COVID-19 Scientific Advisory Group
Rapid Evidence Report

Key Research Question: What non-respiratory tract symptoms and manifestations have been documented in association with COVID-19?

Context

- Coronavirus Disease 2019 (COVID-19) is generally considered a respiratory illness with predominant influenza-like symptoms (eg. fever, dry cough, sore throat).
- There is frequent news coverage of 'unique' presentations of COVID-19, such as rashes (eg. "COVID toes") or gastrointestinal symptoms (eg. diarrhea).
- This question was posed to identify the spectrum of non-respiratory tract documented COVID-19 presentations and unusual presentations that may be clinically important, but that did not fall into the expected upper and lower respiratory tract trajectory of disease.
- It is estimated that the most common case definition of cough and fever, if strictly applied, would miss 7% of hospitalized COVID-19 patients (Docherty et al., 2020).
- Given the very large number of documented COVID-19 infections to date (over 3.7 million as of May 7, 2020) and profusion of case reports, it is challenging to define both the potential clinical significance of rare findings, and the likelihood that specific newly reported clinical feature may be diagnostically discriminating in COVID-19. However, prothrombotic features which can affect multiple clinical presentations are gaining significant attention in defining the pathophysiology of severe disease.
- As of May 4, 2020, COVID-19 testing eligibility criteria for AHS was expanded to include chills, painful swallowing, stuffy nose, headache, muscle/joint pain, feeling unwell/fatigue/severe exhaustion, nausea/vomiting/diarrhea/unexplained loss of appetite, loss of smell or taste, and conjunctivitis.

Key Messages from the Evidence Summary

- COVID-19 infection is increasingly reported to manifest in most systems of the body: cardiopulmonary, gastrointestinal tract, skin, central nervous system, olfactory/gustatory systems, eyes, blood, and musculoskeletal system. Some manifestations may be associated primarily with viral infection and others may be inflammatory or immunologic sequelae, and less likely associated with transmission risk.
- Children and younger adults appear to be more commonly affected by specific chilblain-like lesions ("COVID toes") on the feet. Adults appear more likely to experience vesicular and livedoid rashes, although the incidence of rash varies between case series from various jurisdictions.
- Gastrointestinal (diarrhea, nausea, vomiting and abdominal pain), thrombotic (arterial thrombi and pulmonary emboli, as well as possible microcirculatory thrombi), and ocular manifestations (predominantly conjunctivitis) appear to primarily affect adults rather than children, although this may be related to a lower proportion of cases in children rather than age-related disease manifestation differences. Given the evolving understanding of thrombosis risk, VTE prophylaxis is highlighted as an intervention - AHS guidance for VTE prophylaxis in COVID-19 is available.
- Only GI symptoms and certain cutaneous symptoms have been specifically documented to appear as presenting complaints. Cardiopulmonary, thrombotic, neurological, musculoskeletal, and ocular complaints appear generally to occur in the context of coexisting or antecedent pulmonary or systemic symptoms. Some patients may experience predominantly gastrointestinal manifestations over respiratory manifestations, with 4% of patients experiencing GI symptoms alone in one very large series. In children, an inflammatory syndrome similar to Kawasaki disease shock syndrome is increasingly reported.
- Anosmia and ageusia (inability to smell and taste) appear to be common complaints among COVID-19 patients and have been added to symptom screening questionnaires.

Committee Discussion

The committee appreciated the breadth of the review. It was suggested that a specific discussion of manifestations that could be presenting symptoms be provided. It was agreed that the content may be amenable to presentation as an infographic as well as a full report, as one of the reasons for performing the review was to synthesize evolving information for care providers.

Pragmatic Considerations and Discussion

1. Clinicians should be aware of the many manifestations of COVID-19 and consider the possibility of COVID-19 even in the absence of fever, fatigue, or respiratory symptoms to ensure appropriate investigation of differential diagnoses. Knowledge of the local community prevalence will influence the likelihood that a particular non-respiratory presentation may be COVID-19 related.

   Rationale: COVID-19 manifestations have been identified affecting most major body systems, however the relative likelihood of many of these presentations seems low given the low numbers of cases reported compared to the worldwide burden of COVID-19 disease. Currently patients in Alberta presenting for hospital care without symptoms typically thought to be consistent with COVID-19 are still unlikely to have COVID-19, based on a recent Alberta screening program involving all patients presenting to the Emergency Department in 3 hospitals, screening revealed no SARS-CoV-2 infections in 943 cases.

2. The risk of transmission in non-respiratory presentations of COVID-19 would be related to both the type of interaction or procedure, and the phase of illness of the patient (for example, an immunologically mediated rash presenting after or in the absence of antecedent respiratory symptoms would be unlikely to be associated with transmission of infection.)

   Rationale: Patients may present with COVID-19-related complaints in the absence of fever and cough, but could potentially still transmit infection – however, some multisystem COVID-19 manifestations may be inflammatory or immune responses to infection, in which case transmission risk would be expected to be low. In addition is thought that patients without "droplet generating" respiratory symptoms likely transmit infection less. Although gastrointestinal symptoms are relatively common, there have been no cases of confirmed infection from fecal exposures to date.

Strength of Evidence

The published body of evidence for this topic was relatively large, but consisted mainly of small studies and case reports. Of 73 included articles from the database search, only five pieces of secondary literature (systematic reviews and meta-analyses) were identified and only one guideline was included. Most of the evidence was published as short reports, commentary, or letters to the editor.

The body of evidence on these topics are of very low quality. The sample sizes are generally very small (case series). In studies that used a defined methodology, the risk of bias was high, as participants were often identified after hospitalization. Studies that utilized surveys had a high risk of recall bias and selection bias, especially those that circulated via electronic means like social media. Since so much of the primary literature draws on emergency department presentation or hospitalization, the analyses presented in the secondary literature may be inflate the apparent prevalence or represent more severe cases of the disease. The applicability of the evidence is limited, since the majority of COVID-19 reports are from Europe, China, and the United States and it is unclear if population differences translate to the Alberta context.

The data varies considerably between reports because the evidence is largely observational studies or small case series/reports, The pathophysiology of SARS-CoV-2 is still unclear and study participants are often identified from specific populations rather than from random sampling, so the prevalence and association values of non-respiratory manifestations will continue to be inconsistent until this bias can be corrected by secondary analyses or large-scale association studies.

Limitations of this review

This review has several limitations. First, this is a very broad topic to address in a five-day review cycle. The search was thorough but not exhaustive, and the speed with which evidence is published limits the usefulness of

the indexing terms in literature databases. Further, we did not include articles published in languages other than English and only included articles published in 2020, potentially missing reports from early in the pandemic. The scope of this review limits how detailed and in-depth the report can be in the desired time frame. Each body system below could be its own review. Additional references were added from outside the literature review to address evolving topics, specifically, Kawasaki disease and myocardial involvement.

The COVID literature is rapidly evolving. New reports are published daily as more becomes known about the disease. As a result, most of the evidence collected is observational, with small sample sizes and drawn from specific populations.

Key Findings

Due to the broad scope of this review, a summary of the key messages from the evidence synthesis is provided here. More detail on each manifestation can be found in the Expanded Evidence Synthesis in the appendix of this document.

73 publications from the literature search and 15 articles that were *ad hoc* inclusions were included in the full narrative synthesis. Evidence for cutaneous, gastrointestinal, and ocular manifestations of COVID-19 was relatively robust, while evidence for neurologic, thrombotic, musculoskeletal, cardiac and olfactory manifestations was relatively limited.

The overall distribution of respiratory and non-respiratory symptoms has been described in a large study of 16749 hospitalized COVID-19 patients in the UK. This was a unique series because the symptom assessment was not limited by influenza-like illness (ILI) symptom screening tools, as a more general pandemic protocol was used for case assessment and sampling. In this work, three distinct predominant symptom clusters were identified: respiratory (cough, sputum, sore throat, runny nose, ear pain, wheeze, and chest pain); systemic (myalgia, joint pain and fatigue); and enteric (abdominal pain, vomiting and diarrhea) (Docherty et al., 2020).

After reviewing the literature search results and updated grey literature, the reports were grouped as follows: skin manifestations, neurological manifestations, musculoskeletal, coagulation system abnormalities, loss of smell and taste, gastrointestinal, ocular manifestations, and myocardial inflammation.

Reported Skin Manifestations

- 19 articles were included in the evidence synthesis that describe manifestations of COVID-19 in the skin. A key study of 375 cases in Spain described five clinical patterns of cutaneous manifestations: chilblains-like lesions (19%), urticarial lesions (19%), maculopapules (47%), other vesicular eruptions (9%), and livedo or necrosis (6%) (Galván Casas et al., 2020). The case reports and smaller studies included here aligned with these pattern.
- Skin manifestations rarely appear in the absence of other symptoms in adults. The absence of respiratory or systemic symptoms is most common in children, while rashes in adults appear either very close to the appearance of other symptoms or after respiratory symptoms have developed. The pathophysiology of may be related to infection, immunologic consequences of infection, or microvascular thrombosis, and may be difficult to distinguish from possible reactions to concurrent therapies in some cases, as most patients described received multiple medications.
- Chilblain-like lesions (frequently described as “COVID toes”) seem to be potentially a specific signal rash manifestation of COVID-19, and are not usually associated with severe disease, potentially appearing late after initial infection. This manifestation was more commonly reported in young adults and children, while vesicular, urticarial and livedoid lesions/acral necrotic lesions tended to be observed in adults.
- Maculopapules represent a common category of cutaneous lesions, and is likely non-specific in the context of COVID-19 particularly given the numerous medications utilized in patients described in these series. Multiple reports describe an itchy, generalized rash that usually occurs on the trunk and extremities with some involvement of the head and face that persists for about a week.

Reported Neurological Manifestations

- Ten articles were included in the evidence synthesis. Notably, guidelines from Brigham and Women's Hospital have been published to support clinicians who are assessing and treating neurologic manifestations of COVID-19 (McEntire et al., 2020).
  The most severe neurologic manifestation of COVID19 is stroke, which is increasingly recognized in association with COVID-19. Although the exact mechanism is unclear, it is thought potentially either due to a) coagulopathy b) vascular endothelial injury or c) myocardial injury. Prevalence of COVID-19-related stroke has been estimated at 2.8 – 5.7% (Asadi-Pooya & Simani, 2020; Mao et al., 2020).
- Data supporting specific association of other potential COVID-19 neurological manifestations in patient groups related to age, sex, medical history, or another relevant characteristic is very limited. It appears rare for neurological symptoms to present without any preceding systemic symptoms, as this was only described in two case reports.
- Delirium and confusion are the most common neurologic symptoms of COVID-19, followed by dizziness and headache. Encephalopathy and ophthalmoparesis have been noted in case reports. Rarer complications include Guillian-Barré Syndrome, Miller Fisher syndrome, necrotizing encephalopathy, and myelitis (McEntire et al., 2020).

