Covid-19: acquired acute porphyria?

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ABSTRACT

Pandemic Covid-19 pneumonia, of SARS-CoV-2 aetiology, is of global importance to health systems, national economies, and individual civil liberties. Multiple therapeutic and prophylactic agents are currently undergoing clinical trial and, while progress towards a curative agent is promising, the principal limiting factor in public health emergency is time. A pre-existing licensed therapeutic would offer reprieve to international citizens currently enduring the adverse consequences of lockdown policies. The current review advances the author's original hypothesis and advocates direct testing of the hypothesis by urinalysis of light-protected samples from critical Covid-19 patients to check for elevated aminolevulinic acid and porphobilinogen.

Key words: ABCG2, Chloroquine, Covid-19, Extracorporeal membrane oxygenation, Hematopoietic distress, Heme Biosynthesis, Heme-Binding Motif, Hyponatremia, Ivermectin, Neurological, Neuromuscular, Neurovisceral, Porphyria, Porphyrin, SARS-Cov-2

Introduction

The current review advances the author's original hypothesis published as a preprint in April 2020 (Abrahams, 2020). Erythrocytes are strongly implicated in the pathophysiology of Covid-19 although their role is thought to be under-estimated. Co-efficient of variation of red blood cell distribution width (RDW) is predictive of severity of disease state (Gong et al., 2020). Elevated RDW is correlated with reduced erythrocyte turnover; red blood cells become smaller as they age and the delay in clearance expands the low-volume tail of the volume distribution (Patel et al., 2015). Suppressed erythrocyte turnover may indicate erythropoietic distress and function as a compensatory mechanism to maintain circulating red blood cell levels (Patel et al., 2015). Excess porphyrins in red blood cells can precipitate cell lysis and development of hemolytic anaemia (Sassa, 2006). Macaques infected with SARS-CoV-2 also have decreased red blood cell numbers (Munster et al., 2020) and susceptibility to SARS-CoV-2 appears to be determined by blood group; blood group A is most affected whereas blood group O seems to be protected (Zhao et al., 2020). This finding is concordant with previous studies showing that susceptibility to the 2003 strain of SARS-CoV was determined by blood group (Guillon et al., 2008). Preliminary evidence suggests that CD147, the determinant of the Ok blood group system, binds the spike protein of SARS-CoV-2 (Wang K et al., 2020). Incidentally, CD147 functions as an essential receptor for erythrocyte invasion by Plasmodium falciparum (Crosnier et al., 2011). Blockade of CD147 abrogates the normal recirculation of erythrocytes, from the spleen into the general circulation, leading to selective trapping of red blood cells in the spleen as development of a form of anaemia (Coste et al., 2001). Autopsy of deceased Covid-19 patients reveals that the spleen may be reduced in size (Feng et al., 2020). Reduction in spleen size would be expected in the event of splenic emptying of reserve erythrocytes into the circulation as part of a normal physiological response to anaemia (Dale, 2016).

Primate models of Covid-19 (Munster et al., 2020) and human Covid-19 patients have subnormal hemoglobin levels (Chen N et al., 2020). Clinical evaluation of almost 100 Wuhan patients reveals hemoglobin levels below the normal range in most patients as well as increased total bilirubin and elevated serum ferritin (Chen N et al., 2020). Hyperbilirubinemia is observed in acute porphyria (Sassa, 2006) and would be consistent with ineffective erythropoiesis (Sulovska et al., 2016) and rapid hemoglobin turnover. Elevated serum ferritin levels are typical of acute porphyria (Trier et al., 2013) and would be expected upon dissociation of iron from heme. A mechanism by which SARS-CoV-2 might disrupt the 1beta chain of hemoglobin has been proposed; multiple SARS-Cov-2 ORF proteins are predicted to bind the porphyrin of heme and displace iron (Liu & Li, 2020). If this prediction is accurate, the oxygen-carrying capacity of erythrocytes would be compromised by SARS-CoV-2, thereby exacerbating the difficulties already experienced by the patient, in terms of maintaining partial pressure of oxygen in the alveoli (PaO2).

While the impact of SARS-CoV-2 targeting of hemoglobin on oxygen content of the blood would be considerable, the author proposes that perhaps of greater concern, are potential ramifications upon homeostatic regulation of heme anabolism. Heme biosynthesis is exquisitely controlled by seven enzyme-controlled reactions proceeding from the first intermediate, aminolevulinic acid (ALA), to heme as the final product (Fig. 1). Heme negatively regulates the first step in the pathway by repressing expression of aminolevulinic acid synthase (ALAS). SARS-CoV-2 is predicted to directly interfere with heme production (Liu & Li, 2020), and this prediction is consistent with empirical evidence of reduced hemoglobin levels in Covid-19 patients (Chen N et al, 2020) and in animal models of the disease (Munster et al., 2020). Decreased heme production dampens repression of ALAS and may thereby increase the production of heme precursors leading to accumulation of porphyrin intermediate metabolites. All the heme pathway intermediates are potentially toxic (. During an attack of acute porphyria, ALAS is induced (Sassa, 2006) and this perturbation continues until sufficient heme synthesis is restored.

