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SYSTEMATIC REVIEW – OPEN ACCESS

Clarifying Terminology of Signs in COVID-19

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ABSTRACT

The term "sign" has been used to describe various phenomena observed in patients with coronavirus disease 2019 (COVID-19). Discrepancies in the use of this term have been identified when it is used in context with COVID-19. The goals of this review are to provide an overview, describe signs, and clarify misconceptions regarding the use of these terms in COVID-19 patients. PubMed and Medline databases were searched using individual and Medical Subject Headings (MeSH) terms, including coronavirus, COVID-19, and sign, in human studies within the English literature published from inception to December 31, 2020. Studies where the word "sign" was used in a context different from that for COVID-19 (e.g., sentinel sign) were excluded. Three hundred fifty-seven studies were potentially identified and after applying the exclusion criteria and further adjudication, 92 studies constituted the final data set. The majority of signs found in the COVID-19 literature have been applied and aptly described primarily in radiologic diseases of the chest. The term "sign," in other situations, is often misappropriated as it actually represents a physical finding rather than a sign. A total of 27 radiologic signs have been identified on chest computed tomography (CT) or high-resolution CT (HRCT), and 18 cutaneous signs (or findings) have been observed during the physical examination in COVID-19. Signs lack sufficient sensitivity or specificity by themselves; however, in the appropriate clinical setting, they should raise clinical suspicion for this infectious disease.

Keywords: COVID-19, radiology, pulmonary complications, signs, terminology

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INTRODUCTION

During the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), physicians have identified several findings and have used the term "sign" to account for phenomenon found on assessment. We have identified discrepancies regarding the use of the term "sign" and have undertaken a review of the COVID-19 literature to better understand how physicians have used these terms. We contend that a focus on the COVID-19 literature may provide further insights on how physicians used these terms in general and how this may be applicable and promulgated to other diseases. For consistency and clarity of the literature, it is important to semantically distinguish the terms "sign, symptom, and physical finding" (1).

Signs are *objective markers* identified on physical examination that includes inspection, palpation, percussion, and auscultation. They can also be elicited through a variety of bedside maneuvers. Although signs have been traditionally been identified at the patient's bedside, they may also be found during radiologic or pathologic assessment and with the use of various instruments. Signs represent an attribution, inference, or interpretation of its significance as an aid in identifying and diagnosing diseases. In essence, they provide meaning or an explanation for an observation or finding and are rarely pathognomonic for a particular disease. Signs in the COVID-19 literature are named in several ways, including eponymously in honor of the person who discovered the finding (e.g., Gabrin sign) or through the use of other descriptive terminology with the intent of conveying a message to other clinicians (e.g., halo sign). The term "sign" has also been used in cases where the finding represented a manifestation, stage, severity, prognosis, or an early, late, or presenting finding *of* rather than a finding *in* COVID-19. For example, it has been reported that a rise in respiratory rate during continuous positive airway pressure may be an early sign of COVID-19 (2), and in general, a high respiratory rate of ≥30/min represents more severe disease (3). It is in this latter designation that we challenge current usage regarding its appropriate representation.

A symptom in modern terms refers to a finding or complaint that may occur because of a disease and thus may reflect an abnormal state or manifestation of an illness (4). As our understanding of disease improves, objective symptoms that were previously unexplained now assume relevance, and in some cases, are called "signs." Symptoms are either subjectively announced or objectively observed or identified. Hence, symptoms are subjective because they are expressed by the patients; they can be objective if noted by the observer when they are being expressed or represented by the patient. An objective symptom or physical findings (the preferred term) is the discovery during

the physical examination of something new or departing from the norm, irrespective of whether the patient complains regarding it. We undertook this systematic review in COVID-19 patients to better clarify the words signs and physical findings as well as to clarify the misconception and discrepancies regarding the use of these terms in this disease as well as the medical literature in general.

