Vascular Cutaneous Manifestations of COVID and RNA Viral Pathogens: a systematic review

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Learning Points

- COVID-19 infections can manifest with various skin findings and are categorized as either inflammatory or vasculitic. These include a spectrum of rashes such as erythematous maculopapular/morbilliform rashes, petechial eruptions, urticarial lesions, chilblains-like rashes, papulovesicular eruptions, and livedo retiform rashes.

- SARS-CoV-2, Rubella, Influenza, Dengue, Coxsackie, and Echovirus, amongst others, exhibit varying skin manifestations. However, not all RNA virus families have been linked to vascular cutaneous pathology.
- COVID-19 and COVID-19 vaccinations have been implicated in the reactivation of other viruses, such as HHV-6/7, VZV, EBV, and HZ. This reactivation is believed to be driven by the synergistic effects of elevated cytokines, particularly TH17 and IL-17, which could account for the increased susceptibility to herpes virus reactivation among COVID-19 patients. Future therapeutic strategies may investigate IL-17 signaling modulation as a potential treatment approach.
- Cutaneous eruptions with vascular involvement, such as the distinctive purple-red acral vasculopathy rash resembling chilblains lesions, are frequently observed with SARS-CoV-2 infections and referred to as "COVID toe." These chilblain-like lesions can serve as a sole skin manifestation of SARS-CoV-2 exposure, even when patients test negative.
- While the presentation of cutaneous symptoms may differ, most skin pathology stems from diverse inflammatory responses characterized by heightened proinflammatory markers and cytokine storms. This may explain the prolonged onset of vascular symptoms observed in COVID-19, Influenza, and Chikungunya.
- Enhancing our understanding of the mechanism behind vascular cutaneous manifestations of viral infections is essential for improving the clinical identification, diagnosis, and management of RNA viral-related dermatological symptoms.

Abstract

Background. COVID-19, the widely recognized and highly contagious respiratory tract infection, has had a substantial impact on the field of dermatology since its emergence in 2019.

Various skin-related symptoms have been reported in COVID-infected patients, most notably the distinctive purple-red acral rash resembling chilblain lesions, commonly referred to as "COVID toe." COVID-19 is classified within the viral RNA family category, and similarly, skin-related symptoms have been observed in connection with other RNA viruses.

Aim. This review aims to explore the relationship between RNA viruses and their associated vascular cutaneous manifestations in comparison to those observed in SARS-CoV-2 infected patients.

Methods. A systematic literature review was conducted using the PubMed database and MeSh terms regarding RNA viruses and related skin manifestations.

Results. A total of 3,994 patients diagnosed with COVID-19 presenting with skin rashes were observed. Chilblain-like lesions (CLL) were most frequently observed (30.2%), followed by erythematous maculopapular/morbilliform rashes (9.1%) and urticarial rashes (4.7%). Out of 8,362 patients diagnosed with RNA viruses, more than half of the skin findings reported were erythematous/maculopapular/morbilliform rashes (52.3%), followed by unspecified rashes (11.3%) and purpuric rashes (10.6%).

Conclusion. When comparing RNA viral infections to COVID-19 cases, we observed similarities in reported skin manifestations and their presumed pathways, with many implicated in the pro-inflammatory response. Due to the wide range of cutaneous symptoms associated with RNA viruses and our current limited understanding of their underlying mechanisms, additional research is warranted to investigate the pathology behind viral-induced skin lesions.

Introduction

Since its emergence in 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a ribonucleic acid (RNA) virus known as COVID-19, quickly spread globally, leading to its declaration as a global pandemic.[1,2] Spread via respiratory droplets, classic clinical manifestations include fever, dry cough, diarrhea, shortness of breath, fatigue, and loss of taste or smell. Reported clinical consequences have substantially impacted nearly every medical specialty, including dermatology.[3,4] Cutaneous manifestations of COVID-19 have been categorized into two groups: those resulting from inflammation, like maculopapular and papulovesicular eruptions, and those of a vascular origin, including pseudo-chilblain or chilblain-like lesions, petechiae, and purpura.[5–8]

Cutaneous vascular complications stemming from SARS-CoV-2 infections have been increasingly reported.[9] One of the most prominent examples is the emergence of erythematous, pruritic, and occasionally painful acral lesions resembling chilblain lesions, referred to as "COVID or pernio toes."[10,11] SARS-CoV-2 has also been associated with other vascular sequelae, such as the re-ulceration of infantile hemangiomas.[12]

Vascular skin findings observed in the context of COVID-19 prompt further investigation into reported vascular cutaneous manifestations of other RNA viruses. The primary objective of this review is to provide a comprehensive analysis of cutaneous symptoms associated with RNA viruses, with emphasis on lesions with vascular involvement compared to those seen in patients with SARS-CoV-2 infections. Our goal is to identify comparable morphological patterns to assist in characterizing and depicting clinical presentations and pathology related to cutaneous viral infections.

Methods

An electronic literature search was conducted on the PubMed (NLM) database from their inception to September 30, 2022, using MeSh (Medical Subject Headings) terms. The MeSH terms incorporated keywords and subject headings related to RNA viral families (Influenza, Reovirus, Picornavirus, Hepevirus, Hepatitis Delta Virus, Norovirus, Flavivirus, Togavirus, Retrovirus, Paramyxovirus, Rhabdovirus, Filovirus, Arenavirus, and Bunyavirus), in conjunction with specific vascular cutaneous symptoms: chilblains, purpura, petechiae, thrombosis, coagulopathy, retiform, skin necrosis, livedoid, ecchymosis, disseminated intravascular coagulopathy (DIC), thrombotic thrombocytopenia purpura (TTP), hemolytic uremia syndrome (HUS), and vasculitis.