Reported Musculoskeletal Manifestations

- It is generally accepted that myalgia and arthralgia are systemic symptoms of COVID-19 that occasionally can dominate the clinical presentation. Two case reports were identified that specifically referred to musculoskeletal complaints.
- Of interest, there was one case report of myositis as the initial COVID-19 symptom with fever and COVID-19 chest computed tomography (CT) results, but persistent negative PCR tests until day 11 after admission.

Reported Blood Coagulation Abnormalities

- Eleven articles were included in the evidence synthesis; among them, there were two larger studies with more than 50 patients. Coagulopathy appears to be associated with disease severity, advancing age, and male sex. Generally, coagulopathy complications are described as arising after the onset of other systemic or respiratory symptoms, rather than as the initial symptom, but may be presenting complaints.
- COVID-19-related stroke has been rising in prominence due to the pro-thrombotic properties of SARS-CoV-2. Stroke is described more thoroughly in the "Reported Neurological Manifestations" section of this report. Other manifestations reported in COVID-19 patients include pulmonary embolism, thrombosis, acute limb ischemia, and antiphospholipid antibody syndrome. Venous thromboembolism (VTE) prophylaxis is recommended for patients admitted with COVID-19 and a low threshold for investigation for thrombosis is suggested. Studies are ongoing regarding optimal prophylaxis and management. AHS guidance for VTE prophylaxis in COVID-19 is available.
- The coagulopathy observed in COVID-19 is poorly understood. Three main mechanisms for the hypercoagulable state of COVID-19 patients have been hypothesized: myocardial injury, complement-associated thrombosis, and antiphospholipid antibodies indicative of lupus anticoagulant.
  COVID-19 related thrombotic complications appears to be associated with laboratory abnormalities: high D-dimer concentrations, mildly prolonged INR/ prothrombin time (~ 1–3 s prolongation above normal range), mild thrombocytopenia (platelet count > 100 ×109/L) and normal or increased fibrinogen levels initially, with possible low fibrinogen later in disease.
- Anecdotal evidence suggests that thrombi from COVID-19 patients have a different gross appearance and clinical characteristics than thrombi in non-COVID patients. More evidence is needed to confirm this finding.

Reported Loss of Smell and Taste

- Two large studies were identified that describe anosmia and ageusia in COVID-19 (Beltrán-Corbellini, et al., 2020; Lechien et al., 2020).

- In these series, approximately 81-86% of patients develop anosmia, while approximately 90% of COVID-19 patients develop ageusia. The loss of smell/taste is reported to last 5-10 days and resolves within 8 days of disease resolution for 73% of patients.
- The timing of onset of anosmia and ageusia relative to other symptoms is unclear. Twelve to 36% of patients report it as the initial symptom, while 65% report it occurs after and 23% report occurrence at the same time as other systemic symptoms.
- The underlying mechanism of COVID-19-related anosmia and ageusia is unknown, but is thought possibly related to virally-mediated inflammation in the upper aerodigestive tract, or possibly represent a neurologic symptom.

Reported Gastrointestinal (GI) Manifestations

- The body of literature is relatively robust for GI manifestations of COVID-19. A high-quality systematic review and meta-analysis was released by the American Gastroenterological Association (AGA) on May 4, 2020 and includes best practice recommendations and clinical implications of COVID-19 in gastroenterology (Sultan et al., 2020), and 13 other publications were included in this review.
- Pooled prevalence of GI symptoms in this meta-analysis was 10%, which is lower than previously thought. GI symptoms occur most commonly in middle-aged patients (around 50 years old), with no difference in gender.
- Diarrhea (7.7%), nausea/vomiting (7.8%), and abdominal pain (3.6%) (sometimes observed as back or testicular pain) are the most frequently observed GI symptoms. The majority of studies from China listed lower prevalence estimates than elsewhere, potentially due to case definition evolution as the initial epidemic progressed. When Chinese studies were removed from the analysis, the prevalence of diarrhea increased to 18% and of nausea/vomiting to 15%.
- Liver biochemical enzyme abnormalities are reported inconsistently. Sultan (2020) reports a prevalence of elevated aspartate transaminase (AST) of 15% and elevated alanine transaminase (ALT) of 15% (defined as any value above ULN), while other studies report no change.
- In a report of 16749 hospitalized patients in the UK with documented COVID-19, 29% of all patients had GI symptoms at admission, mostly in association with respiratory symptoms, and 4% had enteric symptoms alone (Docherty et al., 2020).

Reported Ophthalmic Manifestations

- Seven articles were included in the evidence synthesis for this review.
- The prevalence of ophthalmic symptoms of COVID-19 varies widely in case series, from 1% to 32% (Loffredo et al., 2020; Ulhaq & Soraya, 2020). Overall, the pooled prevalence is estimated to be 5.5% (Ulhaq & Soraya, 2020). Underreporting of mild eye symptoms in the absence of targeted screening questions is one possible reason for this variance and low prevalence.
- The primary eye complaint described is conjunctivitis, with symptoms including foreign body sensation, redness, and discharge with or without vision impairment. Swelling of the pre-auricular lymph nodes has also been observed.
- The relationship between systemic/respiratory symptoms and ophthalmic symptoms remains unclear, with conflicting reports of the emergence of symptoms (relative to systemic/respiratory symptoms) and the duration of ophthalmic symptoms.
- Despite evidence of viral conjunctivitis and ophthalmic involvement in COVID-19, tears or conjunctival swabs do not appear to be a good sample collection site. Nasopharyngeal swabs are preferred for molecular SARS-CoV-2 testing.

Reported Myocardial Inflammation and Cardiomyopathy

- Myocardial injury in COVID-19 is associated with higher mortality, but it is unclear if cardiac injury is related directly to viral myocarditis or from indirect complications of COVID-19. Several cases of myocarditis have been described, and one case was reported with an endomyocardial biopsy revealing a T lymphocytic inflammatory infiltrate, with RT-PCR negative for SARSCoV-2. This was felt to be suggestive of reverse Takotsubo cardiomyopathy rather than viral myocarditis.

Other Manifestations

- One case report was identified where persistent hiccups were the presenting complaint, followed rapidly by systemic symptoms upon admission to the medical unit.
- There are increasing media reports of Kawasaki disease (KD), a prolonged febrile illness of children which can cause cardiac complications, as a possible consequence of COVID-19. The pathophysiology and epidemiologic link for this association is not clear. Physicians looking after children should recognize that persistent fever, skin, and oral manifestations should prompt consideration of KD, as therapy may prevent cardiac complications.
- A small case series reported a severe variant presentation reminiscent of Kawasaki disease shock syndrome, with clinical features of an antecedent diarrhea syndrome followed by a hyperinflammatory syndrome with multiorgan involvement (Riphagen et al., 2020). The children tested negative for SARSCoV-2 by RTPCR but were reportedly antibody positive. Cardinal clinical features included fever, conjunctivitis, rash, and antecedent diarrhea.

Evolving Evidence

The evidence for this topic is evolving very quickly – new reports are published daily. This review should be revisited in 2-4 weeks for updating.

Date question received by advisory group: 30 April 2020

Date report submitted to committee: 8 May 2020

Date of first assessment: 12 May 2020

Authorship and Committee Members

This report was written by Rachael Erdmann and scientifically reviewed by Lynora Saxinger (co-chair), Kerri Johansson (external reviewer), Bijoy Menon (external reviewer, Sander Van Zanten (external reviewer), Tom Salopek (external reviewer), Chad Baker (external reviewer), Glen Hazlewood (external reviewer), and Frances Carr (external reviewer). The full Scientific Advisory Group was involved in discussion and revision of the document: Braden Manns (co-chair), John Conly, Alexander Doroshenko, Shelley Duggan, Nelson Lee, Elizabeth MacKay, Andrew McRae, Jeremy Slobodan, James Talbot, Brandie Walker, and Nathan Zelyas.

Appendix

List of Abbreviations

AHS: Alberta Health Services

COVID-19: Coronavirus Disease-2019

SAG: Scientific Advisory Group

KRS: Knowledge Resource Services

GI: Gastrointestinal

AST: Aspartate transaminase

ALT: Alanine transaminase

CT: Computed Tomography

AGA: American Gastroenterological Association

ILI: Influenza-like illness

KD: Kawasaki Disease

RT-PCR: Reverse Transcriptase Polymerase Chain Reaction

ULN: Upper Limit of Normal

Expanded Evidence Synthesis

The full narrative synthesis of the evidence is included below. The key findings presented in the main body of the report are drawn from the reviews presented here.

Reported Skin Manifestations

19 published articles were included that describe manifestations of COVID-19 in the skin. Almost of the published literature exists as letters, with the current body of evidence mostly consisting of case reports and small case series. Four articles with larger populations (n >50) were identified that describe the patterns seen in cutaneous manifestations of COVID-19. There has been increasing recognition of possible skin manifestations of COVID-19 in a large Chinese report of 1099 patients, rash was reported in 2 (0.2%) (Guan et al, 2020), in contrast, in a series of 88 COVID-19 patients assessed by a dermatologist in Italy, 18 (20.4%) developed skin manifestations, 44% at disease onset and 56% after hospitalization. Often, skin complaints were preceded by systemic symptoms such as cough, fever, or gastrointestinal complaints (Piccolo et al., 2020; Landa et al., 2020, Galván Casas et al., 2020; Marzano et al., 2020; Recalcati, 2020a; Fernandez-Nieto et al., 2020). Given the number of cases worldwide, it is unlikely that a specific and common COVID rash exists, and many associations may not prove to be infection related. In most series, patients received multiple medications, and medication related side effects or other concurrent primary skin diseases could not be ruled out. Finally, there is a paucity of biopsy correlation reported thus far and whether there are prognostic or diagnostic correlates to any specific rash remains unclear and preliminary.

Classification systems for the relatively small number of existing reported skin manifestations have been proposed including the suggestion that two pathophysiologic categories of dermatologic manifestations include vascular lesions and inflammatory lesions (Bouaziz et al., 2020). Recalcati (2020) observed three clinical types of skin manifestation: erythematous rash, widespread urticaria, and chickenpox-like vesicles primarily affecting the trunk. A potentially more inclusive set of five clinical patterns, was observed in a large consensus study of cases described by Spanish dermatologists (n=375) (Galván Casas et al., 2020), who

described “chilblains like” lesions, other vesicular eruptions, urticarial lesions, maculopapular rash, and livedoid rash. These patterns are further described below from that series, and from additional case studies.

1) *Maculopapules (47%)*
As suggested by Galván Casas (2020), maculopapular rashes make up a large proportion of COVID-19 associated skin manifestations. Accordingly, this is a broad category of rashes. Seven articles were included that describe this manifestation – five case reports, one small case series and one cross-sectional analysis (n=14). Given the common scenario of multiple medications being used in moderately to severely ill patients the specificity of this presentation in COVID-19 is felt to be low.