Phenotype of SARS-CoV-2 porphyrin excess is hypothesised to mimic extreme lead poisoning; both as examples of acquired acute porphyria. Overproduction of heme precursors - aminolevulinic acid (ALA) and porphobilinogen (PBG), in particular – manifests life-threatening attacks (Pischik & Kauppinen, 2015) with neurovisceral symptoms (Sassa, 2006), including: abdominal pain (85-95% cases), vomiting (43-88%), constipation (48-84%), muscle weakness (42- 60%), mental symptoms (40-58%), pain of the limbs, head, neck and chest (50-52%), hypertension (36-54%), tachycardia (28-80%), convulsion (10-20%), sensory loss (9-38%), fever (9-37%), respiratory paralysis (5-12%) and diarrhoea (5-12%). Neurotoxicity of aminolevulinic acid accounts for the plethora of neurovisceral symptoms and, interestingly, there is considerable overlap between neurovisceral complaints of ALA excess and extra-pulmonary symptoms of critical Covid-19 patients. Extra-pulmonary symptoms of Covid-19 are significant but under-estimated, including gastrointestinal symptoms (Poggiali et al., 2020). Neurological problems also appear to be overlooked by the hyper-focus on respiratory symptoms (Zhao K, 2020). Of 214 Covid-19 patients, 36.4% experienced neurological manifestations including: headache, dizziness, acute cerebrovascular incidents, and impaired consciousness (Mao et al., 2020). Loss of autonomic control of breathing has also been reported and autonomic neuropathy is a clinical feature of acute porphyria (Laiwah et al., 1985). Neuropsychiatric symptoms of Covid-19 may be downstream of irregularities in heme metabolism. SARS-CoV-2 would not be the first known

virus to alter porphyrin metabolism; hepatitis C virus and human immunodeficiency virus infection lead to a non-acute form of porphyria (Blauvelt, 1996).

In summary, the first part of the current hypothesis is that critical Covid-19 patients are experiencing a form of acquired acute porphyria (Fig. 1) and the second part is that treating critical Covid-19 patients with ALA synthase inhibitors may ameliorate extra-pulmonary symptoms of the disease. Diagnosis by urinalysis of porphyrin metabolites would provide a straightforward confirmation or negation of the current hypothesis; ALA urinary excretion of 25-100 mg/d or PBG urinary excretion of 50-200 mg/d is typical of acute porphyria (Sassa, 2006). Current therapeutic interventions licensed for treatment of porphyria include: (i) blood transfusion (erythropoietic porphyria), (ii) glucose, (iii) intravenous haematin; and (iv) chloroquine. Chloroquine induces the release of tissue-bound porphyrins; the initial event following chloroquine administration to porphyria cutanea tarda (PCT) patients is a release of bound hepatic porphyrin and its rapid elimination (Scholnick et al., 1973). The remainder of the review makes five arguments as rationale for testing the acquired acute porphyria hypothesis: (i) extracorporeal membrane oxygenation fails as a functional cure, (ii) symptomology overlap, (iii) abnormal concentrations of serum porphyrins in Covid-19, (iv) heme-binding motifs in SARS-Cov-2 proteins, (v) nascent treatment mechanisms.

1. ECMO fails as a functional cure

The conventional view of SARS-Cov-2 pathology (Hansen, 2020) is that critical disease is a viral pneumonia that progresses to acute respiratory distress syndrome (ARDS), with cytokine-storm induced hyperinflammation (Mehta et al., 2020), and death by multiple organ failure. While this is largely accurate and well- evidenced, elements of the clinical manifestation of SARS-Cov-2 infection in critical patients appear to be novel, when compared with the phenotype of critical SARS-Cov-1 patients. Perhaps the most eloquent ambassador of this opinion within the clinical medical profession is Dr. Cameron Kyle Sidell, advocate of (i) an evidence-based approach to ventilation timepoints/pressures and (ii) re-questioning the Covid-19 phenotype (Sidell, 2020). If the conventional view of Covid-19 as a viral pneumonia - in which ARDS drives hypoxia - is sufficiently accurate, ECMO would be expected to closely represent a functional cure. ECMO bypasses the requirement of the lungs to be functional, by directly oxygenating and circulating blood mechanically, therefore if critical Covid-19 is primarily a pulmonary disease – rather than a hematological disease – recovery rates with ECMO would be extremely high. ECMO fails as a universal cure (Kingston, 2020) for critical Covid-19 patients; mortality rates of critical Covid-19 patients in receipt of ECMO are reported as: 31% of 83 (Schmidt et al., 2020), 35% of 124 (Combes et al., 2018), 41.7% of 12 (Zeng et al., 2020), 66.7% of 15 (Jacobs et al., 2020), 94.1% of 17 (Henry & Lippi, 2020) and 100% of 3 (Campioli et al., 2020). Causes of death in ECMO patients are typically septic shock and multiple organ failure; these results point to the biomedical insufficiency of hypotheses of Covid-19 as principally a pulmonary disease. Conventional views of Covid-19 as primarily a viral pneumonia also fail to explain the phenomenon of chronic symptomology associated with SARS-Cov-2 infection, known colloquially as 'long Covid'. Persistent symptoms include dyspnoea (43%), chronic fatigue (53%), joint pain (27%), chest pain (22%), generalised pain and psychiatric problems (Mahase, 2020). Numerous alternative hypotheses have been proposed to explain the extra-pulmonary dimensions of the Covid-19 phenotype, including cytokine storm-induced hyperinflammation (Mehta et al., 2020), Kawasaki-like or toxic shock syndrome-like systemic paediatric presentation (Rogo et al., 2020) and systemic thromboembolism (Mahajan et al., 2020). Treatment with anti- inflammatory and anti-coagulant agents may reduce mortality (Cano et al., 2020; Carfora et al., 2020) however, to date, there is no globally optimal solution to treatment of critical Covid-19 patients.