Two authors (JLK and CLO) independently evaluated titles, abstracts, and full-text content from the identified records (Figure 1). Discrepancies were resolved through discussion to reach a consensus. Duplicated articles or those unrelated to cutaneous manifestations were excluded. Literature reviews without case studies, articles focusing on fundamental science, histology, pathophysiology, therapeutic strategies, vaccines, and animal studies were also disregarded. Articles that focused on thrombotic symptoms such as deep vein thrombosis (DVT) and pulmonary embolism (PE) without substantial skin-related findings were eliminated. Articles not in English and those unable to be accessed were also excluded. Using Microsoft Excel, data was extracted from the final set of included articles. The count of reported patients included those with confirmed viral diagnoses and skin-related symptoms. Instances of rashes lacking detailed descriptions or possessing unclear characterizations were categorized as unspecified rashes.

Results

A total of 92 articles were included in this review: 49 articles regarding RNA viruses, and 43 regarding COVID-19. Twenty-six case studies, 60 case cohort/case control studies, and 6 cross sectional reviews included for analysis. The most frequently observed lesions chilblain like lesions (30.2%), followed by erythematous maculopapular/morbilliform rashes (9.1%), urticarial rashes (4.7%), papulovesicular rashes (3.7%), and livedo reticularis/racemose (3.5%) (Table 1). Other reported manifestations included oral ulcers, erythema multiforme, and pityriasis rosea.

Eight RNA viral families were included in the final analysis: Coronaviridae, Orthomyxoviridae, Picornaviridae, Flaviviridae, Togaviridae, Retroviridae, Paramyxoviridae, and Bunyaviridae (Table 2). Reoviridae, Hepeviridae, Hepadnaviridae, Rhabdoviridae, Noroviridae, Filoviridae, and Arenaviridae did not produce any studies related to cutaneous vascular phenomena and thus were excluded. Among all the included families, Togaviridae yielded the highest number of studies (58.7%), followed by Flaviviridae (21.2%), and Bunyaviridae (7.8%).

A total of 8,362 patients diagnosed with RNA viruses were included in this study. The most prevalent skin finding reported among RNA viral infections was an erythematous/maculopapular/morbilliform inflammatory rash, accounting for 52.3% of the cases. This was followed by unspecified rashes (11.3%) and petechial/purpuric vasculitic rashes (10.6%). Among the 4,913 patients who contracted Togaviridae, Rubella was the most prevalent pathogen linked to skin findings (89.3%). In cases involving Togaviridae, primary observations included maculopapular/morbilliform inflammatory rashes (93.8%), and vasculitic manifestations like petechiae and purpura were in the minority (0.4%).

Significant skin findings for Flaviviridae were mainly associated with Dengue and encompassed widespread vasculitic petechiae and purpura (34.5%), and unspecified rashes (30.2%). In Bunyaviridae, petechiae/vasculitic symptoms were most commonly reported (29.9%), alongside unspecified rashes (7.7%). Retroviridae was frequently associated with vasculitic cutaneous symptoms (52.3%); erythematous/maculopapular/morbilliform rashes were a minority (11.5%). Paramyxoviridae was dominated by petechiae/vasculitic symptoms (75%). Orthomyxoviridae (Influenza cases) were linked with petechial/vasculitic symptoms (7.7%), maculopapular/morbilliform/erythematous rashes (1.0%), and oral ulcers (1.0%). Patients infected with Picornaviridae (Coxsackie and Echovirus) reported oral ulcers (34.6%) and papulovesicular ulcers (5.3%).

Discussion

RNA viral infections are known to cause various skin eruptions, including characteristic exanthems, maculopapular rashes, papulovesicular eruptions, and urticaria.[13] Particularly noteworthy is the occurrence of skin symptoms associated with the vascular system, such as petechiae and purpura. A proposed hypothesis suggests these viruses trigger systemic inflammation, complement activation, and microvascular injury, subsequently leading to secondary vascular-related cutaneous symptoms.[14]

SARS-CoV-2's implication in vascular skin pathology offers valuable insight into the mechanism for other RNA virus-attributed disruptions in vascular homeostasis (Figure 2).[5,8] Angiotensin-converting enzyme (ACE-2), the functional receptor utilized by SARS-CoV-2, is abundantly expressed on endothelial cells, arterial smooth muscle cells, and microcirculation pericytes, all components of the vascular microcirculation present in all organs, including the

skin. The binding of SARS-CoV-2 to ACE-2 upregulates levels of angiotensinogen II (AngII), a strong vasoconstrictor and potent pro-inflammatory molecule known to generate excess free radicals leading to a cascade of oxidative stress, endothelial cell damage, and thrombosis.[15,16] This explains SARS-CoV-2's ability to interrupt blood supply, injure vascular walls, and ulcerate blood vessels.[9] This severe cytokine storm may also contribute to the high rates of VTE, DVT, PE, and other thrombotic complications observed.[17] Likewise, vascular invasion by other RNA viruses have been known to induce thrombotic ischemia and vascular occlusions.[18] Here we compare the prevalence of cutaneous manifestations associated with viral infections from each family of RNA viruses.