   Maculopapular rashes generally appeared after or close to the initial symptom onset (Amatore et al., 2020; Avellana Moreno et al., 2020; Hunt & Koziatek, 2020; Rivera-Oyola, 2020; Galván Casas et al., 2020). The rash lasts for approximately 8 days and is itchy in approximately 60% of cases (Galván Casas et al., 2020). Reports from Amatore (2020), Avellana Moreno (2020), Hunt & Koziatek (2020), Mahé (2020), and Rivera-Oyola (2020) all describe a rash that is fairly generalized, but is usually seen on the trunk and extremities, with some involvement of the head and face.

   There is limited evidence on whether these occur without respiratory or systemic symptoms. Recalcati et al. (2020b) describes cutaneous symptoms without systemic symptoms in children and young adults, and this is also reported by Amatore et al. (2020). Patients in the group with urticaria and maculopapular eruptions were receiving drugs more commonly than those with pseudo-chilblain or vesicular lesions, but less than those with maculopapules or livedoid lesions, congruent with the association of maculopapular rash and disease severity (Galván Casas et al., 2020).

   One unusual case was reported by Estébanez et al. (2020), where a yellowish papular rash was observed 13 days after COVID-19 testing. In this case, the lesions persisted after corticosteroid treatment and became erythematous plaques that were both hardened and pruritic. This case may belong to a family that was not identified by Galván Casas (2020) or may represent an existing clinical pattern with an expanded case definition

2) *Chillblains-like lesions (19% of cases)*
Chillblains-like manifestations have been dubbed “COVID Toes” in the media and are more common in children and young adults (Landa et al, 2020; Piccolo et al., 2020; Galván Casas et al., 2020; Fernandez-Nieto et al., 2020). These lesions appear on the toes, soles, fingers, extremities and heels of patients (Landa et al., 2020). It is characterized by red to violet macules, plaques and nodules, usually at the distal aspects of toes and fingers (Fernandez-Nieto et al., 2020; Galván Casas et al., 2020; Piccolo et al., 2020; Alramthan & Aldaraji, 2020; Bouaziz et al., 2020; Sigal et al., 2020). An Italian survey of probable COVID-19 cases (untested due to the lockdown) performed through social media suggested that of 63 reported skin lesions, the feet alone were mostly affected (85.7%) followed by feet/hands together (7%) and hands alone (6%) (Piccolo et al., 2020). Further, of 54 uploaded images, 31 (57%) showed erythematous-oedematous lesions and 23 (42%) showed blistering lesions. Pain and/or itch were present in 27% of cases, with both in 21% of cases; lesions were asymptomatic in 25% of cases (Piccolo et al., 2020). A history of perniosis is not common in these cases (Galván Casas et al., 2020).

3) *Urticarial lesions (19%)*
Two articles (3 patients in total) reported urticarial lesions associated with COVID-19. In each of the three cases, the generalized rash appeared within two days (before or after) systemic symptoms such as sore throat, myalgia, and fever (Damme, Berlingin, Suassez & Accaputo, 2020; Henry, Ackerman, Sancelme, Finon & Esteve, 2020). In one included patient, the rash was relatively localized to the forearms (Damme et al., 2020). In all cases, the rash did not extend to the face (Damme et al., 2020; Henry et al., 2020).

   No consistency was seen the ages of the cases – they include a 71-year old male, a 39-year old female (Damme et al., 2020) and a 29-year old female (Henry et al., 2020).

4) *Other vesicular eruptions (9%)*
One study was identified that described chickenpox-like lesions as a manifestation of COVID-19 (Marzano et al. 2020). Marzano (2020 describes a case series of 22 Italian patients. The rash (varicella-like papulovesicular exanthem) was usually observed on the trunk, but also in limbs in 18% of cases. The rash did not spread to the face or mucous membranes, and generally only had mild itching in 41% of cases (Marzano et al., 2020). Male patients were over-represented (73%) and the median age was 60 years.

Galván Casas (2020) notes that vesicular lesions appeared in middle aged patients, lasted for a mean of 10.4 days, appeared more commonly (15%) before other symptoms and were associated with intermediateintermediate severity. Itching was common (68%). These patterns are consistent with Marzano (2020).

5) *Livedo or necrosis (6%)*
One small case series (n=2) (Manalo, Smith, Cheeley & Jacobs, 2020) was identified in addition to the pattern identified by Galván Casas (2020). The livedoid lesions were more common in older adults and are not strongly associated with disease severity (Galván Casas et al., 2020). The livedo-like lesion was characterized by a lacy, asymptomatic rash on the legs (Manalo et al., 2020). In the two cases identified by Manalo (2020), there was little similarity between the two patients, the rash was transient (lasting less than 24 hrs) and did not have similar preceding events. Finally, a case series of 5 patients with severe SARSCoV-2 infections with features of retiform purpura or livedo racemosa had biopsy or autopsy findings of microvascular injury and thrombosis, consistent with activation of the alternative pathway (AP) and lectin pathway (LP) of complement with thrombotic microvascular injury (Magro et al). In these patients complement deposition was also noted in lung septal microvasculature.

Reported Neurological Manifestations

Ten publications were identified that describe the neurological manifestations of COVID-19. Of these, there was one clinical guideline, one systematic review, and one large case series (n=58); the rest were case reports or small case series.

Nervous system involvement appears to be common in COVID-19. Guidelines from Brigham & Women's Hospital suggest that 36-69% of hospitalized patients experience neurological symptoms (McEntire et al., 2020) which is supported by the included systematic review (Asadi-Pooya & Simani, 2020). There does not appear to be a pattern of patient groups related to age, gender, medical history, or other relevant characteristic. It is rare that neurological symptoms appear without any preceding systemic symptom (Joob & Wiwanitkit, 2020; Singhania, Bansal & Singhania, 2020).

Overall, the literature is still highly variable on the prevalence of neurologic symptoms in COVID 19. The guidelines suggest that delirium and confusion are common (McEntire et al, 2020). Headache is less common (ranging from 6-13%) as is dizziness (ranging from 9-18%) (McEntire et al., 2020; Asadi-Pooya & Simani, 2020). Impaired sense of taste and smell has been noted as a potential neurologic symptom, but the exact mechanism of this symptom is unclear (McEntire et al., 2020).

More severe neurological manifestations have been noted as a result of the coagulopathic properties of SARS-CoV-2, such as stroke (2.8-5%), thrombosis (0.5%), and other cerebrovascular problems (McEntire et al., 2020; Asadi-Pooya & Simani, 2020). A case series from Wuhan in China reports a hospital-based prevalence of acute stroke of 5.7% in patients affected with COVID-19 (Mao et al., 2020). A recent case series (n=5) from Mount Sinai Hospital in New York suggests that ischemic strokes due to large vessel occlusions can be seen in the young (Bonow, Fonarow, O'Gara & Yancy, 2020). Encephalitis and encephalomyelitis were documented in two unique case reports (Ye, Ren & Lv, 2020; Zhang, Rodricks & Hirsh, 2020) as well as in the secondary literature (McEntire et al., 2020; Asadi-Pooya & Simani, 2020). Ophthalmoparesis with cranial nerve palsies have been observed in a case report of two patients with COVID-19 (Dinkin et al., 2020).

Cases of rarer complications are also emerging including Guillian-Barré Syndrome, Miller Fisher syndrome, necrotizing encephalopathy, and myelitis (McEntire et al., 2020).

One case series of five infants with neurological symptoms of COVID-19 was identified in the search. The otherwise healthy infants displayed neurological symptoms at admission, such as axial hypotonia or drowsiness and moaning sounds, or both (Nathan, Prevost & Corvol, 2020). They rapidly recovered and were discharged 1-3 days after admission (Nathan, Prevost & Corvol, 2020).

Interested readers are referred to the full Brigham and Women's Hospital guidelines (McEntire et al., 2020) for recommendations on the clinical range and treatment of neurological symptoms of COVID-19.

Reported Musculoskeletal Manifestations

Two articles were included that related to specific musculoskeletal complaints in COVID-10. Both are case reports published as letters, as it is generally accepted that arthralgia and myalgia are systemic symptoms of COVID 19.

One report from Thailand was published early in the pandemic and describes arthralgia as a complaint due to the possibility of a COVID-19 case being misdiagnosed as Dengue (Joob & Wiwanitkit, 2020).

One case report from France described a case of myositis as the initial COVID-19 symptom, with a fever appearing on day 4 and a chest CT showing bilateral ground-glass opacities (Beydon et al., 2020). This case was also notable for the persistent negative nasopharyngeal PCR tests, with SARS-CoV-2 first detected in bronchoalveolar lavage fluid on day 11 after admission.

Reported Blood Coagulation Abnormalities

Eleven publications were included that relate to abnormal clotting properties observed in people infected with SARS-CoV-2. One review was included, two were large studies with >50 patients, and the rest were small case series or reports.

Abnormalities in blood coagulation in the context of COVID-19 are poorly understood. There have been multiple reports of pulmonary embolism (Berre, Marteau, Emmerich, & Zins, 2020; Sulemane, Baltabaeva, Barron, Chester & Rahman-Haley, 2020), thrombotic complications (Klok et al., 2020; Lee, Fralick & Sholzberg, 2020; Magro et al., 2020), limb ischemia due to arterial thrombosis (Perini, Nabulsi, Bianchini Massoni, Azzarone, Freyrie, 2020; Bellosta et al., 2020; Zhang, Xiao & Zhang et al., 2020), and antibodies associated with antiphospholipid syndrome (Zhang, Xiao & Zhang, 2020; Bowles et al., 2020).

Three reports suggest a hyper-coagulant state in patients, via different potential mechanisms. Complement-associated thrombosis is suggested by Magro et al. (2020), and complement-associated injury helps explain both the dermatologic, pulmonary, and thrombotic pathology seen in patients. Anti-phospholipid antibodies were observed by Bowles et al. (2020) and Zhang, Xiao & Zhang et al. (2020) suggesting the presence of lupus anticoagulant. Myocardial injury has also been suggested as a mechanism for hypercoagulability in COVID-19 patients (Bonow et al., 2020)

Coagulopathy appears to be associated with COVID-19 severity (Lee, Fralick & Sholzberg, 2020), advancing age (Bellosta et al., 2020; Klok et al., 2020), and male sex (Klok et al., 2020; Bowles et al., 2020; Bellosta et al., 2020). Pulmonary embolism was the most common complication in a study of 184 COVID-positive ICU patients (Klok et al., 2020), although there were several independent reports of acute limb ischemia (Bellosta et al., 2020, Perini et al., 2020; Zhang, Xiao & Zhang, 2020; Berre et al., 2020) with both venous and arterial involvement (Bellosta et al., 2020; Klok et al., 2020). Generally, coagulopathy complications arose after other systemic or respiratory symptoms, instead of as the initial symptom (Berre et al., 2020; Magro et al., 2020; Sulemane et al., 2020; Zhang, Xiao & Zhang, 2020; Perini et al., 2020; Bellosta et al., 2020). Stroke related to COVID-19 coagulopathy is described more thoroughly in the "Reported Neurological Manifestations" of this report.