MATERIALS and METHODS

PubMed and Medline databases were searched using the individual and following Medical Subject Headings (MeSH) terms: Coronavirus, COVID-19, and signs. The search was limited to human clinical studies published in English until December 31, 2020. We also reviewed the bibliographies of retrieved papers and the reviews for additional relevant studies. Two reviewers independently screened the titles, abstracts, and full texts of the potentially eligible articles that met the inclusion criteria. Differences in the inclusion criteria were resolved through consensus adjudication. Articles that contained the term "sign" when used in cases where the finding represented a manifestation; stage; severity; prognostic; and early, late, or presenting findings rather than a finding *in* COVID-19 were excluded. Information was obtained from multiple sources, such as case reports, case series, meta-analyses, and cohort studies.

RESULTS and DISCUSSION

Using MeSH terms, 357 potential studies were identified. After reviewing the titles and abstracts, 108 studies were shortlisted. On further reviewing of the articles and adjudication, a final data set of 92 studies was available for the review.

Terminology

The distinction between signs and symptoms is not clear; this issue is partially responsible for these terms being commonly used interchangeably (1, 5). Unlike signs, not all symptoms, as expressed by the patient represent a manifestation of disease or a change in the organ or tissue. Classifying symptoms into subjective or objective categories is insufficient in defining these terms.

Definition

A *physical finding* is an objective symptom, observed during physical examination, and elicited through inspection, palpation, percussion, or auscultation, that represents a deviation from the normal state and one that by itself lacks diagnostic specificity. A *clinical finding* refers to an abnormality found on physical, radiologic, or pathologic examination. A physical or clinical finding is named a sign as such if evidence is used to make inference about the abnormality and disease and if it has or may have diagnostic importance. Therefore, a *sign*, as referred to in medical terminology, is an objective finding observed during physical, radiological, or pathological examinations by observation, palpation, percussion, auscultation, or through special maneuvers. Unlike clinical or physical findings, signs provide further information beyond their mere presence to the examiner about the patient and abnormality. They impart significance, albeit to various degrees, that facilitates accurate diagnosis. Physical and clinical findings, in combination with signs and symptoms enhance diagnostic capability. Thus, we propose that the term sign be reserved for situations that refer to an objective physical or clinical finding that uses evidence to provide relevance regarding its significance.

Symptoms, Signs, and Physical Findings

Symptoms, signs, and physical findings may be descriptive or eponymously named in recognition and honor of the persons who identified them. As stated, an objective symptom may become a sign if it meets the requirements of the latter. In COVID-19, fever, chills, prolonged fatigue, myalgias, arthralgias, cough, and shortness of breath represent nonspecific (subjective) symptoms. Rales, wheezing, rhonchi, and pleural friction rub auscultated on physical examination represent (objective) symptoms or more appropriately, physical findings. A sign found on physical examination may include for example, Andral decubitus sign, a finding observed by the examiner wherein the patient is lying on the bed with his unaffected hemithorax down while the pleural on the opposite side is inflammed. Signs on chest computed tomography (CT) may show a halo and/or reverse halo sign, a manifestation of exudative and chronic inflammatory changes in the lungs. Although these signs alone lack sufficient sensitivity or specificity in diagnosis, their presence along with symptoms and physical findings further enhance understanding of the extent and type of the underlying disease process.

I. Radiographic Assessment

Radiologic Signs

COVID-19 related pulmonary findings are typically peripherally based, with ground glass opacities and patchy alveolar infiltration located in the lower lobes of the lung (6). Ground glass opacities reflect partially filled alveoli that contain edema, inflammatory cells, blood, and/or proteinaceous exudates along with a thickened alveolar wall and/or the interstitium (7). The ground glass opacities noted on CT scan are nonspecific and observed in other benign and malignant pulmonary diseases. Furthermore, a false positive result may be obtained in patients who do not take a sufficiently deep breath during the CT scan (8). Authors have referred to several CT findings, such as vascular enlargement (vascular enhancement, micro-vascular dilation, bronchovascular enlargement), bronchiectasis or bronchus distortion, fibrosis cavitation nodules, pleural effusion, and lymphadenopathy, as "signs" of COVID although in essence, they represent radiographic findings (9).