Coronaviridae - SARS-CoV-2 (COVID-19)

Coronaviridae consists of a linear, positive-stranded RNA virus encased in a helical envelope.[19] Reports indicate that dermatologic manifestations linked to COVID-19 infection have been identified in as many as 20% of patients, with 44% showing symptoms at the onset of the disease.[5,6] Among the spectrum of cutaneous manifestations that emerged during the COVID-19 pandemic, the most frequently reported lesions include pseudo chilblains, maculopapular/morbilliform eruptions, urticarial lesions, papulovesicular eruptions, and livedo-like lesions. While evidence regarding COVID-19's predominant skin manifestations has varied, recent studies indicate an increasing prevalence of maculopapular/erythematous rashes, with pseudo-chilblains as the second most common presentation.[20–24]

Other cutaneous markers less commonly reported include acrodynia, dyshidrotic-like lesions, periorbital erythema, eyelid dermatitis, skin rash resembling drug-related intertriginous and flexural exanthema, erythema nodosum-like lesions, cutaneous hyperesthesia, dermatomyositis, erythema nodosum-like Sweet's syndrome, pityriasis rosea (PR) and pityriasis rosea like

eruptions (PR-LE) and follicular eruptions.[22] These non-specific skin symptoms may indicate a potential SARS-CoV-2 infection, leading a provider to consider a diagnosis of COVID-19.

When cutaneous symptoms arise, and COVID-19 is suspected, providers may consider conducting virological studies due to the potential for concurrent viral reactivation.[25,26] COVID-19, as well as COVID-19 vaccinations, have been associated with the reactivation of other viruses. Implicated viruses include human herpes virus 6 and 7 (HHV-6/7), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and herpes zoster (HZ). Research has suggested genetic crosstalk between COVID-19 and herpes viruses, driven by elevated cytokine signaling involving TH17 and interleukin-17 (IL-17).[25,26] Both cytokines are elevated in COVID-19 and herpes infections, and when concurrent, act synergistically, leading to excessive TH17 differentiation and a subsequent increase in circulating IL-17A. IL-17A can hinder viral clearance by increasing pro-inflammatory and anti-apoptotic cytokines, impairing the destruction of virus-infected cells.[25,26]

This interaction may explain the risk of herpes virus reactivation in the presence of COVID-19 infections, indirectly contributing to the activation of PR. [25,26] To differentiate between PR and PR-LE, which mimics a drug eruption but is unrelated to HHV-6/7 infections, virological studies are necessary. Considering the role of cytokines, particularly IL-17, future therapeutic approaches may explore the modulation of IL-17 signaling as a possible treatment strategy.[25,26]

Our findings of pseudo chilblains as the most frequently reported skin manifestation may be attributed to the classification of nonspecific or generalized rashes under the category of "unspecified rashes", which may have included a significant proportion of morbilliform,

maculopapular, or erythematous rashes. These results are consistent with recent retrospective multicenter reviews and other published studies.[21,23,27]

COVID toes are frequently observed in children and young adults, typically presenting with mild systemic COVID symptoms or even remaining asymptomatic.[5,28] These cases usually test negative on COVID-19 PCR tests, possibly due to the low viral load.[29] This could account for underreporting of true rates of pernio toes, as asymptomatic individuals who tested negative for COVID-19 are less likely to report their lesions. Individuals infected with pseudo chilblain may exhibit mild flu-like symptoms 1-2 weeks preceding the appearance of pernio toes.[5,28,30,31] An alternative hypothesis proposes that pernio toes may represent an effective immune response against COVID-19, particularly in patients with mild clinical symptoms.[30]

Orthomyxoviridae

Influenza falls under the Orthomyxoviridae, and are single stranded, enveloped RNA with a segmented genome.[32] Rashes in influenza are infrequently observed, with approximately 2% of patients exhibiting a maculopapular rash, consistent with our findings.[33,34] Our study revealed a small percentage of cases exhibited vasculitic rashes, with the majority being petechial in nature. These observations are consistent with documented petechial exanthems in influenza patients, particularly among febrile children.[30,31,33,35] Petechial rashes are typically indicative of severe viral infections, and often present as terminal symptoms, hypothesized to be enduring effects of an inflammatory response to the virus.[31]

The occurrence of petechial rashes in COVID-19 is similarly infrequent, with a reported prevalence of 3% among COVID-19 infections.[5,36] These cases also tend to emerge after the

onset of severe infection and manifest during the resolution phase, particularly among middle-aged adults.[31]

Picornaviridae

Picornaviridae are small, positive sensed, non-enveloped, single stranded RNA viruses.[37] Coxsackie and enterovirus are infamous for causing hand, foot, and mouth disease (HFM).[38,39] HFM typically presents with herpangina, marked by oral ulcers as vesicles with erythematous halos that rupture into superficial ulcers with a grey-yellow base. While skin lesions are not common, they may manifest as maculopapular and vesicular rashes on the hands, feet, buttocks, legs, and arms.[38,39] Reports of localized maculopapular exanthems with petechiae have also been reported.[40] Atypical echovirus infections, like Echovirus 9, are marked by a maculopapular and petechial eruption that starts on the face or neck and spreads cephalocaudally.[39] Additionally, punched-out ulcers on the soft palate or tonsils and grayish-white dots resembling Koplik spots can appear as a typical enanthem.[39]

Two distinct types of vesicular rashes associated with SARS-CoV-2 have been previously established: the first characterized by a localized, monomorphic rash primarily affecting the trunk, and the second marked by widespread, polymorphic vesicular rashes, distinguishing it from varicella like lesions.[41] COVID vesicular rashes are hypothesized to stem from an inflammatory reaction and cytokine storm triggered by ACE2 in the skin, or alternatively, a direct cytopathic impact of SARS-CoV-2 on the endothelial cells of dermal vessels.[2,41]