2. Symptomology: neurovisceral, neuromuscular, neurological

Although highly speculative, porphyria would explain many of the extra-pulmonary symptoms of Covid-19 including neurovisceral, neuromuscular and neurological symptoms. Porphyria, as a phenotype, would also explain why ECMO is inadequate as a treatment for critical patients and may explain the long-term symptomology of Covid-19. To assess the comparative symptomology of SARS-Cov-1, SARS-Cov-2 and porphyria, literature search was performed, and the results are summarised in Table 1. Overlap between symptomologies was visualised in Venny (Oliveros, 2007) under both conservative and liberal inclusion criteria (Fig. 2). The result is that: (i) under liberal comparison criteria, sensory loss and paralysis are shared by porphyria and Covid-19 but not SARS-1, (ii) under conservative comparison criteria, sensory loss and neuropsychiatric symptoms (and constipation) are shared by porphyria and Covid-19 but not SARS-1. If the porphyria hypothesis were to be confirmed, symptoms of sensory loss, paralysis and neuropsychiatric symptoms would be explained in Covid-19 patients as an outcome of porphyrin excess.

3. Abnormal concentrations of serum porphyrins in Covid-19

Moreover, since publication of the original hypothesis, abnormal concentrations of serum porphyrins have been detected; uroporphyrin I (UROI) plus coproporphyrins I (COP I) and III (COPIII) are elevated (San Juan et al., 2020). Levels of aminolevulinic acid and porphobilinogen, however, were not observed to be elevated in serum of acute Covid-19 patients relative to non-Covid pneumonia patients. San Juan et al conclude that this serum porphyrin profile does not match those of porphyrias. This evaluation is inaccurate: plasma porphyrins are markedly increased only in variegate porphyria (VP); however, most types of acute porphyria show normal or only slightly elevated serum porphyrin profiles. Diagnosis of acute porphyrias requires urinalysis rather than serum sample analysis as demonstrated by The Porphyrias Consortium. Further evidence supporting the porphyria hypothesis derives from Pang Z et al, whose meta-analysis of metabolomics datasets found that the most significantly perturbed pathway in Covid-19 is porphyrin metabolism, or heme biosynthesis.

4. Heme-binding motifs in SARS-Cov-2 proteins

Preliminary work from the University of Bonn and Fraunhofer Institute (Hopp et al., 2021) suggests multiple potential heme-binding motifs in SARS-Cov-2 proteins, spike and 7a. Initial lists of potential heme-binding motifs were compiled using HeMo Quest, a primary structure-based HBM prediction server, trained on a large array of heme-binding peptides that has 92% accuracy (Paul George et al., 2020; Hopp et al., 2021). The initial list was refined on the basis of surface accessibility of the motifs within isomers or oligomers of the proteins. A shortlist of candidate heme-binding motifs (three candidates in spike and two in protein 7a) was subjected to experimental validation by incubation of each SARS-Cov-2 peptide with heme followed by UV spectroscopy analysis. Notably, the spike protein shortlist of HBMs are all present in the N-terminal domain of the S1 subunit and the sequences are: (1) FLGVY144YHKN, 2) IYSKH207TPIN, (3) LHRSY248LTPG. Shortlisted protein 7a HBM sequences are: (1) DGVKH73VYQL, (2) VKHVY75QLRA. Further, SARS-Cov-2 spike protein is conjectured to bind the heme metabolites biliverdin and bilirubin as

an immunoevasion mechanism (Rosa et al., 2021), a finding that awaits peer review and which would support the suggestion that spike may bind heme.

In complement of the findings of Hopp et al and Rosa et al, the current author performed search for the protein FASTA sequences of heme-binding motifs in NCBI, specifying a motif length of 3-20 amino acids. Search criteria specified in NCBI were: ((heme binding[Protein Name] OR (heme[All Fields] AND binding[All Fields])) AND motif[All Fields]) AND ("3"[SLEN] : "20"[SLEN]). There were 48 results and one (HXXXXH) of these was noticed to be present in SARS-Cov-2 spike protein using Python code (Fig. 3). HXXXXH is a histidine box that is known, in other proteins, to be involved in iron-binding (Hsieh et al., 2004; Hasan et al., 2019). Moreover, various HX(n)H motifs have been shown experimentally to bind heme and act as heme regulatory motifs (Syllwasschy et al., 2020). Further known heme-binding motifs were identified (Table 2) by utilising the same code, including the canonical heme-binding dipeptide cysteine-proline, located within the receptor binding domain (RBD) of spike glycoprotein. Presence of heme regulatory motifs in spike glycoprotein does not automatically imply porphyrin-binding functionality; surface accessibility and physicochemical properties of the spacer residues are important considerations, in the global context of the spike glycoprotein. However, the highlighted sub-sequences represent candidate motifs for further investigation.