High D-dimer concentrations (≥ 2 times above normal range) were noted in patients with coagulation abnormalities, and were associated with poorer outcomes (Lee, Fralick & Sholzberg, 2020; Bellosta et al., 2020; Sulemane et al., 2020). Other laboratory values associated with COVID thrombosis include mildly prolonged prothrombin time (~ 1–3 s prolongation above normal range), mild thrombocytopenia (platelet count > 100 ×109/L)

and, in late disease and decreased fibrinogen levels (< 2 g/L [5.88 µmol/L]) (Lee, Fralick & Sholzberg, 2020), while in other studies a normal or elevated fibrinogen has been observed (Spiezia et al., 2020.) Therefore a high index of suspicion for thrombosis assessment, and routine use of venous thromboembolism (VTE) prophylaxis has been recommended. Alberta Health Services guidance is available for VTE prophylaxis in COVID-19 (AHS VTE Working Group, 2020). Studies regarding intermediate or high dose prophylaxis are planned (Bikdeli et al, 2020).

Anecdotally, Bellosta et al. (2020) noted that the thrombi extracted from patients in their study were appeared markedly different than thrombi in non-COVID patients. COVID thrombi have a typical gelatinous appearance and are striped black and grey (images are available here) (Bellosta et al., 2020). More histological evidence is needed to confirm the reason for this morphology.

Reported Loss of Smell and Taste

Two publications were included that described the extent of olfactory and gustatory involvement in COVID-19. Loss of smell and taste as a symptom of COVID-19 has been reported in the media, but limited evidence was identified in the search. Both included studies were peer-reviewed and included large (>50) case numbers.

A large retrospective cohort of European centres (n=417) found that 86% of patients lost their sense of smell and 89% of patients lost their sense of taste (Lechien et al., 2020). A Spanish case-control study (case n=79, control n = 40) showed that among COVID-19 patients with new-onset smell/taste disorders, 81% presented with smell disorders and 90% with taste disorder (Beltrán-Corbellini et al., 2020). Smoking and nasal obstruction increase the odds ratio of a smell/taste disorder from 4.5 to 21.4 (Beltrán-Corbellini, et al., 2020). It is unclear if specific populations are affected by loss of smell and taste. The reported mean age in the two studies is very different – 62 years (Beltrán-Corbellini et al., 2020) vs. 36 years (Lechien et al., 2020). This may be an artifact of the fact that the population in Beltrán-Corbellini (2020) was hospitalized patients, while Lechien (2020) utilized a questionnaire that was sent to COVID-19 positive patients following testing. No significant difference was shown related to gender (Beltrán-Corbellini et al., 2020).

Onset of anosmia and ageusia relative to other symptoms varies, with 12%-36% reporting it as the initial manifestation (Beltrán-Corbellini, et al., 2020; Lechien et al., 2020), while others report loss of smell and taste after (65%) or at the same time (23%) as other symptoms (Lechien et al., 2020). The underlying mechanism of COVID-19-related anosmia and ageusia is unknown, but is thought possibly related to virally-mediated inflammation in the upper aerodigestive tract, possibly a neurological symptom. Changes in sense of smell are observed as a spectrum – 80% of patients were anosmic, 20% were hyposmic. 13% reported phantosmia, and 32% reported parosmia (Lechien et al. 2020). There is a significant positive association between loss of smell and taste. In patients without gustatory dysfunction, 44% have no olfactory dysfunction, whereas 37% and 9% of patients had anosmia or hyposmia (Lechien et al., 2020).

On average, the loss of smell and taste lasted 7.5±3.2 days (Beltrán-Corbellini et al., 2020), but was also seen to persist past the resolution of other symptoms in the majority (63%) of cases (Lechien et al., 2020). Symptom recovery was observed within 8 days following disease resolution in 73% of patients (Lechien et al., 2020).

Although it may seem trivial, loss of smell and taste significantly affects the patient's quality of life. (Lechien et al., 2020).

Reported Gastrointestinal Manifestations

Fourteen publications related to gastrointestinal (GI) symptoms were identified for inclusion. The body of evidence for this manifestation is relatively large but is hampered by methodological shortcomings. The American Gastroenterological Association (AGA) (Sultan et al., 2020) has recently (May 4, 2020) released a large systematic review and meta-analysis on GI manifestations of COVID-19. In addition to this article, eight small case reports/series and five larger analysis studies (including >50 patients) were included in this synthesis.

Reports of the prevalence of GI symptoms vary wildly in the literature due to persistent methodological bias in sample collection. Estimates range from 18.6% (Pan et al., 2020) to 61% (Lin et al., 2020). The analysis by Sultan et al. (2020) shows that the probable true prevalence of any GI symptom is lower than previously thought at 10%

of cases. Patients with GI symptoms appear to be middle-aged (around age 50) on average, with no difference in gender (Pan et al., 2020; Poggiali, Ramos, Bastoni, Vercelli & Magnacavallo, 2020)

The most common GI symptoms associated with COVID-19 are diarrhea, nausea/vomiting, and abdominal pain (Sultan et al., 2020; Henry, de Oliveira, Santos, Benoit & Lippi, 2020; Lin et al., 2020; Pan et al., 2020; Gahide, Frandon & Vendrell, 2020; Azwar, Kirana, Kurniawan, Handayani & Setiati, 2020). Some case reports suggested back pain (Pazgan-Simon, Rorat, Bucyńska, Zińczuk & Simon, 2020; Poggiali et al., 2020; Kim, Thomsen, Sell & Goldsmith, 2020) and testicular pain (Kim et al., 2020) as associated symptoms.. Anorexia was reported in three studies (Lin et al., 2020; Poggiali et al., 2020; Redd et al., 2020), although this may be a result of the GI symptoms rather than the infection itself. GI symptoms are often described as concurrent with respiratory and systemic symptoms (Pan et al., 2020;; Redd et al., 2020; Wei et al., 2020), and the prevalence of GI symptoms without respiratory symptoms is unclear (Sultan et al., 2020) but has been noted (Pautrat & Chergui, 2020). In a large study of 16749 inpatients with COVID-19 in the UK 4% had GI symptoms without other symptoms (Docherty et al, 2020). Chest imaging following suspicion of SARS-CoV-2 infection confirmed COVID-19 to complement or in the absence of molecular testing (Yang, Zhao, Yan, Zhang, Wang & Li, 2020; Pautrat & Chergui, 2020; Poggiali et al., 2020; Pazgan-Simon et al., 2020; Lin et al., 2020; Li, Chu, Luo, Huang, Hao & Fan, 2020; Gahide, Frandon & Vendrell, 2020; Fu, Qian & Fu, 2020).

Diarrhea and nausea/vomiting have a similar pooled prevalence of 7.7% and 7.8%, respectively, compared to the pooled prevalence of abdominal pain (3.6%) (Sultan et al., 2020). It was noted in Sultan (2020) that the preponderance of studies from China skew the evidence downwards – when Chinese studies were removed from the analysis, the prevalence of diarrhea rises to 18.3% and of nausea/vomiting to 15%. GI symptoms are variably associated with disease severity – Abdominal pain was significantly associated with increased COVID-19 severity (OR 3.93 [95% CI 1.64–9.38), while nausea/vomiting were significantly associated with a marginally increased odds of severe COVID-19 (OR 1.65 [95% CI 1.06–2.57), and diarrhea was not associated with disease severity (OR 1.24 [95% CI 0.90–1.71) (Henry et al., 2020).

Liver biochemical abnormalities have been noted in cases where GI symptoms are reported, but this is not seen consistently. Sultan (2020) reports a pooled prevalence of elevated aspartate transaminase (AST) of 15.0% (13.6 to 16.5) and elevated alanine transaminase (ALT) of 15.0% (13.6 to 16.4); Pan (2020), Poggiali (2020), and Pazgan-Simon (2020) also report elevated liver enzymes associated with GI symptoms. Wei (2020) and Redd (2020) report no difference in liver enzymes.

Despite the evidence for GI involvement in COVID-19, stool should not be relied upon as sampling site, as only 70% of samples from stool were positive after respiratory testing was negative (Sultan et al., 2020).

For best practices and further information about best practices and clinical implications of COVID-19 in gastroenterology, it is highly recommended that interested parties read the full report (Sultan et al., 2020) released by the AGA.

Reported Ophthalmic Manifestations

Seven articles were included that related to ocular/ophthalmic symptoms of COVID-19. Two meta-analyses were identified, and the rest are case reports or small case series.

The prevalence of ophthalmic symptoms varies widely, from 1% (Loffredo et al., 2020) to 32% (Ulhaq & Soraya, 2020). Notably in these two meta-analyses, all of the included studies were from China – there is very limited data from Europe or North America. Overall, pooled prevalence was calculated to be 5.5% (Ulhaq & Soraya, 2020).

The primary eye complaint associated with COVID-19 is conjunctivitis (Chen et al., 2020; Khavandi, Tabibsadeh, Naderan, & Shoar, 2020; Loffredo et al., 2020; Salducci & La Torre, 2020), however, the report that did not specifically name conjunctivitis referred to similar symptoms such as foreign body sensation, redness, and discharge with or without vision blurring (Daruich, Martin & Bremond-Gignac, 2020). There was one case report of keratoconjunctivitis (Cheema et al., 2020). Swelling of the preauricular lymph nodes has also been observed (Salducci & La Torre, 2020; Cheema et al., 2020; Chen et al., 2020).

The relationship between systemic/respiratory symptoms and ocular symptoms is unclear. Loffredo (2020) and Chen (2020) suggest that non-ophthalmic symptoms come first, while case reports from Khavandi (2020), Cheema (2020), Daruich (2020), and Salducci (2020) suggest that conjunctivitis can be observed prior to the development of respiratory or systemic symptoms. It is unclear how long ophthalmic symptoms last, with two reports suggesting at least 10 days (Cheema et al., 2020; Khavandi et al., 2020), while one report suggested a duration of 3 days (Chen et al., 2020).

Despite evidence of viral conjunctivitis and ophthalmic involvement in COVID-19, tears are not a good sample collection site. Three studies reported that it was difficult to detect SARS-CoV-2 in tears (Ulhaq & Soraya, 2020; Cheema et al., 2020; Loffredo et al., 2020), and that a nasopharyngeal swab was preferred for molecular testing.