Coxsackie oral infections are caused by the binding of coxsackie to an adenovirus receptor, a component of the tight junction between cells in intact epithelium, while enteroviruses enter cells via receptor mediated endocytosis.[42] Coronaviruses affect the oral mucosa by inducing an

inflammatory response, causing significant increases in tumor necrosis factor related apoptosis and interferon gamma production.[43] Oral mucosa is especially susceptible to SARS-CoV-2, as these epithelial cells and salivary glands express ACE2, the entry receptor protein for COVID-19.[43] This interaction allows COVID-19 replication and subsequent destruction, possibly triggering the oral lesions. Other hypotheses suggest these lesions result from opportunistic infections, potentially linked to immune system alterations and systemic damage.[43]

Flaviviridae

Flaviviridae are linear, positive sensed, enveloped, single stranded RNA viruses.[44] Although several diseases comprise the Flavivirus family, Dengue is the only disease that contributed to this study. Dengue is the most common arbovirus infection, and 50-82% of patients report a generalized skin eruption, including macules, papules, morbilliform, and petechial rashes coinciding with our findings.[45] Mucosal involvement in up to 30% of cases has been reported.[45]

Dengue is characterized as a hemorrhagic fever, commonly presenting with bleeding symptoms such as petechiae, purpura, and gingival bleeding. Dengue and COVID-19 share symptoms such as fever, arthralgia, myalgias, and thrombocytopenia, making it difficult to differentiate. There has been reports of COVID-19 mistakenly misdiagnosed as dengue.[46] Petechial/purpuric lesions in COVID-19 infections have been described in approximately 3% of patients, consistent with our findings.[5] Petechiae/purpuric lesions occur later in the clinical presentation; possible causes may include a pauci-inflammatory thrombogenic vasculopathy, secondary viral infection, COVID-19 drugs side effects, severe infection, or thrombocytopenia.[5]

Togaviridae

Togaviridae are positive sense, enveloped, single stranded RNA viruses.[44,47] Togaviridae family encompass the diseases of Rubella, Chikungunya, Zika and eastern and western equine encephalitis. Rubella presents with a classic exanthem of maculopapular rash, described as a fine, non-confluent rash beginning at the head and extending to the extremities, excluding the palms and soles. [47,48] Petechiae on the soft palate, also called Forchheimer spots, are observed in approximately 20% of the patients. Although rare, thrombocytopenic purpura is also a known complication of rubella. Rubella induces an immune response via spread by receptor mediated endocytosis.[47]

Skin manifestations in Zika typically occur 24 to 48 hours after the onset of the general flu-like symptoms.[45] Rashes are mainly maculopapular and start on the face but can also be arranged in a linear net-shape or wheals, with widespread distribution of blanching erythema. Skin findings are variable and affect the face, palms, and soles accompanied by intense itching and scratching. Oral aphthous ulcerations are also common.[45,48]

The clinical symptoms of Chikungunya virus consist of fever, polyarthralgia, generalized skin rash, and joint edema.[45] Skin findings include maculopapular rashes in a third of patients, and petechial rashes are found in up to 80% of patients. [39,45] Facial melanosis with nose pigmentation, acral edema, chilblain like toes, purpura accentuated in photo-exposed areas, vesicle-bullous eruptions, and ulcers, as well as hyperpigmentation over the axilla, perioral, and genital areas have also been reported. [49] The initial site of infection in the human body is the skin, where keratinocytes, melanocytes, and dermal fibroblasts are known to harbor the virus, contributing to the observed hyperpigmentation. This viral presence prompts a robust interferon and proinflammatory response.[45]

The exact cause of acral edema observed in Chikungunya is not yet fully understood and is hypothesized to arise from involvement of the lymphatic system secondary to systemic inflammation, where inflammatory mediators such as interleukin 6, along with cryoglobulinemia, may contribute. Pedal edema has been observed to occur after the resolution of systemic symptoms in both Chikungunya and COVID-19 infected patients. Currently, no link has been established between these two conditions, or whether there is a pathological connection between acral edema and pernio toes seen in Chikungunya and SARS-CoV-2 infections.[50]

Retroviridae

Retroviridae are positive sense, enveloped, single stranded RNA viruses that utilize reverse transcriptase for replication.[51,52] There are two types: HIV, responsible for AIDS, and HTLV, linked to adult T cell leukemia. HIV exhibits varied symptoms based on infection stage and opportunistic infections, leading to diverse skin manifestations. HTLV commonly results in xerosis and ichthyosis-related conditions. Vasculitic lesions are the sole shared skin finding in both viruses.[51,52]

Paramyxoviridae

Paramyxoviridae are negative sensed, linear, enveloped, single stranded RNA viruses.[53] Subtypes include Pneumovirinae that manifests respiratory syncytial virus (RSV), Paramyxovirinae encompassing Morbillivirus (Measles and Rubeola), Respirovirus (para-influenza), and Rubulavirus (mumps and para-influenza). Viral infections within this family, measles in particular, exhibit an erythematous maculopapular/morbilliform rash as a characteristic feature.[48,53] In addition, petechial lesions may also occur on the soft palate.[39]

Morbilliform rashes are characteristic indicators of viral infections and adverse drug reactions.[5,7,48] Among patients with COVID-19, maculopapular rashes are among the most prevalent skin manifestations, accounting for 70% of cases. Similarly, urticaria has been associated with a prevalence as high as 19%, with 92% of cases associated with pruritis.[2]

These rashes have been associated with severe COVID infections, making it challenging to distinguish them from drug reactions, as individuals with severe illness are often on medication. Additionally, there are reports of rash development in the absence of medication use. One hypothesis is that the heightened immune response to the body's inflammation may lead to increased medication sensitivity.[5,7] Another possibility is the result of direct localization of the virus on the skin.[2,41]