Signs used to describe findings on imaging are based on their location (e.g., silhouette), resemblance, or similarity to something known in nature, whether natural (e.g., feather or batwing), man-made (e.g., bowler hat sign), or descriptive of how the image appears radiographically and correlated to an underlying pathophysiologic process occurring within the lung parenchyma and bronchi. In our review of the COVID radiology literature, we noted that the term "sign" was most often accurately applied to imaging findings where inference was made regarding their significance and pathologic finding. Similar to nearly all radiologic signs, their presence alone is suggestive but not diagnostic of the disease.

Halo and Reverse Halo Sign

The halo sign, as found on chest CT or high-resolution computed tomography (HRCT), is a peripheral-based complete ring-like ground glass opacity or shadow surrounding a pulmonary nodule or mass (10). The ground glass opacity is presumed to represent perinodular alveolar edema and hemorrhage, while the nodule or mass indicate foci of the pulmonary infarction, tumor, or organized

inflammatory nodule (11). The halo sign has been reported in several diseases, including other viral pneumonia, angioinvasive pulmonary aspergillosis, Kaposi sarcoma, and adenocarcinoma of the lung, metastasis, and other infections (bacterial, fungi and viral) and inflammatory (granulomatosis with polyangiitis) conditions (12).

In the reverse halo sign, also referred to as the Atoll sign, a dense crescentic shape of partial or near complete high-density ring-like consolidations surround central focal, round, or half-moon shaped areas of ground glass opacity (10, 13–17). In this case, the central ground glass opacity represents alveolar septal inflammation and cellular debris in the alveolar, while the ring-like surrounding consolidation represents granulomatous tissue within the distal air spaces. Thus, this radiographic finding represents a type of lung injury formed because of an organizing process that occurs in response to inflammatory pneumonitis or a pulmonary infarction (18). If the clinical suspicion for the later remains high, particularly in the presence of elevated D-dimer or sudden deterioration, CT angiography should be performed (15). The early versus later appearance of this sign depends on the underlying pathophysiologic process because it is typically absent in cases of organizing pneumonitis near the time of the onset of initial symptoms (17, 19). The reverse halo sign is found late after symptom onset and has been reported in several conditions, causing an organizing pneumonia, such as other viral pneumonias, fungal infections, granulomatous diseases (sarcoid, granulomatosis with polyangiitis, lymphomatoid granulomatous, tuberculosis), and neoplastic diseases (17, 18).

Double Halo Sign, Target Sign, and Bull's-eye Sign

Poerio *et al*. (20) described a double halo sign with another rim of thicker ground glass opacity around the outer or peripheral thinner rim of consolidation. The target sign is a central nodular ground glass opacity and peripheral ring opacity resembling a "shooting star" (21). The bull's eye appearance or sign is similar to or a variant of the reverse halo sign that represents a central or centrilobular ground glass nodule surrounded by a peripheral or perilobular inner air ring and outer consolidation or ground glass opacity that is distributed peripherally (22). Both, the inner and outer ground glass appearance are believed to represent inflammation or areas of organizing pneumonia confined to a centrilobular and perilobular distribution, while more central lesions indicate either an organizing pneumonia, vascular and perivascular inflammation, or focal pulmonary artery enlargement (22, 23). The pathogenesis of these signs as an organizing process is consistent with their delayed appearance and presence in patients with more moderate to severe disease (22).

Dandelion Clock-Like Sign and Feather Sign

The dandelion clock-like sign and feather sign are caused by a similar histopathologic process that includes vascular enlargement, vascular thickening, micro-vascular dilation, or bronchovascular enlargement (8). In the dandelion clock-like sign (24), the imaging appearance resembles a dandelion–the stem representing the pulmonary blood vessel and seeds, the grid-like interstitial tissue containing small, thickened interlobular septum (24). The round ground glass opacity microscopically shows diffuse alveolar damage caused by alveoli filled with blood, pus, water, or cells (25). Feather sign is another descriptive term; however, in this case, its radiographic appearance resembles a feather. The pathogenesis is believed to be similar in that the shaft corresponds to the thickened blood vessel and stripe, corresponding to ground glass opacity filled with exudate (blood, pus, water, or cells) (25).