Reported Myocardial Inflammation and Cardiomyopathy

Myocardial injury in COVID-19 is associated with higher mortality, but it is unclear if cardiac injury is related directly to viral myocarditis or from indirect complications of COVID-19. Several cases of myocarditis have been described, and one case was reported with an endomyocardial biopsy revealing a T lymphocytic inflammatory infiltrate, with RT-PCR negative for SARSCoV-2. This was felt to be suggestive of reverse Takotsubo cardiomyopathy rather than viral myocarditis.

Other Manifestations

Only one case report was identified that did not involve any of the body systems described above as an initial presentation of COVID-19 (Prince & Sergel, 2020). A 62-year old male presented to emergency with persistent hiccups and unintended weight loss, and denied fever, nasal congestion, sore throat, chest pain or shortness of breath. A chest CT revealed bilateral ground glass opacities consistent with COVID-19, and upon arrival at the medical unit the man had developed a fever and elevated heart rate.

There is increasing attention on Kawasaki disease (KD), a prolonged febrile illness of children which can cause cardiac complications, as a possible consequence of COVID-19 in the media (Lord, 2020).A media report suggested that more than an atypically large number of cases of KD have been noted in Montreal although none have tested positive for COVID-19 (Szlarski, 2020). 4 children have been hospitalized with KD in New York City, with similar reports from the UK and Italy. A preprint case report described a single case, identifying also that a series of 2143 predominantly minimally symptomatic children with suspect or confirmed COVID-19 identified no cases of Kawasaki disease (Jones et al., 2020). A 6-month old child presented with a rash, conjunctivitis and dry cracked lips, with note of edematous hands and legs, and prominent tongue papillae as well, thus meeting KD criteria. She received ASA and IVIG and had a normal echocardiogram and was confirmed COVID-19 positive. The pathophysiology and epidemiologic link for this association is not clear, but physicians looking after children should recognize that persistent fever, skin, and oral manifestations should prompt consideration of KD as therapy may prevent cardiac complications (Veena et al., 2020.)

A severe, variant presentation thought to represent Kawasaki disease shock syndrome has been reported in 8 children in the UK, with clinical features of an antecedent diarrhea syndrome followed by a hyperinflammatory syndrome with multiorgan involvement (Riphagen et al., 2020). The children tested negative for SARSCoV-2 but were said to be antibody positive. Six of the children were Afro-Caribbean and 4 had COVID-19 household exposures. The clinical presentations included unrelenting fever (38–40°C), variable rash, conjunctivitis, peripheral edema, and generalised extremity pain with significant gastrointestinal symptoms. All progressed to warm, vasoplegic shock, refractory to volume resuscitation and eventually required vasoactive support. (Riphagen et al., 2020)

Methods

Literature Search

A literature search was conducted by Lauren Seal from Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services. KRS searched databases for articles published in 2020 and included: Medline, CINAHL, TRIP Pro, Google Scholar, and LitCovid. Briefly, the search strategy involved combinations of subject headings and related including:

- SARS-CoV-2 or novel coronavirus or COVID

- Atypical presentation or non-respiratory symptoms
- Thrombosis (MeSH), Pulmonary Embolism (MeSH), Neurologic Manifestations (MeSH), Gastrointestinal Diseases (MeSH), Exanthema (MeSH), Frostbite (MeSH), Skin diseases (MeSH), Ophthalmology (MeSH), Appendicitis (MeSH)

Articles identified by KRS in their search were initially screened by title against the inclusion/exclusion criteria listed in Table 1 below. 137 articles were identified by KRS with references and abstracts provided for further review, and 15 articles were identified *ad hoc*. 69 articles were excluded from the review in accordance with the inclusion/exclusion criteria stated below. 73 articles were included in the full narrative synthesis.

Table 1. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
- Describes non-respiratory presentation of COVID-19 - Primary literature, any design - Secondary literature - Grey literature - Published in 2020 - English language or can be translated by Google scholar - Any jurisdiction	- Article is not from a credible source - Article does not have a clear research question or issue - Presented data/evidence is not sufficient to address the research questions - Non-human study - Does not describe extrapulmonary presentation - Opinion, editorial, commentary without data

Critical Evaluation of the Evidence

Exclusion criteria for study quality were adapted from the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). Potential articles were evaluated on three criteria: 1) Peer reviewed or from a reputable source; 2) Clear research question or issue; 3) Whether the presented data/evidence is appropriate to address the research question. Preprints and non peer-reviewed literature (such as commentaries and letters from credible journals) are not excluded out of hand due to the novelty of COVID-19 and the speed with which new evidence is available.

Table 2 below is a narrative summary of the body of evidence included in this review. The categories, format, and suggested information for inclusion were adapted from the Oxford Centre for Evidence-Based Medicine, the Cochrane Library, and the AGREE Trust (Urwin, Gavinder & Graziadio, 2020; Viswanathan et al, 2012; Wynants et al., 2020; Brouwers et al., 2010).

Table 2. Narrative overview of the literature included in this review.

	Description
Volume	The vast majority of the evidence for this topic was small case reports, case series, or observational studies. Out of 73 included studies, only 5 pieces of secondary literature were identified, and one guideline was identified. Most of the literature was published as short reports, commentary, or letters to the editor.
Quality	The body of evidence on this topic is low quality. The sample sizes in general are very small, with some larger case series. There were some larger observational studies that improved confidence in the reports of non-pulmonary manifestations. The risk of bias was often high, as participants were often identified after hospitalization making assessment of initial presenting symptoms less reliable. Studies that utilized surveys

	had a high risk of recall bias and selection bias, especially those that circulated via electronic means like social media. The low quality of the primary evidence limits the quality of the secondary evidence. Since so much of the primary literature draws on emergency department presentation or hospitalization, the analyses presented in the secondary literature may be showing higher prevalence or representing more severe cases of the disease. One study was a high-quality systematic review, with rigorous inclusion/exclusion criteria and appropriate methodology to limit duplication and assess heterogeneity (Sultan et al., 2020). However, it is not a peer-reviewed study so must be considered with caution.
Applicability	The applicability of the evidence is limited, since the majority of COVID-19 reports are from Europe, China, and the United States and it is unclear if population differences translate to the Alberta context.
Consistency	Since the evidence is largely uncontrolled observational studies or small case series/reports, the data varies wildly. The pathophysiology of SARS-CoV-2 is still unclear and study participants are often identified from specific populations rather than from random sampling, so the prevalence and association values will continue to be inconsistent until this bias can be corrected.

Search Strategy
Medline/Pubmed

1 exp Coronavirus/ or exp Coronavirus Infections/ or coronaviru*.mp. or "corona virus*".mp. or ncov*.mp. or n-cov*.mp. or "novel cov".mp. or COVID-19.mp. or COVID19.mp. or COVID-2019.mp. or COVID2019.mp. or SARS-COV-2.mp. or SARSCOV-2.mp. or SARSCOV2.mp. or SARSCOV19.mp. or Sars-Cov-19.mp. or SarsCov-19.mp. or SARSCOV2019.mp. or Sars-Cov-2019.mp. or SarsCov-2019.mp. or "severe acute respiratory syndrome cov 2".mp. or "2019 ncov".mp. or "2019ncov".mp. (21255)
2 exp Thrombosis/ (128422)
3 exp Pulmonary Embolism/ (38505)
4 exp Stroke/ (132297)
5 "macrovascular thrombosis".mp. (17)
6 microthrombrosis.mp. (0)
7 exp Hypoxia/ (66554)
8 "silent hypox*".mp. (2)
9 "happy hypox*".mp. (0)
10 exp Neurologic Manifestations/ (1134944)
11 (neurologic* adj2 present*).mp. (3768)
12 "cerebrovascular accident*".mp. (6860)
13 exp Gastrointestinal Diseases/ (947973)
14 gastrointestinal*.mp. (363614)
15 enteritis.mp. (15643)
16 gastroenteritis.mp. (25390)
17 diarrhea.mp. (100601)
18 exp Exanthema/ (7449)
19 rash.mp. (25991)
20 dermatologic*.mp. (53912)
21 Livedo Reticularis/ (294)

22 exp Chilblains/ (347)
23 pernio.mp. (231)
24 (atypical adj2 present*).mp. (8970)
25 (atypical adj2 manifest*).mp. (1723)
26 "covid toes".mp. (0)
27 "covid-19 toes".mp. (0)
28 dermatotropic*.mp. (37)
29 "skin errupt*".mp. (1)
30 "skin manifest*".mp. (5592)
31 epidermis.mp. (50417)
32 epidermal.mp. (133627)
33 exp Skin Diseases/ (1008969)
34 (non-respiratory adj2 present*).mp. (5)
35 (non-respiratory adj2 manifest*).mp. (11)
36 (non-respiratory adj2 symptom*).mp. (56)
37 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (3714451)
38 1 and 37 (3341)
39 limit 38 to yr="2020" (140)
40 limit 39 to (editorial or "expression of concern" or interview or newspaper article or retracted publication or "retraction of publication") (5)
41 39 not 40 (135)

CINAHL

S1 (MH "Coronavirus+")
S2 (MH "Coronavirus Infections+")
S3 coronaviru*
S4 "corona virus"
S5 ncov*
S6 n-cov*
S7 COVID-19 OR COVID19 OR COVID-2019 OR COVID2019
S8 SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019
S9 "severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus*"
S10 "2019 ncov" OR 2019ncov OR Hcov*
S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 4,919
S12 thrombosis 36,596
S13 (MH "Thrombosis+") 38,115
S14 (MH "Pulmonary Embolism") 10,180
S15 (MH "Stroke+") 72,405
S16 macrovascular thrombosis OR microthrombosis 59
S17 (MH "Anoxia+") 7,377
S18 "silent hypoxic" OR "silent hypoxia" OR "happy hypoxic" OR "happy hypoxia" 0
S19 "silent hypoxic" OR "silent hypoxia" OR "happy hypoxic" OR "happy hypoxia" 10
S20 (MH "Neurologic Manifestations+") 384,854
S21 neurologic* N2 present* OR neurologic* N2 symptom* 5,656
S22 "cerebrovascular accident" 60,072
S23 (MH "Gastrointestinal Diseases+") 164,403
S24 gastrointestinal OR enteritis OR gastroenteritis OR diarrhea 88,324
S25 (MH "Exanthema") 3,464
S26 (MH "Frostbite") 497
S27 (MH "Skin Diseases+") 137,868
S28 rash OR pernio OR dermatologic* OR "livedo reticularis" OR chilblains OR "covid toes" OR "covid-19 toes" OR dermatotropic* OR "skin errupt*" OR "skin manifest*" OR epidermis OR epidermal

33,493
S29 atypical N2 present* OR atypical N2 manifest* OR atypical N2 symptom* OR non-respiratory N2 present* OR non-respiratory N2 manifest* OR non-respiratory N2 symptom* 3,577
S30 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 858,626
S31 S11 AND S30 207
S32 S11 AND S30 Limiters - Published Date: 20200101-51