Bunyaviridae

Bunyaviridae are negative sensed, spherical, enveloped, single stranded RNA viruses.[54] Members of this family encompass a spectrum of hemorrhagic fevers and tickborne illnesses, including but not limited to the Crimean Congo virus, Hantavirus, La Crosse virus, and Rift Valley fever virus. Consistent with other types of viral hemorrhagic fevers, expected patient symptoms include those associated with bleeding manifestations: petechiae, purpura, and ecchymosis. Crimean Congo virus often begins with a petechial rash as the presenting symptom.[55] Morbilliform eruptions and facial rashes are also well-known skin findings of Crimean Congo virus, consistent with our findings. This virus also induces a proinflammatory response and cytokine storm that can lead to shock.[54,55]

The absence of documented vascular cutaneous manifestations in various RNA virus families, particularly the Rhabdoviridae family, which, like the Coronaviridae family, is transmitted via

respiratory droplets, highlights the distinct nature of each family of viruses. Moreover, observing these manifestations solely in specific RNA family members, such as Dengue within the Flaviviridae family, further underscores that each family has unique members with specific characteristics, and there may be exceptions or variations within each family.

Limitations

Adherence to specific exclusion criteria may have resulted in omitting relevant articles. Additionally, restricted accessibility to articles published over 20 years ago could have limited the historical perspective on the topic. Moreover, the rapidly increasing number of publications on COVID-19 during the study execution may have led to certain recent findings not being included. Certain factors related to patient characteristics, vaccination, and health status were not accounted for in the selected articles, which could have influenced the observed skin manifestations and severity. Also, variables such as the impact of drug usage, the presence of multiple concurrent illnesses, and the possibility of coinfection with multiple viruses may have contributed to the reported skin findings. Lastly, cases that tested negative for COVID were excluded, which could impact the comprehensiveness of our analysis.

Conclusion

Various skin manifestations were observed across a range of RNA viruses, both inflammatory and vascular. In the context of COVID and RNA infections, similar skin symptoms were observed, including perniosis or edematous toes, maculopapular/morbilliform rashes, urticarial rashes, vesicular rashes, and oral ulcers, each with distinct mechanisms of infection linked to the inflammatory response. Importantly, no vascular cutaneous pathology was linked to the

Reoviridae, Hepeviridae, Hepadnaviridae, Rhabdoviridae, Noroviridae, Filoviridae, and Arenaviridae families. This review highlights the need for further exploration into the underlying mechanisms driving cutaneous manifestations found in SARS-CoV-2 infected patients and related RNA viruses.

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Figure legends

Figure 1: Exclusion Criteria for RNA and Coronaviruses.

Figure 2: Inflammatory Response-Induced Coagulopathy in SARS-CoV-2 Infection

Table 1 Study Characteristics of Reported Skin Manifestations in patients infected with SARS-CoV-2

Author	Sample size	Erythematous/ Maculopapular/ Morbilliform (n, %)	Papulovesicular/ Varicella like lesions (n, %)	Petechiae/ Purpuric/ Ecchymosis Vasculitis (n, %)	Urticarial (n, %)	Chilblain lesions (CLL)(n, %)	Livedo Reticularis/ Racemosa (n, %)	Other (n, %)
Ghafoor et al. 2022[56]	102	27 (26.5)	15 (14.7)	27 (26.5)	10 (9.8)	-	-	-
Waqas et al. 2006 [57]	6	-	-	-	-	-	6 (100)	-
Hasbani et al. 2021[58]	1	-	-	1 (100)	-	-	-	-
Fujimoto et al. 2021[59]	1	1 (100)	-	-	-	-	-	-
Shenker et al. 2020[60]	1	-	-	1 (100)	-	-	-	-
Silva et al. 2020[61]	1	-	-	-	-	1 (100)	-	-
Levraut et al. 2021[62]	1	-	-	1 (100)	-	-	-	-
Ciccarese et al. 2021[63]	1	1 (100)	-	1(100)	-	-	-	-
Karaca et al. 2020[64]	1	1 (100)	-	-	-	-	-	-
Wollina 2020[65]	1	-	-	1 (100)	-	-	-	-

Zulfiqar et al. 2020[66]	1	-	-	1 (100)	-	-	-	-
Maestro et al. 2020[67]	75	4 (5.3)	1 (1.3)	-	2 (2.7)	6 (8.0)	1 (1.3)	-
Fulgencio-Barbarin et al. 2020[68]	1	-	-	-	-	-	-	-
Ghimire et al. 2021[69]	1	1	-	-	-	-	-	-
Morales et al. 2020[70]	1	-	-	-	-	-	-	Phlegmasia cerulea dolens, 1 (100)
Berrebi et al. 2021[71]	1	-	-	-	1 (100)	-	-	-
Calton et al. 2021[72]	1	-	-	-	-	1 (100)	-	-
Phamduy et al. 2021[73]	1	1 (100)	-	-	-	-	-	-
Capoferri et al. 2022[74]	1	-	-	-	-	-	1 (100)	Oral ulcer, 1 (100)

Bibbo 2021[75]	1	-	-	-	-	-	-	Necrosis/clear hemorrhagic bullae, 1 (100)
Gaspar et al. 2022[76]	6	-	-	-	-	-	-	Unspecified skin rash, 6 (100)
Novara et al. 2020[77]	1	-	-	-	-	-	-	Acral cyanosis progressing to gangrene, 1 (100)