5. Nascent treatment mechanisms

Hydroxychloroquine and, more recently, ivermectin – have been proposed as candidates in the prophylaxis and treatment of Covid-19. The latter has been eloquently advocated by Dr Pierre Kory. Mechanisms of action of each drug have been respectively suggested as: (i) interference in the endocytic pathway, blockade of sialic acid receptors, restriction of pH mediated spike (S) protein cleavage at the angiotensin-converting enzyme 2 (ACE2) binding site and prevention of cytokine storm (Satarker et al., 2020); and (ii) inhibition of SARS-Cov-2 replication (Caly et al., 2020) by an as-yet undefined mechanism. Ivermectin is mostly associated with anthelmintic binding and activation of glutamate-gated chloride channel receptors, and separately, with antiviral inhibition of importin α/β1 heterodimer-mediated nuclear transport (Rizzo, 2020).

If porphyria is an important component of the Covid-19 phenotype, pharmacological mechanisms relevant to porphyrin metabolism would be expected. Two alternative mechanisms of action are proposed in the event that porphyria is a significant driver of pathology. Firstly, as aforementioned, chloroquine induces the release of tissue-bound porphyrins; the initial event following chloroquine administration to porphyria cutanea tarda (PCT) patients is a release of bound hepatic porphyrin and its rapid elimination (Scholnick et al., 1973). Secondly, ivermectin interacts with the transporter ABCG2 (Jani et al., 2011). ABCG2 is essential for the transport of porphyrins; ABCG2 location at the plasma membrane modulates removal of excess porphyrins from the cell (Krishnamurthy & Schuetz , 2011). ABCG2 is upregulated by hypoxia and is therefore important in maintaining porphyrin homeostasis in hypoxic cells (Krishnamurthy & Schuetz, 2011). Therefore, one potential mechanism of ivermectin activity is acceleration of porphyrin clearance via ABCG2 (Fig. 4).

Conclusion

Since publication of the original hypothesis in April 2020, hematological dimensions of Covid-19 have increasingly become apparent, including hypercoagulability (Panigada et al., 2020) as well as pulmonary vascular endothelialitis, thrombosis and angiogenesis (Ackermann et al., 2020). Erythroid progenitors are one possible site of SARS-Cov-2 infection (Shahbaz et al., 2020) and erythroid precursor cells have been detected in peripheral blood (Bernardes et al., 2020). Although highly speculative, porphyria would explain many peculiarities of the Covid-19 phenotype including neurovisceral, neuromuscular and neurological symptomology, as well as the phenomenon of 'long Covid'. Hyponatraemia is another hallmark of acute porphyria and systematic reports of hyponatraemia in critical Covid- 19 patients are growing (Ata et al., 2020; Khan et al., 2020; Lippi et al., 2019). Exploratory analysis of erythropoiesis and hemoglobin metabolism may provide insight into the nature of the Covid-19 phenotype. Specifically, the author recommends testing the porphyria hypothesis by urinalysis of light-protected samples from critical Covid-19 patients to check for elevated aminolevulinic acid and porphobilinogen. Readily available interventions exist to treat acute porphyria (Stein et al., 2012) including intravenous heme arginate; intravenous glucose in water solutions are contraindicated due to aggravated hyponatraemia, which can prove fatal (Stein et al., 2012). Mortality rates for acute porphyria vary by patient population; in an Argentinian population of 102 patients, 15% with symptomatic acute porphyria died during an acute attack (De Siervi et al., 1999). Of the patients who died, respiratory failure induced by the porphyria attack itself was the precipitating factor in 61% of cases (De Siervi et al., 1999).

Conflict of interest statement

The author reports no conflict of interest

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Figure Legends

Figure 1. Covid-19 as acquired acute porphyria. There are multiple types of inherited porphyria, each of which affect enzyme functionality in catalysing specific steps in the ultimate conversion of aminolevulinic acid to heme. All the heme precursors are thought to be toxic88 and the liver is a major site of hemoglobin synthesis. Acute attacks of porphyria are usually associated with hepatic, rather than erythropoietic, involvement. SARS-Cov-2 receptors ACE2 and CD147 are both expressed in the liver (Wu et al 2014, Stebbing et al 2020, Li et al 2015) and liver is a known target organ of SARS-Cov-2 infection (Wang Y et al 2020). If SARS-Cov-2 disrupts any one or more steps in the heme biosynthesis pathway, porphyria may result; in particular, disruption of the final step may dampen negative feedback control on ALA-synthase.

Table 1. Comparison table of clinical signs and symptoms between SARS-Cov-1, SARS-Cov-2, and porphyria. Combinations of the symptom and disease terms were searched in the title of articles published in any year in Google Scholar; any combinations returning zero hits were cross-checked in PubMed. Between one and ten papers are cited per symptom-disease combination; for some combinations, the availability is greater than reported, and the present data are intended to be indicative rather than exhaustive.

