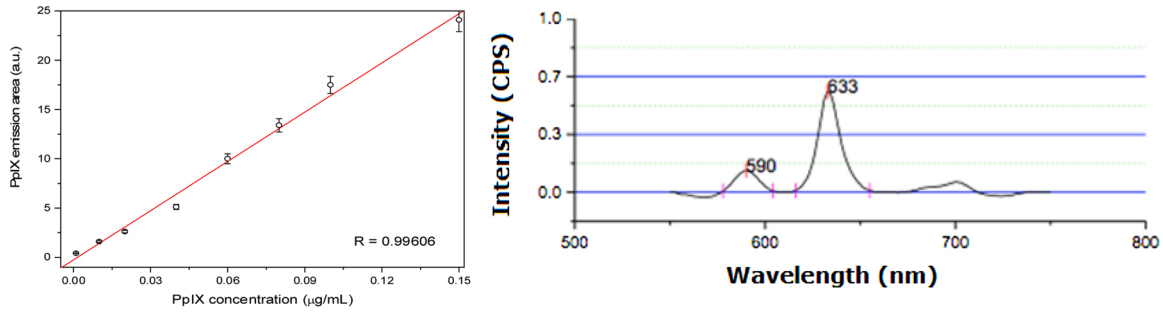

Fig. 2. a) Calibration curve of synthetic protoporphyrin IX prepared in acetone (Sigma). b) PpIX was extracted from blood samples from thirty people without Covid-19 and blood disorders. PpIX fluorescence was obtained under excitation at 410 nm and the presented spectrum is an average of the thirty spectra.

increase in porphyrin level in blood or body fluids. Several publications demonstrated that highly multiplying cells, like cancer cells [4,5], show an intracellular accumulation of PpIX [71,72]. In these cases, the accumulation of PpIX in cells is affected by multiple biological factors, which include 5-ALA uptake [73], ABC transporters, such as ABCG2, that excrete PpIX from cells, enzymes in the heme biosynthesis pathway, and the intracellular Fe^{2+} content [71].

So, it is important to point out that the PpIX fluorescence method should be employed preferably in patients with less than 40 years old to avoid false-positive results, but further investigations are necessary to assess this role. However cancer incidence is much less, and it has its well-defined symptoms with no overlap with that of Covid-19 cases.

6. Covid-19: PpIX-treatment perspectives

RNA-type microorganisms are more easily photo-inactivated than their DNA-type counterparts. This suggests that SARS-CoV-2, which is an enveloped RNA-type virus, can be easily neutralized by photodynamic therapy (PDT) [74]. Extracorporeal photoinactivation of coronaviruses and other clinically relevant pathogens using methylene blue (MB)-mediated PDT has been reported [74,75]. PDT has been used for decades in lung cancer treatment and in laryngeal papilloma treatment, which was a success [76]. More recently, Schikora et al. reported successful use of PDT to disinfect oral and nasal cavity of patients in the early stages of COVID-19 infection [77].

Porphyrins are natural sensitizers in photodynamic and sonodynamic therapies (PDT and SDT) and innumerous publications applying these therapies to diseases like cancer or atherosclerosis, or infections were described [78–83]. Both light and ultrasound can excite porphyrins from the ground state (S_0) to the excited singlet state (S_1). Porphyrins can then either relax back to S_0 state emitting light or go to the excited triplet state (T_1) by intersystem crossing. The energy of porphyrins in the T_1 state can either be relaxed by phosphorescence or be transferred to oxygen molecules through type I and type II reactions. In type I reaction an electron transfer process produces free radicals, which interact with water or oxygen molecules leading to the production of hydroxyl radicals (OH) or superoxide anions (O_2^-). In the type II reaction, an energy transfer process between the T_1 state of porphyrins with $^3O_2$ results in the formation of highly cytotoxic singlet oxygen ($^1O_2$). The reactive oxygen species (ROS) can interact with proteins, lipids, and nucleic acids, causing their oxidation and, consequently, damage to cells, tissues, and microorganisms as SARS-CoV-2 [19]. The use of Photofrin ®, a porphyrin derivative, as a photosensitizer could help to mitigate the COVID-19 [19] and prevent severe stages, however, there is no data available on the photodynamic inactivation. Furthermore, porphyrins when excited by light, like sunlight, with sufficient intensity could effectively destroy SARS-CoV-2 by photobiomodulation (PBM). In the case of photobiomodulation, ROS are present at low concentrations, below that required for cytotoxicity, and have a wide range of positive stimulatory effects on the cell. PMB employing low levels of red light could be an alternative to acute lung injury, for example [84]. Nevertheless, to date, no experimental data was supporting the influence of PBM on COVID-19.

PDT is limited to local effects and COVID-19 is a systemic disease. The optical radiation penetration into the biological tissue with wavelengths around 400 nm, which is the maximum porphyrins absorption band, is around 250 μm [85]. As a result, only a superficial effect can be obtained. Nevertheless, an endoscopic fiber could be applied for the delivery of light into deeper tissues. Additionally, sonodynamic therapy (SDT) could be employed to eliminate SARS-CoV-2 in deeper regions as the lungs [86]. SDT involves the exposure of the sensitized tissues with relatively low-intensity ultrasound (US). This suggests that sonodynamic therapy may find wider clinical application particularly for the non-invasive treatment of difficult accessible lesions.

The cavitation effect of ultrasound is responsible for the SDT mechanism [79]. The acoustic cavitation promotes the formation, growth, and collapse of bubbles during US wave propagation in liquids. The bubbles explosion lead to sonoluminescence and endogenous PpIX activation [87]. Recently it was observed that the PpIX was activated from the ground to an excited state induced by methyl aminolevulinate gold nanoparticles (MALA:AuNPs) and exposed to a 1 MHz and 1 W/cm^2 ultrasound [88]. On returning to the ground state it released energy, which was transferred to oxygen to produce ROS, such as singlet oxygen and free radicals. So, both nanoparticles and PpIX were responsible for macrophages' total reduction.

Pre-clinical and clinical studies are planned to examine the early feasibility, safety, and efficacy of the proposed approaches. In this future prospective work, we must avoid interference from cancer patients.

7. Conclusions

The early diagnosis and treatment of Covid-19 can drastically improve the prognosis of this disease. SARS-CoV- 2 attacks hemoglobin through its structural protein ORF3a dissociating the iron from the heme molecules since iron is necessary for the virus replication. In this process, PpIX is released. In this context, PpIX fluorescence could be employed on the Covid-19 diagnosis or potentially be used as a marker for the evaluation of the patient's response to the treatment. Furthermore, from our perspective, photobiomodulation, photodynamic and sonodynamic therapies taking advantage of the increased endogenous PpIX concentration in the acute phase of the disease could be employed as an additional option for the treatment of Covid-19 patients. A mechanism to prevent virus replication by interrupting hemoglobin rupture could serve as an effective way to help combat the disease.

Ethical approval

Not required/not applicable.

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Author's contribution

L.C.C. conceived the idea presented. All authors discussed the ideas and contributed to the final manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

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