Demissie et al. 2020[78]	1	1 (100)	-	-	-	-	-	Mucocutaneous inflammation, 1 (100)
Sachdeva et al. 2020[75]	45	26 (57.8)	4 (8.9)	1 (2.2)	8 (1.8)	3 (6.7)	5(11.1)	-
Paparella et al. 2022[79]	1	-	-	-	-	1 (100)	-	-
Colonna et al. 2022[80]	1	-	-	-	-	1 (100)	-	-
Mascitti et al. 2021[81]	2756	-	-	-	-	1082 (39.3)	-	-
Gooch et al. 2021[82]	1	1 (100)	-	-	-	-	-	-
Ocampo-Candiani et al. 2021[83]	347	72 (20.7)	61 (17.6)	39 (11.2)	72 (20.7)	27 (7.8)	97 (28)	pityriasis rosea-like lesions, 15 (4)
Brancaccio et al. 2021[84]	7	-	-	-	-	3 (42.9)	-	-

Larenas-Linnemann et al. 2021[85]	6	1 (16.7)	1 (16.7)	-	1 (16.7)	1 (16.7)	-	EM, 1(16.7); KD, 1(16.7)
Vázquez-Osorio et al. 2021[86]	2	-	-	-	-	2 (100)	-	-
Jacquin-Porretaz et al. 2021[87]	12	2 (16.7)	2 (16.7)	-	3 (25)	-	1 (8.3)	Photo distributed rash, 1 (8.3)
Marzano et al. 2021[17]	200	48 (24)	29 (14.5)	13 (6.5)	19 (9.5)	46 (23)	4 (2)	-
Widysanto et al. 2021[88]	1	-	-	1 (100)	-	-	-	-
Rubin et al. 2021[89]	1	-	-	-	-	1 (100)	-	-
Andina et al. 2021[90]	1	-	-	1 (100)	-	-	-	-
Fertitta et al. 2021[91]	1	-	-	-	-	1 (100)	-	-
Gambichler et al. 2021[92]	1	-	-	-	-	1 (100)	-	-
Andina et al. 2020[93]	1	-	-	-	-	1 (100)	-	-

Garcia-Lara et al. 2020[94]	25	-	-	-	-	25 (100)	-	-
Landa et al. 2020[95]	2	-	-	-	-	2 (100)	-	-
Galván Casas et al. 2020[21]	375	176 (47)	34 (9)	-	71 (19)	-	23 (6.1)	-
Total	*3994 (100)*	*363.3 (9.1)*	*147 (3.7)*	*87 (2.2)*	*187 (4.7)*	*1205 (30.2)*	*138 (3.5)*	*29 (0.7)*

EM- Erythema Multiform, KD- Kawasaki Disease

Table 2: Skin Finding by RNA Virus Families

Viral Family (N=Sample Size)	Characteristics and Key Features	Disease (n)	Erythematous/ Maculopapular/ Morbilliform n,(%)	Papulovesicular n,(%)	Petechiae/ Purpuric Vasculitis n,(%)	Facial Rash n,(%)	Unspecified n,(%)	Other n,(%)
Bunyaviridae (642)[55,96–102]	Negative-sense segmented.	Brucellosis (52)	-	-	3 (5.8)	-	18 (34.6)	-

	Enveloped. Transmitted through arthropod vectors. Cause diseases such as hantavirus pulmonary syndrome, Crimean-Congo hemorrhagic fever, and Rift Valley fever.	Crimean Congo Virus (479)	23 (4.8)	-	143 (29.9)	128 (26.7)	37 (7.7)	Multiple Skin Findings, 60 (12.5) Skin eruption, 21 (4.4) Hematoma, 2 (0.4)
		Hemorrhagic Fever Renal Syndrome (HFRS) (34)	22 (64.7)	-	24 (70.6)	-	-	-

		Phleboviral Hemorrhagic Fever (HYSHF) (34)	14 (41.2)	-	9 (26.5)	-	-	-
		Severe fever with thrombocytopenia syndrome (43)	-	-	9 (20.9)	-	-	-
Flaviviridae (1,769)[103–113]	Positive-sense single-stranded. Enveloped. Transmitted by arthropod vectors	Dengue (1,769)	83 (4.7)	-	610 (34.5)	-	-	Non specified rash 535 (30.2) Facial rash 51(2.9) Itching 166

	like mosquitoes and ticks. Cause diseases such as hepatitis C, dengue fever, Zika virus infection, and yellow fever.							(9.4) Cold hands/feet 20 (1.1) Flushing 53 (3.0)
Orthomyxoviridae 104[34,114–117]	Negative-sense segmented. Enveloped. Responsible for influenza viruses, causing seasonal	Influenza (104)	1 (1.0)	-	7 (6.7)	-	-	Oral ulcer, 1 (1.0)

	epidemics and occasional pandemics. Includes Influenza A, B, and C.							
Paramyxoviridae 8[117–121]	Negative-sense single-stranded. Enveloped. Cause respiratory infections (measles, mumps), as well as other diseases. May also lead to	Measles (5)	1 (20.0)	-	3 (60.0)	-	-	Erythema elevatum diutinum, 1 (20.0)
		Mumps (1)	-	1	-	-	-	
		Parainfluenza and Respitory Syncitial Virus (2)	-	-	2 (100)	-	-	

	syncytium formation. Members include paramyxoviruses and pneumoviruses.							
Picornaviridae 546[122–128]	Positive-sense single-stranded. Non-enveloped. Cause a variety of diseases, including the common cold, polio, and various enteric infections.	Coxsackie A/B (321)	16 (4.9)	29 (9.0)	1 (3.1)	-	146 (45.5)	HFM, 99 (30.8) Oral ulcer, 146 (45.5) Facial involvement, 13 (4.0) Pain/itching, 4 (1.2) EM, 3 (0.9)