TRIP Pro/Google Advanced

(coronavirus OR “corona virus” OR sars-cov-2 OR covid-19) AND (thrombosis OR embolism OR stroke or hypoxia or “happy hypoxia” OR “silent hypoxia” OR neurologic OR “cerebrovascular accident” OR gastrointestinal OR enteritis OR gastroenteritis OR diarrhea or rash OR dermatologic OR “livedo reticularis” OR chilblains OR pernio OR “covid toes” OR “covid-19 toes” OR “atypical symptom” OR “atypical presentation” OR “atypical manifestation” OR “non-respiratory symptom” OR “non-respiratory presentation” OR “non-respiratory manifestation”) from:2020

LitCovid/WHO Database

(thrombosis OR embolism OR stroke or hypoxia or “happy hypoxia” OR “silent hypoxia” OR neurologic OR “cerebrovascular accident” OR gastrointestinal OR enteritis OR gastroenteritis OR diarrhea or rash OR dermatologic OR “livedo reticularis” OR chilblains OR pernio OR “covid toes” OR “covid-19 toes” OR “atypical symptom” OR “atypical presentation” OR “atypical manifestation” OR “non-respiratory symptom” OR “non-respiratory presentation” OR “non-respiratory manifestation”) – 2020 only

Medline/Pubmed

1 exp Coronavirus/ or exp Coronavirus Infections/ or coronaviru*.mp. or "corona virus*".mp. or ncov*.mp. or n-cov*.mp. or "novel cov".mp. or COVID-19.mp. or COVID19.mp. or COVID-2019.mp. or COVID2019.mp. or SARS-COV-2.mp. or SARSCOV-2.mp. or SARSCOV2.mp. or SARSCOV19.mp. or Sars-Cov-19.mp. or SarsCov-19.mp. or SARSCOV2019.mp. or Sars-Cov-2019.mp. or SarsCov-2019.mp. or "severe acute respiratory syndrome cov 2".mp. or "2019 ncov".mp. or "2019ncov".mp. (21435)
2 exp Appendicitis/ (18978)
3 Appendix/ (6785)
4 exp Ophthalmology/ (22414)
5 opthalmolog*.mp. (359)
6 exp Optometry/ (5449)
7 optometr*.mp. (7657)
8 exp Conjunctivitis/ (18974)
9 exp Eye Infections/ (36824)
10 exp Eye/ (347376)
11 exp Eye Diseases/ (560718)
12 ocular.mp. (197575)
13 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (830159)
14 1 and 13 (126)
15 limit 14 to yr="2020" (22)

CINAHL

S1 (MH "Coronavirus+")
S2 (MH "Coronavirus Infections+")
S3 coronaviru*
S4 "corona virus"
S5 ncov*
S6 n-cov*
S7 COVID-19 OR COVID19 OR COVID-2019 OR COVID2019
S8 SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019
S9 "severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus*"
Database - CINAHL Plus with Full Text Display

S10	"2019 ncov" OR 2019ncov OR Hcov*	
S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	4,951
S12	(MH "Appendicitis") OR (MH "Appendix")	4,089
S13	(MH "Ophthalmology")	5,382
S14	(MH "Optometry")	3,343
S15	(MH "Conjunctivitis+")	2,981
S16	optometr* OR ophtamolog*	4,363
S17	(MH "Eye Diseases+")	92,733
S18	(MH "Diagnosis, Eye+")	21,088
S19	(MH "Eye Infections+")	4,154
S20	(MH "Eye+")	24,792
S21	ocular	18,084
S22	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	124,261
S23	S11 AND S22	28
S24	S11 AND S22 Limiters - Published Date: 20200101-20201231	17

TRIP Pro/Google Advanced

(coronavirus OR “corona virus” OR sars-cov-2 OR covid-19) AND (appendicitis OR appendix OR eye OR ocular OR ophthalmology OR ophthalmic OR optometry OR “eye disease” OR “eye infection” OR conjunctivitis) from:2020

LitCovid/WHO Database

(appendicitis OR appendix OR eye OR ocular OR ophthalmology OR ophthalmic OR optometry OR “eye disease” OR “eye infection” OR conjunctivitis)– 2020 only

Reference List

AHS VTE Working Group. (2020). Memorandum regarding VTE prophylaxis for admitted COVID-19 patients. Retrieved from: https://www.albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-phm-vte-prophylaxis-for-covid-19-patients-memo.pdf. Accessed 11 May 2020.

Alramthan, A., & Aldaraji, W. (2020). A case of COVID-19 presenting in clinical picture resembling chilblains disease. first report from the middle east. Clinical and Experimental Dermatology, doi:10.1111/ced.14243 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32302422. Accessed 5 May 2020.

Amatore, F., Macagno, N., Mailhe, M., Demarez, B., Gaudy-Marqueste, C., Grob, J. J., . . . Richard, M. A. (2020). SARS-CoV-2 infection presenting as a febrile rash. Journal of the European Academy of Dermatology and Venereology: JEADV, doi:10.1111/jdv.16528 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32330336/. Accessed 5 May 2020.

Asadi-Pooya, A. A., & Simani, L. (2020). Central nervous system manifestations of COVID-19: A systematic review. Journal of the Neurological Sciences, 413, 116832. doi:10.1016/j.jns.2020.116832 Retrieved from https://www-ncbi-nlm-nih-gov.ahs.idm.oclc.org/pmc/articles/PMC7151535/. Accessed 5 May 2020.

Avellana Moreno, R., Villa, E., Avellana Moreno, V., Estela Villa, C., Aparicio, M., & Fontanella, A. (2020). Cutaneous manifestation of COVID-19 in images: A case report. J. Eur. Acad. Dermatol. Venereol, Retrieved from https://dx.doi.org/10.1111/jdv.16531. Accessed 5 May 2020.

Azwar, M. K., Kirana, F., Kurniawan, A., Handayani, S., & Setiati, S. (2020). Gastrointestinal presentation in COVID-19 in indonesia: A case report. Acta Medica Indonesiana, 52(1), 63-67. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/32291373. Accessed 5 May 2020.

Bellosta, R., Luzzani, L., Natalini, G., Pegorer, M. A., Attisani, L., Cossu, L. G., Ferrandina, C., Fossati, A., Conti, E., Bush, R. L., & Piffaretti, G. (2020). Acute limb ischemia in patients with COVID-19 pneumonia. Journal of

vascular surgery, S0741-5214(20)31080-6. Advance online publication. https://doi.org/10.1016/j.jvs.2020.04.483. Accessed 6 May 2020.

Beltrán-Corbellini, Á, Chico-García, J. L., Martínez-Poles, J., Rodríguez-Jorge, F., Natera-Villalba, E., Gómez-Corral, J., . . . Alonso-Cánovas, A. (2020). Acute-onset smell and taste disorders in the context of covid-19: A pilot multicenter PCR-based case-control study. Eur. J. Neurol, Retrieved from https://dx.doi.org/10.1111/ene.14273. Accessed 5 May 2020.

Berre, A. L., Marteau, V., Emmerich, J., & Zins, M. (2020). Concomitant acute aortic thrombosis and pulmonary embolism complicating COVID-19 pneumonia. Diagnostic and Interventional Imaging, 101(5), 321-322. doi:10.1016/j.diii.2020.04.003 Retrieved from http://www.sciencedirect.com/science/article/pii/S2211568420300966. Accessed 5 May 2020.

Beydon, M., Chevalier, K., Al Tabaa, O., Hamroun, S., Delettre, A., Thomas, M., . . . Mariette, X. (2020). Myositis as a manifestation of SARS-CoV-2. Ann. Rheum. Dis, Retrieved from https://dx.doi.org/10.1136/annrheumdis-2020-217573. Accessed 5 May 2020.

Bikdeli, B., Madhavan, M. V., Jimenez, D., Chuich, T., Dreyfus, I., Driggin, E., ... & Tang, L. V. (2020). COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *Journal of the American College of Cardiology*. Retrieved from: http://www.onlinejacc.org/content/early/2020/04/15/j.jacc.2020.04.031.full. Accessed 10 May 2020.

Bonow, R. O., Fonarow, G. C., O'Gara, P. T., & Yancy, C. W. (2020). Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. JAMA cardiology. Retrieved from: https://jamanetwork.com/journals/jamacardiology/fullarticle/2763844. Accessed 7 May 2020.

Bouaziz, J. D., Duong, T., Jachiet, M., Velter, C., Lestang, P., Cassius, C., . . . Rybojad, M. (2020). Vascular skin symptoms in COVID-19: A french observational study. Journal of the European Academy of Dermatology and Venereology: JEADV, doi:10.1111/jdv.16544. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32339344/. Accessed 5 May 2020.

Bowles, L.., Platton, S., Yartey, N., Dave, M., Lee, K., Hart, D., MacDonald, V., Green, L., Sivapalaratnam, S., Pasi, K.J., MacCallum, P. (2020). Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with Covid-19. New England Journal of Medicine. ePub 5 May 2020. DOI: 10.1056/NEJMc2013656. Retrieved from https://www.nejm.org/doi/full/10.1056/NEJMc2013656. Accessed 5 May 2020.

Bratis K. (2017). Cardiac Magnetic Resonance in Takotsubo Syndrome. European cardiology, 12(1), 58–62. https://doi.org/10.15420/ecr.2017:7:2. Accessed 7 May 2020.

Brouwers, M. C., Kho, M. E., Browman, G. P., Burgers, J. S., Cluzeau, F., Feder, G., Fervers, B., Graham, I. D., Grimshaw, J., Hanna, S. E., Littlejohns, P., Makarski, J., Zitzelsberger, L., & AGREE Next Steps Consortium (2010). AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, *182*(18), E839–E842. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001530/

Cheema, M., Aghazadeh, H., Nazarali, S., Ting, A., Hodges, J., McFarlane, A., . . . Solarte, C. (2020). Keratoconjunctivitis as the initial medical presentation of the novel coronavirus disease 2019 (COVID-19). Canadian Journal of Ophthalmology/Journal Canadien D'Ophtalmologie, doi:10.1016/j.jcjo.2020.03.003 Retrieved from http://dx.doi.org/10.1016/j.jcjo.2020.03.003. Accessed 5 May 2020

Chen, L., Liu, M., Zhang, Z., Qiao, K., Huang, T., Chen, M., . . . Wang, J. (2020). Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease. The British Journal of Ophthalmology, doi:10.1136/bjophthalmol-2020-316304 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32265202/. Accessed 5 May 2020.

Damme, C. v., Berlingin, E., Saussez, S., & Accaputo, O. (2020). Acute urticaria with pyrexia as the first manifestations of a COVID-19 infection. Journal of the European Academy of Dermatology and Venereology,

n/a(n/a) doi:10.1111/jdv.16523 Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1111/jdv.16523. Accessed 5 May 2020.