Batwing Sign

The batwing sign, also known as angel wing or butterfly sign, indicates bilateral perihilar airspace opacities with the base pointing toward the hilum; a reverse batwing sign represents the opposite CT image appearance, a bilateral peripheral wedge-shaped opacity with the base pointing toward the pleural (26). The reverse batwing sign was first described by Gaensler and Carrington in 1977 in patients with chronic eosinophilic pneumonia and has been observed in other pulmonary parenchymal diseases, such as pulmonary vasculitis, organizing pneumonias, and lung adenocarcinoma (27).

Rime sign refers to the appearance of white rime or "frost" covering tree branches. This radiographic finding represents multiple exudative and punctate hemorrhage with interstitial fibrosis (25). In this sign, some alveoli contain edema and hemorrhagic necrosis along with bronchiole wall thickening because of mucus and hemorrhagic exudate along with interstitial infiltration of inflammatory cells and interstitial fibrosis (25).

Nearly 20 other signs found on CT or HRCT imaging are described in COVID-19 (6, 23–40) (Table 1).

Studies have reported on the frequency of occurrence of various signs based on the disease severity, as identified on chest CT or HRCT scan in COVID-19 patients (28). In a systematic review and meta-analysis of chest CT imaging in COVID-19 patients, the pooled prevalence of airway secretions/tree-in bud sign, halo sign, and reversed halo or Atoll sign with 95% confidence intervals was 4.1% (1.5%–6.7%), 34.5% (13.8%–55.3%), and 11.1% (4.5%–17.7%), respectively (29). In a study on 74 children in whom 37 underwent chest CT, the imaging sign findings included feeding vessel sign (16/37, 43%), and halo sign (9/37, 24.3%) (30).

Çinkooğlu *et al*. (31) assessed 185 COVID-19 patients; 147 of them who underwent HRCT scan of the chest showed the presence of parenchymal infiltrates along with other findings, including a crazy paving pattern in 32 (21.8%), a halo sign in 15 (10.2%), and a reverse halo sign and air bubble or vacuolar sign in 22 (15%). Unlike in previous studies, the tree-in bud sign was not detected. In 180 patients with COVID-19 who underwent a chest CT, an air bronchogram sign was noted in 52 (48%) patients, crazy paving pattern sign was observed in 43 (40%) patients, and a halo sign was present in 69 (64%) patients (6). In a study on 246 patients with COVID-19 who underwent chest CT imaging, crazy paving sign was found in 110 (44.7%) patients, the bat wing sign was present in 58 (23.6%) patients, halo sign was present in 40 (16.3%) patients, and reverse halo sign was noted in 22 (8.9%) patients (32). Thus, individually, the imaging signs lack sufficient sensitivity or specificity for diagnosis. The presence of multiple signs in association with other clinical features and setting increases the likelihood of diagnosing this infection.

Table 1. Signs identified on CT or HRCT imaging in patients with COVID-19 infection