Figure 2. Three-way symptomology comparison between SARS-Cov-1, Covid-19, and porphyria patients (a) liberal comparison (b) conservative comparison. Liberal comparison includes symptoms that have been reported in isolated cases in the literature and that have not necessarily been confirmed as being statistically associated with each condition. Conservative comparison excludes symptoms that are only reported in isolated cases. (a) Eighteen reported symptoms are shared between all three conditions. As expected, Covid-19 has high overlap of symptoms with SARS-1, with the two conditions sharing 22 symptoms and 4 symptoms differing between SARS-1 and Covid-19. The four symptoms that differ will, presumably, provide insight into the pathophysiological novelty of Covid-19 relative to SARS-Cov-1. The four symptoms are: paralysis, anosmia, ageusia and hyperinflammatory syndrome. Note that most of these symptoms have neurological involvement. The symptoms of overlap between Covid-19 and porphyria specifically are paralysis and sensory loss. (b) Similarly, to the liberal comparison, conservative comparison reveals that sensory loss and neuropsychiatric symptoms (and constipation) are shared by Covid-19 and porphyria specifically. As aforementioned, the three symptoms of sensory loss, paralysis and neuropsychiatric disorders have strong neuromuscular and neurological components - and may provide insight into the pathophysiology that is unique to Covid-19, in contrast with SARS-1.

Figure 3. Motif search for HXXXXH in SARS-Cov-2 Spike. Upper: script code imports the module regular expressions. HXXXXH motif is assigned to the variable 'motif' and the FASTA protein sequence of SARS-Cov-2 is assigned to the object 'protein' prior to motif search. Lower: output shows the position of histidine box origin as residue 1082 in spike.

Table 2. Tabular overview of sub-sequences identified within SARS-Cov-2 surface glycoprotein. Corresponding generic heme-binding motif structures are shown in the second column and sources of the generic motifs are listed on the RHS. Origin position of sub-sequences within the global spike glycoprotein are given in the middle column and the fourth column cites the region of spike in which the sub-sequence is located. Regions: NTD, N-terminal domain; RBD, receptor binding domain; S2, S2 domain.

Figure 4. Putative drug actions in Covid-19. LHS: chloroquine has been known since the 1970s to promote clearance of hepatic tissue-bound porphyrins via porphyrinuria. RHS: ivermectin interacts with the porphyrin transporter ABCG2 and may accelerate porphyrin export. PBG, porphobilinogen; PPIX, protoporphyrin IX.