Daruich, A., Martin, D., & Bremond-Gignac, D. (2020). Ocular manifestation as first sign of coronavirus disease 2019 (COVID-19): Interest of telemedicine during the pandemic context. J. Fr. Ophtalmol, Retrieved from https://dx.doi.org/10.1016/j.jfo.2020.04.002. Accessed 5https://dx.doi.org/10.1016/j.jfo.2020.04.002. Accessed 5 May 2020.

Dinkin, M., Gao, V., Kahan, J., Bobker, S., Simonetto, M., Wechsler, P., ... & Tsiou ris, A. J. (2020). COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. Neurology. Retrieved from https://n.neurology.org/content/early/2020/04/28/WNL.0000000000009700. Accessed 7 May 2020.

Docherty, A. B., Harrison, E. M., Green, C. A., Hardwick, H. E., Pius, R., Norman, L., … Semple, M. G. (2020). Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol. MedRxiv, 2020.04.23.20076042. https://doi.org/10.1101/2020.04.23.20076042. Accessed 7 May 2020.

Estébanez, A., Pérez-Santiago, L., Silva, E., Guillen-Climent, S., García-Vázquez, A., & Ramón, M. D.Cutaneous manifestations in COVID-19: A new contribution. Journal of the European Academy of Dermatology and Venereology, n/a(n/a) doi:10.1111/jdv.16474 Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1111/jdv.16474. Accessed 5 May 2020.

Fernandez-Nieto, D., Jimenez-Cauhe, J., Suarez-Valle, A., Moreno-Arrones, O. M., Saceda-Corralo, D., Arana-Raja, A., & Ortega-Quijano, D. (2020). Characterization of acute acro-ischemic lesions in non-hospitalized patients: a case series of 132 patients during the COVID-19 outbreak. Journal of the American Academy of Dermatology. https://www.jaad.org/article/S0190-9622(20)30709-X/pdf. Accessed 5 May 2020.

Fu, B., Qian, K., & Fu, X. (2020). SARS-CoV-2-induced vomiting as onset symptom in a patient with COVID-19. Digestive Diseases and Sciences, doi:10.1007/s10620-020-06285-4 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32347435/. Accessed 5 May 2020.

Gahide, G., Frandon, J., & Vendrell, J. (2020). COVID-19 patients presenting with afebrile acute abdominal pain. Clinical Medicine (London, England), doi:10.7861/clinmed.2020-0150 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32341078/. Accessed 5 May 2020.

Galván Casas, C., Català, A., Carretero Hernández, G., Rodríguez-Jiménez, P., Fernández Nieto, D., Rodríguez-Villa Lario, A., . . . García-Doval, I. (2020). Classification of the cutaneous manifestations of COVID-19: A rapid prospective nationwide consensus study in spain with 375 cases. The British Journal of Dermatology, doi:10.1111/bjd.19163 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32348545/. Accessed 5 May 2020.

Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., ... & Du, B. (2020). Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine, 382(18), 1708-1720. Retrieved from https://www.nejm.org/doi/full/10.1056/NEJMoa2002032. Accessed 7 May 2020.

Henry, B. M., de Oliveira, Maria Helena Santos, Benoit, J., & Lippi, G. (2020). Gastrointestinal symptoms associated with severity of coronavirus disease 2019 (COVID-19): A pooled analysis. Internal and Emergency Medicine, doi:10.1007/s11739-020-02329-9 Retrieved from https://pubmed.ncbi.nlm.nih.gov/3230397. Accessed 5 May 2020.

Henry, D., Ackerman, M., Sancelme, E., Finon, A., & Esteve, E. (2020). Urticarial eruption in COVID-19 infection. Journal of the European Academy of Dermatology and Venereology: JEADV, doi:10.1111/jdv.16472 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32294273/. Accessed 5 May 2020.

Hong, Quan Nha et al. (2018). The Mixed Methods Appraisal Tool (MMAT) Version 2018 for Information Professionals and Researchers'. 1 Jan. 2018 : 285 – 291. Retrieved from: http://mixedmethodsappraisaltoolpublic.pbworks.com/w/file/fetch/127916259/MMAT_2018_criteria-manual_2018-08-01_ENG.pdf

Hunt, M., & Koziatek, C. (2020). A case of COVID-19 pneumonia in a young male with full body rash as a presenting symptom. Clinical Practice and Cases in Emergency Medicine, doi:10.5811/cpcem.2020.3.47349. Retrieved from https://pubmed.ncbi.nlm.nih.gov/32282312. Accessed 5 May 2020.

Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, Cerini M, Farina D, Gavazzi E, Maroldi R, Adamo M, Ammirati E, Sinagra G, Lombardi CM, Metra M. (2020). Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol doi: 10.1001/jamacardio.2020.1096. Accessed 7 May 2020.

Jones, V. G., Mills, M., Suarez, D., Hogan, C. A., Yeh, D., Segal, J. B., ... & Mathew, R. (2020). COVID-19 and Kawasaki disease: novel virus and novel case. Hospital Pediatrics, hpeds-2020. Retrieved from: https://hosppeds.aappublications.org/content/early/2020/04/06/hpeds.2020-0123. Accessed 7 May 2020.

Joob, B., & Wiwanitkit, V. (2020a). Alteration of consciousness as initial presentation in COVID-19: Observation. Annals of Indian Academy of Neurology, 23, S44. doi:10.4103/aian.AIAN_123_20. Retrieved from http://www.annalsofian.org/article.asp?issn=0972-2327;year=2020;volume=23;issue=7;spage=44;epage=44;aulast=Joob . Accessed 5 May 2020.

Joob, B., & Wiwanitkit, V. (2020b). Arthralgia as an initial presentation of COVID-19: Observation. Rheumatology International, 40(5), 823. https://dx.doi.org/10.1007/s00296-020-04561-0. Accessed 5 May 2020.

Kawai S, Shimada T. (2013). Inflammation in takotsubo cardiomyopathy? Inquiry from 'Guidelines for Diagnosis and Treatment of Myocarditis (JCS 2009)'. J Cardiol 2014;63:247–249. Retreived from: https://www.journal-of-cardiology.com/article/S0914-5087(13)00331-6/fulltext Accessed 7 May 2020.

Khavandi, S., Tabibsadeh, E., Naderan, M., & Shoar, S. (2020). Corona virus disease-19 (COVID-19) presenting as conjunctivitis: Atypically high-risk during a pandemic. Contact Lens and Anterior Eye, Retrieved from https://www.contactlensjournal.com/article/S1367-0484(20)30083-7/pdf. Accessed 5 May 2020

Kim, J., Thomsen, T., Sell, N., & Goldsmith, A. J. (2020). Abdominal and testicular pain: An atypical presentation of COVID-19. The American Journal of Emergency Medicine, doi:10.1016/j.ajem.2020.03.052. Retrieved from https://pubmed.ncbi.nlm.nih.gov/32273141. Accessed 5 May 2020.

Klok, F. A., Kruip, M., van der Meer, N., Arbous, M. S., Gommers, D., Kant, K. M., Kaptein, F., van Paassen, J., Stals, M., Huisman, M. V., & Endeman, H. (2020). Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis research, S0049-3848(20)30120-1. Advance online publication. https://doi.org/10.1016/j.thromres.2020.04.013 Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7146714/. Accessed 5 May 2020.

Landa, N., Mendieta-Eckert, M., Fonda-Pascual, P., & Aguirre, T. (2020). Chilblain-like lesions on feet and hands during the COVID-19 pandemic. International Journal of Dermatology, n/a(n/a) doi:10.1111/ijd.14937. Retrieved from: https://onlinelibrary.wiley.com/doi/abs/10.1111/ijd.14937. Accessed 5 May 2020.

Lechien, J. R., Chiesa-Estomba, C. M., De Siati, D. R., Horoi, M., Le Bon, S. D., Rodriguez, A., . . . Saussez, S. (2020). Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): A multicenter european study. European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): Affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery, doi:10.1007/s00405-020-05965-1. Accessed 5 May 2020.

Lee, S. G., Fralick, M., & Sholzberg, M. (2020). Coagulopathy associated with COVID-19. CMAJ. Retrieved from https://www.cmaj.ca/content/early/2020/05/01/cmaj.200685. Accessed 5 May 2020.

Li, R., Chu, S., Luo, Y., Huang, Z., Hao, Y., & Fan, C. (2020). Atypical presentation of SARS-CoV-2 infection: A case report. World Journal of Clinical Cases, 8(7), 1265-1270. doi:10.12998/wjcc.v8.i7.1265 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32337201/. Accessed 5 May 2020.

Lin, L., Jiang, X., Zhang, Z., Huang, S., Zhang, Z., Fang, Z., . . . Shan, H. (2020). Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut, doi:10.1136/gutjnl-2020-321013 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32241899/. Accessed 5 May 2020.

Loffredo, L., Pacella, F., Pacella, E., Tiscione, G., Oliva, A., & Violi, F. (2020). Conjunctivitis and COVID-19: A meta-analysis. Journal of Medical Virology, doi:10.1002/jmv.25938 Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/32330304. Accessed 5 May 2020.

Lord, D. (2020). Kawasaki disease: Dozens of children hospitalized with coronavirus-linked syndrome. Boston 25 News. Retrieved from: https://www.boston25news.com/news/trending/coronavirus-children-uk-italy-have-died-rare-syndrome-that-may-be-linked-covid-19/UXVWN5TDNBEMPKMEYV2CFIYFPY/. Accessed 7 May 2020.

Magro, C., Mulvey, J. J., Berlin, D., Nuovo, G., Salvatore, S., Harp, J., . . . Laurence, J. (2020). Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Translational Research: The Journal of Laboratory and Clinical Medicine, doi:10.1016/j.trsl.2020.04.007 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32299776. Accessed 5 May 2020.

Mahé, A., Birckel, E., Krieger, S., Merklen, C., & Bottlaender, L.A distinctive skin rash associated with coronavirus disease 2019 ? Journal of the European Academy of Dermatology and Venereology, n/a(n/a) doi:10.1111/jdv.16471 Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1111/jdv.16471. Accessed 5 May 2020.

Manalo, I. F., Smith, M. K., Cheeley, J., & Jacobs, R. (2020). A dermatologic manifestation of COVID-19: Transient livedo reticularis. Journal of the American Academy of Dermatology, doi:10.1016/j.jaad.2020.04.018 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32283229/. Accessed 5 May 2020

Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Li, Y., & Hu, B. (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA neurology, e201127. Advance online publication. https://doi.org/10.1001/jamaneurol.2020.1127. Accessed 7 May 2020.

Marzano, A. V., Genovese, G., Fabbrocini, G., Pigatto, P., Monfrecola, G., Piraccini, B. M., . . . Calzavara-Pinton, P. (2020). Varicella-like exanthem as a specific COVID-19-associated skin manifestation: Multicenter case series of 22 patients. Journal of the American Academy of Dermatology, doi:10.1016/j.jaad.2020.04.044 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32305439/. Accessed 5 May 2020.