Sign	CT or HRCT image
Air bronchogram (bronchi) sign (6, 35)	Outline of the airway caused by opacities surrounding the airway die to fluid or inflammatory exudate.
Air bubble (vacuolar) sign (31)	Small air-containing spaces within the infiltrates.
Arch bridge sign (36)	Early pulmonary sign located in the subpleural region of the lower lobes caused by ground glass opacity or consolidation resembling an arched bridge with an internal lucent hole.
Cavity sign (37)	Low-density region in a mass or nodule in the lung representing a space for gas accumulation.
Central vascular sign (38)	Dilated vessels ≥1 passing through the middle of a round-like opacity resembling a "target."
Comb sign (38)	Multiple, somewhat parallel dilated vessels vertically oriented and entering into a subpleural arch-shaped opacity.
Crazing paving pattern or sign or Paving stone sign (37, 40)	Patchy or diffuse ground glass opacities with intralobular interstitial and interlobular septal thickening and partial consolidation resembling a mosaic like pattern of disorganized paver stones. Paving stone appearance caused by inflammation in an interlobular septal distribution.
Feeding vessel sign (30)	A branch of the pulmonary artery entering a nodule or mass. This is also referred to as a "fruits on branch" sign.
Ginkgo leaf sign (38)	≥1 trunks consisting of dilated blood vessels distributed in a fan-shaped lesion extending from the tip and oriented toward the hilum.
Grid-form sign (39)	Ground glass density exudate forming a "grid-form" shadow.
Gypsum sign (23, 35)	Patchy bilateral consolidations of varying densities.
Large cable sign (28)	Linear opacity that enlarges, resembling a cable running either parallel or bridged to the pleural.
Parallel pleural sign (40)	Subpleural location whereby the long axis of the lesion maximum diameter is parallel to the pleura.
Pomegranate sign (25)	Round ground glass opacities arranged in an imbricated fashion resembling pomegranate seeds representing exudative lesions with a small amount of bleeding.
Rosa roxburghii (rose) sign (23, 35)	Focal semi-nodular ground glass opacities located in the peripheral lung zone.
Sieve sign (35)	Sieve-like shape or patchy shadow with interlobular septal thickening and bronchodilation in the transverse section.
Spider web sign (38)	Ground glass opacity triangular or angular in form located in the subpleural with thickening of the interlobular septa. The lesion resembles a spider web due to pulling of the adjacent pleural.
Tree-in bud sign (37)	Resemble a budding branch of a tree such as it is a linear branching V or Y shaped opacities with one or more contiguous branching sites connected to nodules with soft tissue attenuation. The nodules are located peripherally, centrilobular, and small in size.
White lung (blizzard sign) (23, 35)	Diffuse, bilateral, flocculent, nodular, and flaky high-density opacities with partial merging consolidation.

HRCT: High-resolution CT; COVID-19: Coronavirus disease 2019

Sonographic Signs

Sonographic signs have been described in COVID-19, including the waterfall sign (full integration of the B-line), rocket sign (dispersed B-line), and C-lines (33). Those signs are demonstrative of peripheral infiltrations (e.g., GGO or consolidation) and pleural irregularities. Thorax ultrasonography is an efficient, bedside, radiation-safe imaging method for both, adults and children (34).

II. Physical Assessment

Cardiovascular

Heart failure secondary to viral myocarditis is a diagnosis rather than a sign (41). Relative bradycardia is a sign that has been reported in COVID-19 patients. Relative bradycardia, pulse-temperature dissociation, or the eponym Faget sign represent the inverse or paradoxical relationship between body temperature and pulse. In this physical finding, the pulse is lower than expected, given the elevated temperature (42). Relative bradycardia is considered the most reliable and sensitive parameter when applied to cases where the body temperature is >38.9°C (102°F). Faget sign was named in honor of Jean Charles Faget (1818–1884) and initially reported in cases of yellow fever (42–44). Relative bradycardia has been described in a variety of infectious and noninfectious conditions, including a host of viral illness. Although the mechanism is unknown, it has been hypothesized that it may be caused by a direct pathogenic effect on the myocardium or nodal tissue, inflammatory cytokines increasing the vagal tone and decreasing the heart rate variability or systemic autonomic dysregulation, or a possible link between angiotensin-converting enzyme 2 (ACE2), the receptor for COVID-19, and its expression on cardiac cells regulating autonomic heart rate control (44–46).