	Members include enteroviruses, rhinoviruses, and hepatoviruses.	Echovirus (215)	-	-	2 (0.9)	-	78 (36.3)	Herpangina, 3 (1.4) HFM 6, (2.8)
		Hepatitis A (1)	1 (100)	-	1 (100)	-	-	-
Retroviridae 381[129–137]	Positive-sense single-stranded RNA viruses that are reverse-transcribed into DNA. Enveloped. Includes human immunodeficiency	Hepatitis B (2)	1 (50)	-	1 (50)	-	-	-
		Hepatitis C (321)	61 (19.0)	-	-	-	-	Unspecified skin rash, 55 (17.1) Psoriasis, 1 (0.1) PCT, 3 (0.9) LP, 3 (0.9)
		HIV (44)	-	-	14 (31.8)	-	-	-
		HTLV II	-	-	2 (14.3)	-	-	-

	virus (HIV), causing AIDS, and other retroviruses. Key feature: integration into host genome.	(14)						
Togaviridae 4913[138–141]	Positive-sense single-stranded. Enveloped. Transmitted by arthropod vectors. Include alphaviruses	Chikungunya (495)	27 (5.9)	-	-	-	63 (12.7)	Oral ulcer, 63 (7) Pain/itching, 286 (57.8)
		Rubella (4387)	4116 (93.8)	104 (2.4)	19 (0.4)	-	-	-
		Zika (31)	17 (54.8)	-	-	-	-	-

	(e.g., Chikungunya virus) and rubiviruses (e.g., rubella virus).							
Total		8362	4376 (52.3)	133 (1.6)	887 (10.6)	399 (4.8)	949 (11.3)	

(PCT)= Porphyria cutaneous tarda, (LP)-Lichen Planus

CPD Questions

Learning Objective: To gain up-to-date knowledge about the latest documentation of vascular cutaneous manifestations associated with RNA viruses.

Question 1. What percentage of COVID infected patients present with dermatologic symptoms?

(a) 5%
(b) 10%
(c) 20%
(d) 30%
(e) 40%

Question 2. What are the two main categories of COVID-19 cutaneous manifestations?

(a) Inflammatory and autoimmune reactions
(b) Vascular and hematologic abnormalities
(c) Allergic and immunological responses
(d) Inflammatory and vascular reactions
(e) All of the above

Question 3. Which of the following statements about SARS-CoV-2's impact on the vascular system is true?

(a) SARS-CoV-2 only affects arterial smooth muscle cells.
(b) The binding of SARS-CoV-2 to ACE-2 downregulates the levels of angiotensinogen II (Ang II) causing oxidative stress, endothelial damage, and thrombosis.
(c) ACE-2 is the functional receptor utilized by SARS-CoV-2
(d) SARS-CoV-2 binding to ACE-2 can lead to an increase in Ang II levels, causing oxidative stress, endothelial damage, and thrombosis.
(e) Both (c) and (d)

Question 4. In light of their shared respiratory droplet transmission method with the Coronaviridae family, which RNA virus family demonstrates a distinct absence of vascular cutaneous manifestations?

(a) Coronaviridae
(b) Flaviviridae
(c) Rhabdoviridae
(d) Orthomyxoviridae
(e) Bunyaviridae

Question 5. A virus belonging to which of the following families causes pedal edema with an onset timing similar to that of COVID-19?

(a) Picornaviridae
(b) Flaviviridae
(c) Bunyaviridae
(d) Retroviridae
(e) Togaviridae