McEntire C, Misra A, O'Hare M, et al. (2020). Neurologic Complications of COVID-19. https://covidprotocols.org/protocols/11-neurology/. Accessed 5 May 2020.

Nathan, N., Prevost, B., & Corvol, H. (2020). Atypical presentation of COVID-19 in young infants. Lancet (London, England), S0140-6736(20)30980-6. Advance online publication. https://doi.org/10.1016/S0140-6736(20)30980-6. Accessed 5 May 2020.

Pan, L., Mu, M., Yang, P., Sun, Y., Wang, R., Yan, J., . . . Tu, L. (2020). Clinical characteristics of COVID-19 patients with digestive symptoms in hubei, china: A descriptive, cross-sectional, multicenter study. The American Journal of Gastroenterology, doi:10.14309/ajg.0000000000000620 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32287140/. Accessed 5 May 2020.

Pautrat, K., & Chergui, N. (2020). L'infection par SRAS-CoV-2 peut se traduire par un syndrome appendiculaire : Tomodensitométrie thoracique avant appendicectomie. Journal De Chirurgie Viscérale, doi:10.1016/j.jchirv.2020.04.007 Retrieved from http://www.sciencedirect.com/science/article/pii/S1878786X20300929. Accessed 5 May 2020. (Translated with Google Translate).

Pazgan-Simon, M., Rorat, M., Buczyńska, I., Zińczuk, A., & Simon, K. (2020). Gastrointestinal symptoms as the first, atypical indication of SARS-CoV-2 infection. Polish Archives of Internal Medicine, doi:10.20452/pamw.15278 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32250094. Accessed 5 May 2020.

Perini, P., Nabulsi, B., Bianchini Massoni, C., Azzarone, M., Freyrie, A. (2020). Acute limb ischaemia in two young, non-atherosclerotic patients with COVID-19. The Lancet. ePub 5 May 2020. DOI: 10.1016/S0140-6736(20)31051-5. Retrieved from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31051-5/fulltext. Accessed 6 May 2020.

Piccolo, V., Neri, I., Filippeschi, C., Oranges, T., Argenziano, G., Battarra, V. C., . . . Bassi, A. (2020). Chilblain-like lesions during COVID-19 epidemic: A preliminary study on 63 patients. Journal of the European Academy of Dermatology and Venereology, n/a(n/a) doi:10.1111/jdv.16526. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1111/jdv.16526. Accessed 5 May 2020.

Poggiali, E., Ramos, P. M., Bastoni, D., Vercelli, A., & Magnacavallo, A. (2020). Abdominal pain: A real challenge in novel COVID-19 infection. European Journal of Case Reports in Internal Medicine, 7(4), 001632. https://dx.doi.org/10.12890/2020_001632. Accessed 5 May 2020

Prince, G., & Sergel, M. (2020). Persistent hiccups as an atypical presenting complaint of COVID-19. The American Journal of Emergency Medicine, doi:10.1016/j.ajem.2020.04.045 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32345563/. Accessed 5 May 2020.

Recalcati, S. (2020a). Cutaneous manifestations in COVID-19: A first perspective. Journal of the European Academy of Dermatology and Venereology: JEADV, doi:10.1111/jdv.16387 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32215952/ Accessed 5 May 2020

Recalcati, S., Barbagallo, T., Frasin, L. A., Prestinari, F., Cogliardi, A., Provero, M. C., . . . Fantini, F. (2020b). Acral cutaneous lesions in the time of COVID-19. Journal of the European Academy of Dermatology and Venereology, n/a(n/a) doi:10.1111/jdv.16533. Retrieved from https://onlinelibrary.wiley.com/doi/10.1111/jdv.16533. Accessed 5 May 2020.

Redd, W. D., Zhou, J. C., Hathorn, K. E., McCarty, T. R., Bazarbashi, A. N., Thompson, C. C., . . . Chan, W. W. (2020). Prevalence and characteristics of gastrointestinal symptoms in patients with SARS-CoV-2 infection in the united states: A multicenter cohort study. Gastroenterology, doi:10.1053/j.gastro.2020.04.045 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32333911/. Accessed 5 May 2020.

Riphagen, S., Gomez, X., Gonzalez-Martinez, C., Wilkinson, N., Paraskevi, T. (2020). Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet. epub 7 May 2020. Retrieved from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31094-1/fulltext. Accessed 7 May 2020.

Rivera-Oyola, R., Koschitzky, M., Printy, R., Liu, S., Stanger, R., Golant, A., & Lebwohl, M. (2020). Dermatologic findings in two patients with COVID-19. JAAD Case Reports, doi:10.1016/j.jdcr.2020.04.027 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32346588/. Accessed 5 May 2020.

Sala S, Peretto G, Gramegna M, Palmisano A, Villatore A, Vignale D, De Cobelli F, Tresoldi M, Cappelletti AM, Basso C, Godino C. (2020). Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. Eur Heart J 2020; doi:10.1093/eurheartj/ehaa286. Accessed 7 May 2020.

Salducci, M., & La Torre, G. (2020). COVID-19 emergency in the cruise's ship: A case report of conjunctivitis. Clinica Terapeutica, 171(3), e189-e191. https://dx.doi.org/10.7417/CT.2020.2212. Accessed 5 May 2020.

Sigal, A.C., Zirn, J.R., Lipper, G.M., Shapiro, P.E. (2020). A case of pernio-like lesions (“COVID toes”) with histologic confirmation of microthrombi. Retrieved from: https://docs.google.com/document/d/1QrCmMYX1eXRfhDewC-Y6lugEfGPwOq-U4ppUAnhlibg/mobilebasic. Accessed 5 May 2020.

Singhania, N., Bansal, S., & Singhania, G. (2020). An atypical presentation of novel coronavirus disease 2019 (COVID-19). The American Journal of Medicine, doi:10.1016/j.amjmed.2020.03.026 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32320693. Accessed 5 May 2020.

Spiezia, L., Boscolo, A., Poletto, F., Cerruti, L., Tiberio, I., Campello, E., ... & Simioni, P. (2020). COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. *Thrombosis and Haemostasis*. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/32316063. Accessed 10 May 2020.

Sulemane, S., Baltabaeva, A., Barron, A. J., Chester, R., & Rahman-Haley, S. (2020). Acute pulmonary embolism in conjunction with intramural right ventricular thrombus in a SARS-CoV-2-positive patient. European Heart Journal - Cardiovascular Imaging, doi:10.1093/ehjci/jeaa115. Retrieved from: https://academic.oup.com/ehjcimaging/advance-article/doi/10.1093/ehjci/jeaa115/5825632. Accessed 5 May 2020.

Sultan, S., Altayar, O., Siddique, S., Davitkov, P., Feuerstein, J., Lim, J., Falck-Ytter, Y., El-Serag, H. (2020). AGA Institute Rapid Review of the GI and Liver Manifestations of COVID-19, Meta-Analysis of International Data, and Recommendations for the Consultative Management of Patients with COVID-19. American Gastroenterological Association. Retrieved from: https://els-jbs-prod-cdn.jbs.elsevierhealth.com/pb/assets/raw/Health%20Advance/journals/ygast/AGA_COVID_GI_Rapid_Review.pdf . Accessed 6 May 2020.

Szklarski, C. (2020). Canadian Paediatric Society eyes mysterious syndrome for suspected COVID links. CP24 News. Retrieved from: https://www.cp24.com/news/canadian-paediatric-society-eyes-mysterious-syndrome-for-suspected-covid-links-1.4928019. Accessed 7 May 2020.

Ulhaq, Z. S., & Soraya, G. V. (2020). The prevalence of ophthalmic manifestations in COVID-19 and the diagnostic value of ocular tissue/fluid. Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht Von Graefes Archiv Fur Klinische Und Experimentelle Ophthalmologie, doi:10.1007/s00417-020-04695-8 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32328758/. Accessed 5 May 2020.

Urwin, S; Gavinder K, Graziadio S. (2020). What prognostic clinical risk prediction scores for COVID-19 are currently available for use in the community setting? Centre for Evidence-Based Medicine. Retrieved from: https://www.cebm.net/covid-19/what-prognostic-clinical-risk-prediction-scores-for-covid-19-are-currently-available-for-use-in-the-community-setting/

Viswanathan, M., Ansari, M. T., Berkman, N. D., Chang, S., Hartling, L., McPheeters, M., ... & Treadwell, J. R. (2012). Assessing the risk of bias of individual studies in systematic reviews of health care interventions. In *Methods guide for effectiveness and comparative effectiveness reviews [Internet]*. Agency for Healthcare Research and Quality (US). Retrieved from: https://www.ncbi.nlm.nih.gov/books/NBK91433/

Wei, X., Wang, X., Niu, Y., Ye, L., Peng, W., Wang, Z., . . . Zhou, Q. (2020). Diarrhea is associated with prolonged symptoms and viral carriage in COVID-19. Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association, doi:10.1016/j.cgh.2020.04.030 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32311512/. Accessed 5 May 2020

Wynants, L., Van Calster, B., Bonten, M. M., Collins, G. S., Debray, T. P., De Vos, M., ... & Schuit, E. (2020). Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. *BMJ*, *369*. Retrieved from https://www.bmj.com/content/369/bmj.m1328.long

Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420–422. Retrieved from: https://www.thelancet.com/journals/lancet/article/PIIS2213-2600(20)30076-X/fulltext. Accessed 7 May 2020.

Yang, X., Zhao, J., Yan, Q., Zhang, S., Wang, Y., & Li, Y. (2020). A case of COVID-19 patient with the diarrhea as initial symptom and literature review. Clinics and Research in Hepatology and Gastroenterology, doi:10.1016/j.clinre.2020.03.013 Retrieved from https://pubmed.ncbi.nlm.nih.gov/32305249/. Accessed 5 May 2020.

Ye, M., Ren, Y., & Lv, T. (2020). Encephalitis as a clinical manifestation of COVID-19. Brain Behav. Immun, Retrieved from https://dx.doi.org/10.1016/j.bbi.2020.04.017 Accessed 5 May 2020.

Zhang, T., Rodricks, M. B., & Hirsh, E. (2020). COVID-19-associated acute disseminated encephalomyelitis: A case report. medRxiv, , 2020.04.16.20068148. doi:10.1101/2020.04.16.20068148 Retrieved from http://medrxiv.org/content/early/2020/04/21/2020.04.16.20068148.abstract. Accessed 5 May 2020.

Zhang, Y., Xiao, M., Zhang, S., Xia, P., Cao, W., Jiang, W., ... & Wang, C. (2020). Coagulopathy and antiphospholipid antibodies in patients with Covid-19. New England Journal of Medicine. Retrieved from: https://www.nejm.org/doi/pdf/10.1056/NEJMc2007575?articleTools=true. Accessed 5 May 2020.