Cutaneous Signs and Findings

Cutaneous findings are classified, as is conventional in dermatology, based on the appearance of the skin lesion as detected on visual observation and palpation and as a descriptor of what is being observed and felt. The types of lesions include primary or basic and secondary or sequential lesions, the latter a reflection of that resulting from infection, excoriation, and manual or other destruction obliteration techniques. Examples of primary lesions are macules, papules, vesicles, and bulla; examples of secondary lesions are scales, scares, and ulcers. Other aspects that are important for diagnosis include the lesion color; shape; margin; arrangement; distribution; and consistency, temperature, mobility, tenderness, and depth on palpation. Although signs have been reported, the majority represent physical findings (47–50) (Table 2).

The red half-moon nail sign has been observed in COVID-19 patients and represents a reversible red-violet band above the nail lunula (47). Although the etiology remains unknown, it is hypothesized to represent micro-vascular injury secondary to pro-coagulation and the inflammatory state (48). Maculopapular eruptions have been described as being morbilliform, plaques, or as a pityriasis rosea-like eruption (49, 50). Based on our case definition these cutaneous findings described are physical findings and do not represent signs of the disease.

Table 2. Cutaneous findings identified in COVID-19 infection (47–50)

- Acro-ischemia lesions
- Androgenic alopecia
- Bullous eruption
- Chickenpox-like rash
- Chilblain or Chilblain-like (pseudo-chilblain) eruptions
- Enanthema
- Erythema multiform-like rash
- Erythematous pomphoid rash
- Livedo-reticularis or livedo-like
- Morbilliform exanthem with petechiae/purpuric urticarial or maculopapular features
- Palmar erythema
- Perianal desquamation
- Periorbital dyschromia
- Pityriasis-rosea-like eruption
- Retiform purpura
- Striae rubrae
- Urticarial rash with plaque features
- Vesicle

Endocrinology

Gabrin sign is eponymously named in honor of Frank Gabrin (1959–2020) who had androgenic alopecia and was the first American physician to die because of COVID-19. The sign refers to the association between androgenic alopecia and severe COVID-19 (51). Younger men aged 35–45 years without known comorbidities had more severe acute respiratory distress syndrome than those without this phenotype (51).

Nasopharyngeal and Oropharyngeal Sign

Anosmia and dysgeusia have been reported as early signs of COVID-19 infection (52–54). These represent subjective and physical findings, with the latter identified via further diagnostic testing. Vesiculobullous, ulcerative, macular lesions, angina bullosa hemorrhagic like lesion, and desquamative gingivitis have been described in association with COVID-19 within the oral cavity (55). Based on our case definition, all findings except those of desquamative gingivitis represents physical findings rather than signs associated with COVID-19, the latter a descriptive diagnosis.

Neurologic

The presence of the claustrum sign in an 18-year-old girl was believed to be a marker for autoimmune encephalitis/epilepsy secondary to COVID-19. The claustra represent a vertical curved sheet of subcortical gray matter external to the basal ganglia, lying between the white matter tracts of the external and extreme capsules (56). The sign is observed as a hyperintensity area in both claustra during MRI on T2 and fluid-attenuated inversion recovery (FLAIR) sequences during the acute phase of febrile infection-related epilepsy syndrome (FIRES) and has been described in a patient with autoimmune epilepsy (57). It is commonly observed after an episode of status epilepticus.

Ophthalmologic

Episcleritis and conjunctivitis have been reported as signs of COVID-19. Based on the proposed case definition, these would more appropriately be classified as physical findings rather than signs (58, 59).

CONCLUSION

Several signs have been identified on chest CT or HRCT in COVID-19. The signs lack sufficient sensitivity or specificity by themselves; however, in the appropriate clinical setting, these should raise clinical suspicion for this infectious disease. Symptoms represent observations whether conveyed by the patient or identified by the examiner or patient; the later were more appropriately referred to as physical findings. Signs provide a tool to assist in the diagnosis and to understand the pathophysiologic process responsible for the phenomenon and the significance of the phenomenon. Distinctions in terminology are important for consistency and for appropriate classification of symptoms, physical findings, and signs.

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