Figures & Tables

Figure 1

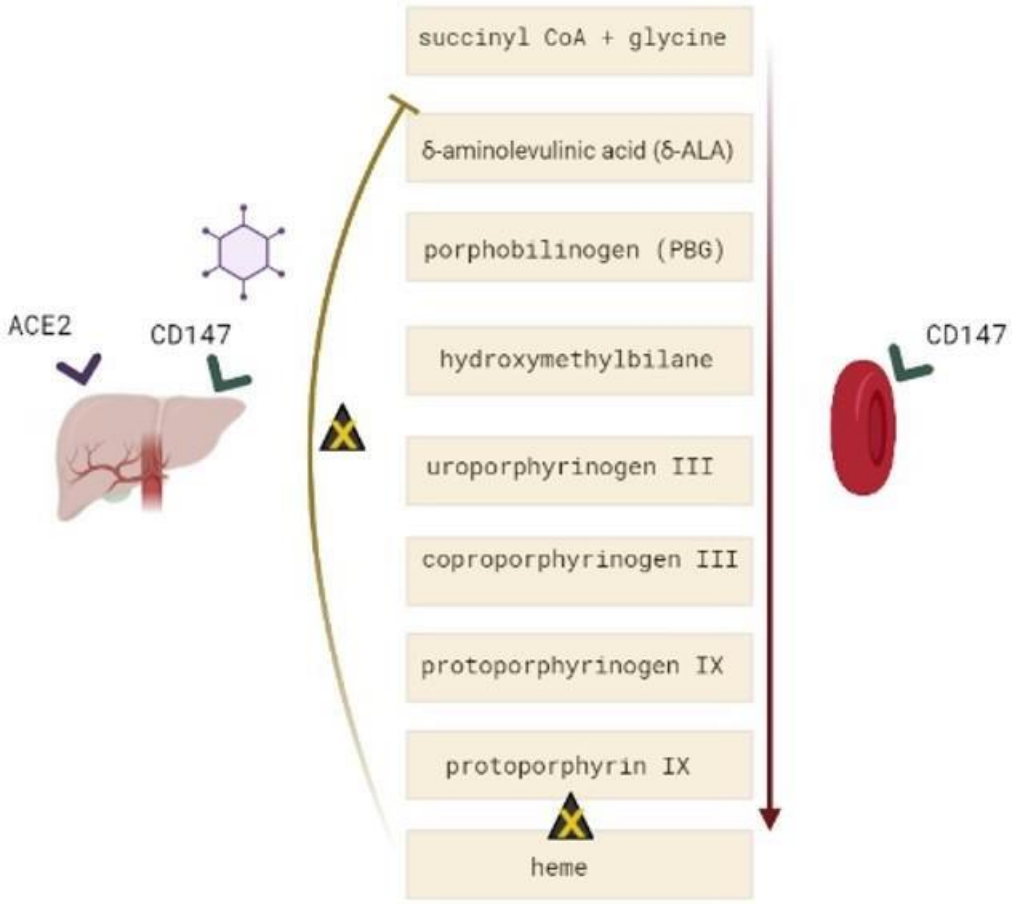


Table 1

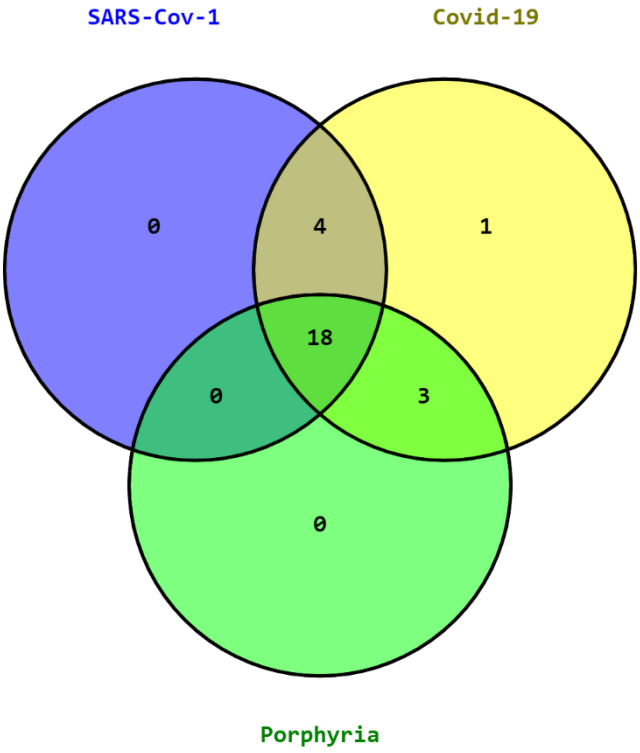
Symptom	*SARS-Cov-1*	*% patients or respondents*	*Source*	*SARS-Cov-2*	*% patients or respondents*	*Source*	*Porphyria*	*% patients or respondents*	*Source*
Fever	Y	100% 100% of 138 (H) 100% of 10 (H) 100% of 10 (H) 99-100% 99% of 144 (H) 99% of 357 (H) 91% of 21 (H)	WHO Lee 2003 Bitnun 2003 Hon 2003 Hui 2003 Booth 2003 Yin 2018 Chiu 2003	Y	85% of 180 (H) 83% of 99 (H) 87% of 249 (H) 77% of 244 (H) 45% of 7,123 (R) 34% of 6,452 (R)	Garg 2020 Chen N 2020 Chen J 2020 Takeuchi 2020 Hopkinson 2020 Menni 2020	Y	Isolated cases	Cohen 2005
Chills	Y	97% 73% of 138 (H) 50% of 10 (H) 48% of 21 (H) 28% of 144 (H) 15-73% 10% of 10 (H)	WHO Lee 2003 Hon 2003 Chiu 2003 Booth 2003 Hui 2003 Bitnun 2003	Y	46% of 251 (H) 85% of 180 (H)	Campioli 2020 Garg 2020	N	Not applicable	Not applicable
Myalgia	Y	81% 61% of 138 (H) 59% of 357 (H) 49% of 144 (H) 45-61% 40% of 10 (H) 10% of 21 (H)	WHO Lee 2003 Yin 2018 Booth 2003 Hui 2003 Hon 2003 Chiu 2003	Y	34% of 7,123 (R) 34% of 180 (H) 11% of 99 (H)	Garg 2020 Chen N 2020	Y	30% of 149 (H)	Bylesjö 2009
Persistent cough	Y	80% of 10 (H) 75% of 144 (H) 60% of 10 (H) 58% of 357 (H) 57-75% 50% of 138 (H) 43% of 21 (H) 39%	Hon 2003 Booth 2003 Bitnun 2003 Yin 2018 Hui 2003 Lee 2003 Chiu 2003 WHO 2003	Y	86% of 180 (H) 82% of 99 (H) 87% of 7,123 (R) 57% of 6,452 (R) 44% of 244 (H) 37% of 249 (H)	Garg 2020 Chen N 2020 Hopkinson 2020 Menni 2020 Takeuchi 2020 Chen J 2020	Y	Isolated cases	Quansah 2014
Sore throat	y	30% 13-25% 23% 17% of 357 (H) 13% of 144 (H) 10% of 10 (H) 5% of 21 (H)	Hon 2003 Hui 2003 WHO Yin 2018 Booth 2003 Bitnun 2003 Chiu 2003	Y	45% of 7,123 (R) 18% of 180 (H) 12% of 244 (H) 5% of 99 (H) 6% of 249 (H)	Hopkinson 2020 Garg 2020 Takeuchi 2020 Chen N 2020 Chen J 2020	N	Not applicable	Not applicable
Abdominal pain	Y	10% of 10 (H) 4% of 144 (H)	Hon 2003 Booth 2003	Y	30% of 7,123 (R) 21% of 6,452 (R) 8% of 180 (H) 1% of 204 (H)	Hopkinson 2020 Menni 2020 Garg 2020 Pan 2020	Y	100% of 102 (H) 99% of 91 (R) 94% of 50 (H) 86% of 149 (H)	De Siervi 1999 Andersson 2003 Yang 2019 Bylesjö 2009
Diarrhoea	Y	8% of 1,291 (H) 20-25% 24% of 144 (H) 17% of 357 (H) 10-20% (H) 10% of 21 (H) 10% of 10 (H)	Lai 2004 Hui 2003 Booth 2003 Yin 2018 CDC Chiu 2003 Bitnun 2003	Y	38% of 7,123 (R) 27% of 180 (H) 26% of 6,452 (R) 17% of 204 (H) 3% of 249 (H) 1% of 244 (H)	Hopkinson 2020 Garg 2020 Menni 2020 Pan 2020 Chen J 2020 Takeuchi 2020	Y	Typical	Kauppinen 2005
Nausea & vomiting	Y	20-35% 20% of 10 (H) 20% of 10 (H) 19% of 144 (H) 15% of 357 (H)	Hui 2003 Hon 2003 Bitnun 2003 Booth 2003 Yin 2018	Y	24% of 180 (H) 1% of 99 (H)	Chen N 2020	Y	72% of 50 (H) 51% of 91 (R) 36% of 149 (H) 11% of 102 (H)	Yang 2019 Andersson 2003 Bylesjö 2009 De Siervi 1999