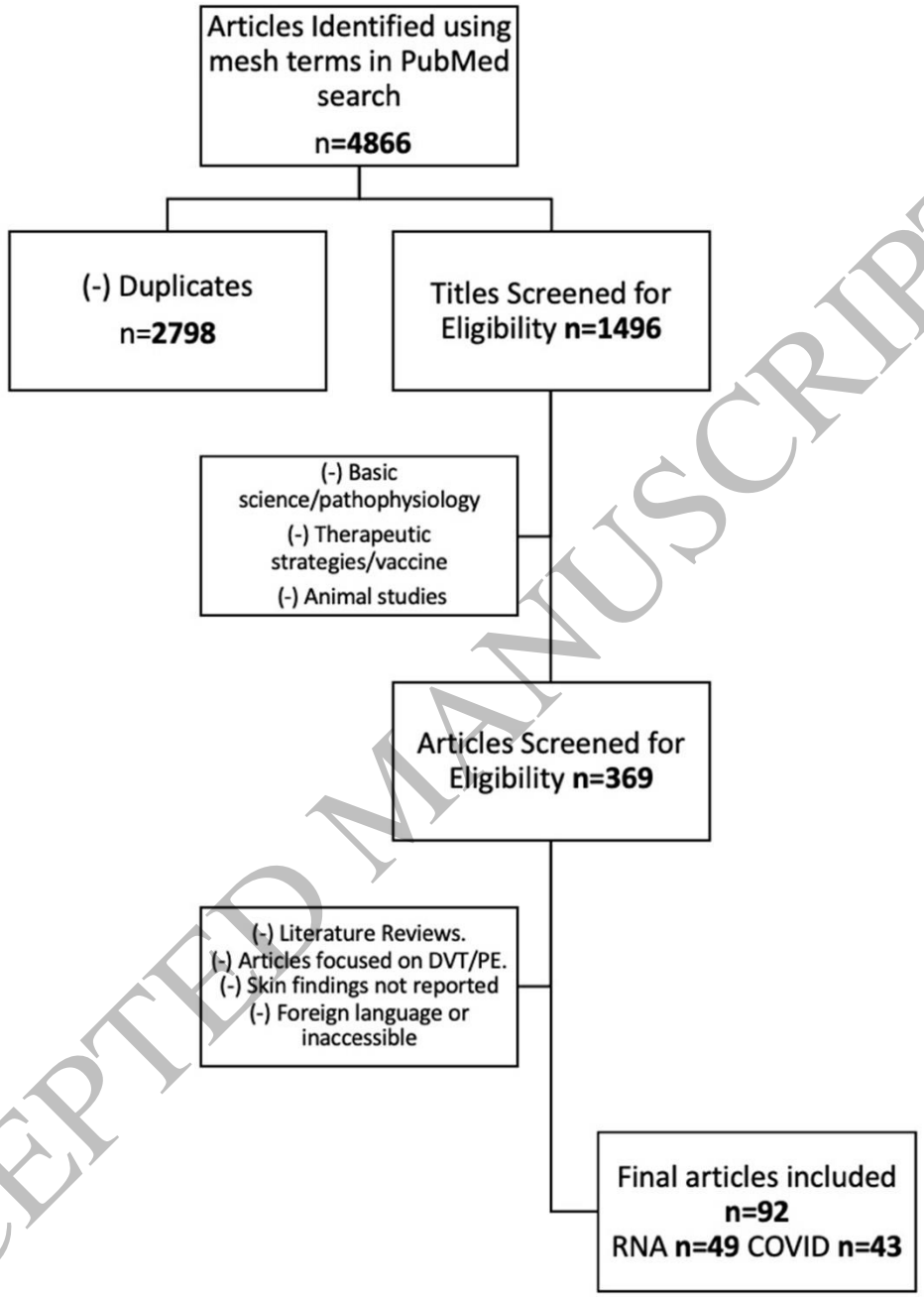

Figure 1
144x185 mm (x DPI)

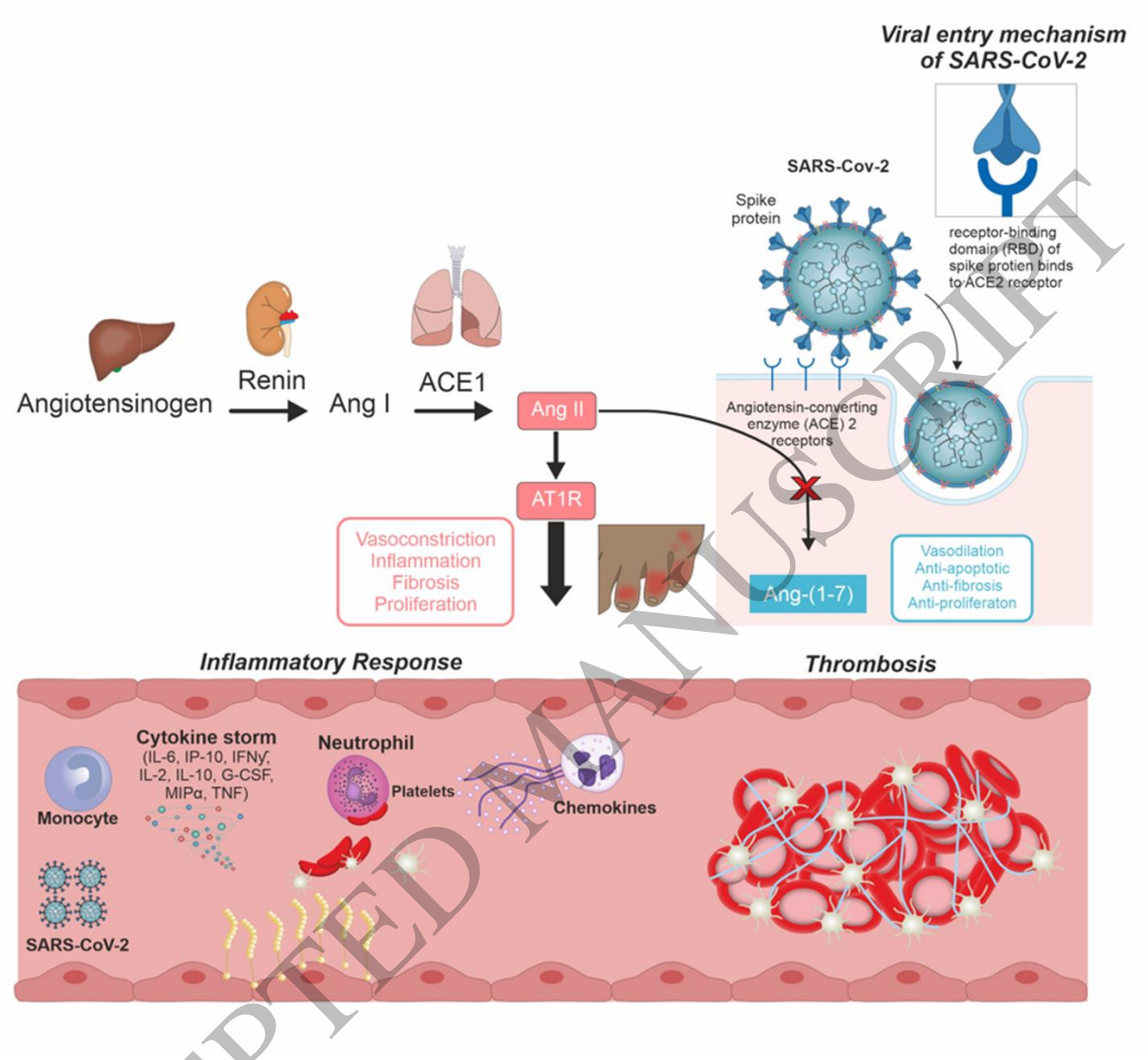

Figure 2
165x151 mm (x DPI)