Constipation	Y	Isolated cases	Lin 2003 Jin-Pan 2003	Y	Isolated cases	Chow 2020 Alvarez-Troncoso 2020	Y	57% of 91 (R) 42% of 50 (H) 41% of 149 (H) 37% of 102 (H)	Andersson 2003 Yang 2019 Bylesjö 2009 De Siervi 1999
Anorexia		57% of 21 (H)	Chiu 2003	Y	50% of 7,123 (R) 42% of 6,452 (R) 40% of 204 (H) 3% of 249 (H)	Hopkinson 2020 Menni 2020 Pan 2020 Chen J 2020	Y	37% of 102 (H)	De Siervi 1999
Headache	Y	84% 20-56% 50% of 138 (H) 39% of 357 (H) 35% of 144 (H) 40% of 10 (H) 14% of 21 (H) 10% of 10 (H)	WHO Hui 2003 Lee 2003 Yin 2018 Booth 2003 Hon 2003 Chiu 2003 Bitnun 2003	Y	68% of 7,123 (R) 16% of 180 (H) 8% of 99 (H) 11% of 249 (H) 3% of 244 (H)	Hopkinson 2020 Garg 2020 Chen N 2020 Chen J 2020 Takeuchi 2020	Y	13% of 149 (H)	Bylesjö 2009
Dizziness	Y	4-43% 61% 38% of 21 (H) 10% of 10 (H) 4% of 144 (H)	Hui 2003 WHO Hon 2003 Booth 2003	Y	2% of 141 (M) 11% of 249 (H)	Saniasiaya 2020 Chen J 2020	Y	Isolated cases	Solinas 2008
Neuropsychiatric	Y	Isolated cases	Sheng 2005 Hui 2009	Y	25% of 7,123 (R) 18% of 6,452 (R) 6% of 180 (H)	Hopkinson 2020 Menni 2020 Garg 2020	Y	72% of 50 (H) 59% of 91 (R) 29% of 149 (H) 18% of 102 (H)	Yang 2019 Andersson 2003 Bylesjö 2009 De Siervi 1999
Paralysis	N	Not applicable	Not applicable	Y	Isolated cases	Maurier 2020 Figueiredo 2020 Casas 2020	Y	20% of 149 (H)	Bylesjö 2009
Dyspnea	Y	42% of 144 (H) 14% of 21 (H) 40-42% 27% of 357 (H) 10% of 10 (H)	Booth 2003 Chiu 2003 Hui 2003 Yin 2018 Bitnun 2003	Y	80% of 180 (H) 60% of 7,123 (R) 31% of 99 (H) 15% of 6,452 (R) 8% of 249 (H) 8% of 244 (H)	Garg 2020 Hopkinson 2020 Chen N 2020 Menni 2020 Chen J 2020 Takeuchi 2020	Y	Isolated cases	Kauppinen 2005
ARDS	Y	10-20% 13-26%	WHO Lau 2004	Y	17% of 99 (H)	Chen N 2020	Y	Isolated cases	Kauppinen 2005
Septic shock	Y	15%	Lau 2004	Y	4% of 99 (H)	Chen N 2020	N	Not applicable	Not applicable
Multiple organ dysfunction	Y	15%	Lau 2004	Y	12% of 249 (H)	Chen J 2020	N	Not applicable	Not applicable
Pneumonia	Y	17% of 357 (H)	Yin 2018	Y	36% of 244 (H) 1% of 99 (H)	Takeuchi 2020 Chen N 2020	Y	Isolated cases	Kauppinen 2005
Thrombosis	Y	50% of 8 (H) 3% of 153 (H)	Chong 2004 Wong 2003	Y	16% of 3,334 (H)	Bilaloglu 2020	Y	Isolated cases	Dowman 2012
Tachycardia* arrhythmia	Y	72% of 121 (H) 46% of 144 (H)	Yu 2006 Booth 2003	Y	16.7% of 138 (H) Isolated cases	Wang 2020 Miglis 2020 Umapathi 2020 Gianfranco 2020 Babapoor-Farrokhran 2020 Reddy 2020	Y	30% of 102 (H) 10% of 149 (H)	De Siervi 1999 Bylesjö 2009

Chest pain	Y	10% of 144 (H)	Booth 2003	Y	50% of 7,123 (R) 43% of 6,452 (R) 15% of 180 (H) 2% of 99 (H)	Hopkinson 2020 Menni 2020 Garg 2020 Chen N 2020	Y	50-52% (H)	Sassa 2006
Anosmia* sensory loss	N	Not applicable	Not applicable	Y	68% of 7,123 (R) 65% of 6,452 (R)	Hopkinson 2020 Menni 2020	Y	7% of 149 (H) 17% of 91 (R)	Bylesjö 2009 Anderssson 2003
Ageusia* sensory loss	N	Not applicable	Not applicable	Y	65% of 6,452 (R)	Menni 2020	Y	7% of 149 (H)	Bylesjö 2009
Hyperinflammatory syndrome	N	Not applicable	Not applicable	Y	Isolated cases	Riphagen 2020	N	Not applicable	Not applicable
Rash* skin lesions	Y	5% of 21 (H)	Chiu 2003	Y	Isolated cases	Hay 2020	Y	Typical	Andersen 2014

Figure 2

a


SARS-Cov-1
Covid-19
0
4
1
18
0
3
0
Porphyria

b

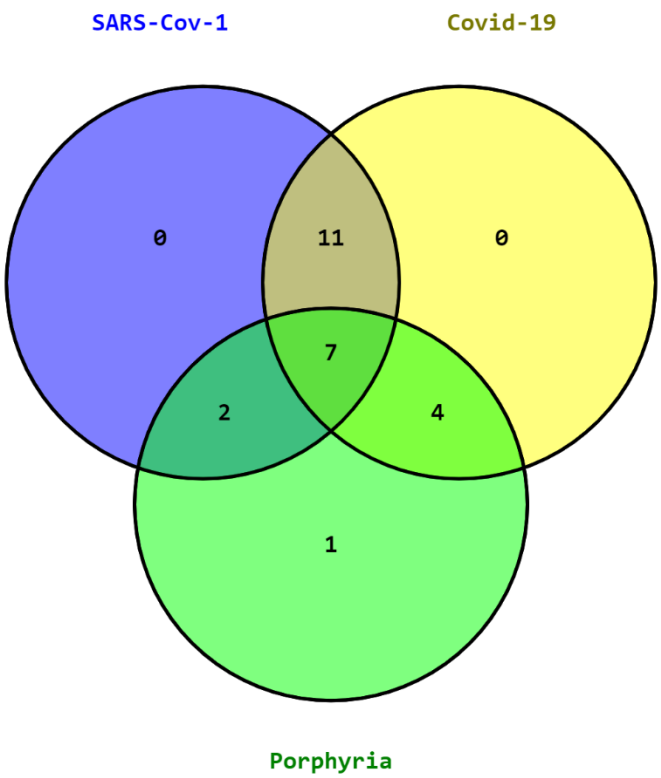

SARS-Cov-1
Covid-19
0
11
0
7
2
4
1
Porphyria

Figure 3

```
import re
motif = re.compile("H....H")
protein =
"MFVFLVLLPLVSSQCVNLITRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF
NDGVYFASTEKSNIIRG" \

"WIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNL
REFVFKNIDGYFKIYSK" \

"HTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCA
LDPLSETKCTLKSFTVE" \

"KGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNV
YADSFVIRGDEVRQIAP" \

"GQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQ
PTNGVGYQPYRVVVLSF" \

"ELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPG
TNTSNQVAVLYQDVNCT" \

"EVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSIIAYTMSLGAENS
VAYSNNSIAIPTNFTISV" \

"TTEILPVSMTKTSVDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPD
PSKPSKRSFIEDLLFNKV" \

"TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT
QNVLYENQKLIANQFNSA" \

"IGKIQDSLSSTASALGKLQDVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAA
EIRASANLAATKMSECVL" \

"GQSKRVDFCGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNT
FVSGNCDVVIGIVNNTVY" \

"DPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWLGFIAGL
IAIVMVTIMLCCMTSCCS" \
          "CLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT"
m = motif.search(protein)
if m:
    print("Found: ", m.group(), "at", m.start())
else:
    print("Not found")
```

```
C:\Users\Lianne\anaconda3\python.exe C:/Users/Lianne/PycharmProjects/motif/main.py
Found:  HDGKAH at 1082

Process finished with exit code 0
```

Table 2

Sub-sequence	Motif	Position	Region	Motif Source
HDGKAH	HXXXXH	1082	S2	NCBI accession AHE16524.1
CP	Cys-Pro	335	RBD	Kühl et al 2013
HY	His-Tyr	1270	S2	Syllwasschy et al (2020)
YH	Tyr-His	144	NTD	Syllwasschy et al (2020)
YY	Tyr-Tyr	36	NTD	Syllwasschy et al (2020)
YYH	YXH	143	NTD	Syllwasschy et al (2020)
YNY	YXY	420	RBD	Syllwasschy et al (2020)
HAIH	HXXH	65	NTD	Syllwasschy et al (2020)
HRSY	HXXY	244	NTD	Syllwasschy et al (2020)
YSKH	YXXH	203	NTD	Syllwasschy et al (2020)
YVGY	YXXY	265	NTD	Syllwasschy et al (2020)
YFKNH	YXXXH	1154	S2	Syllwasschy et al (2020)
YFKIY	YXXXY	199	NTD	Syllwasschy et al (2020)

Figure 4