

Review Article,

Dermatological Manifestations in Covid-19: A Systematic Review

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Abstract:

Methods: This article is a systematic review of literature about dermatological manifestations in SARS-CoV-2 infection. The database used for this research were PubMed Central® (PMC), Literatura Latino-americana e do Caribe em Ciências da Saúde (LILACS) e Scientific Electronic Library Online (SciELO). This search filters has been applied: articles published in 2020, descriptors only in the title or abstract and full text. After that, 34 articles were selected as base for this data research. **Results:** It was observed that urticaria is the most frequent manifestation, presented in 10 articles (71,4%) of 14 evaluated, followed by maculopapular eruptions, mentioned in 6 articles (42,8%), and itching, related in 5 articles (35,7%). In the case report analysis, specifically, it is possible to notice bigger prevalence of maculopapular lesions, mentioned in 8 case reports (40%), and urticarial, described in 7 case reports (35%). About the most affected parts by dermatological manifestations, stands out chest area, presented in 29 studies (85,3%), extremities, presented in 21 studies (61,8%), face, presented in 16 studies (47%) and oropharyngeal, presented in 10 studies (29,4%). **Conclusion:** concrete information about dermatological manifestations in COVID-19 is still unknown. Therefore, bigger studies are needed about these skin lesions to clarify pathophysiological knowledge of this virus with huge impact nowadays.

Keywords: COVID-19, dermatological manifestations, skin lesions, urticaria, maculopapular lesions.

Introduction:

The coronavirus disease (COVID-19) is caused by SARS-COV2 and represents the agent of a fatal disease which is the biggest worry to the global health public system nowadays [1]. Coronavirus is one of the main pathogens that affect the human respiratory system. Other outbreaks before coronavirus (CoVs) include severe acute respiratory syndrome (SARS) -CoV and Middle East Respiratory Syndrome (MERS) -CoV was previous characterized as big threat agents to public health [1]. In Brazil, the disease has presented badly, with high taxes of contamination and mortality, putting the country in rank of the most affected countries. In all states, population

has been compromised, reflecting on social, sanitary, economic and politics impact. SARS-CoV-2 is an enveloped virus made by one chain simple-stranded RNA and belongs to coronavirus family [2]. The virus enters the cell through angiotensin-converting enzyme 2 (ACE2) receptor, found in the cell surface [2]. The transmission occurs through released of breathing droplets or touch with contaminated object with the virus [3]. Lungs are the first place compromised by COVID-19, and the patients presents diverse symptoms like common cold to fulminant pneumonia with lethal breath discomfort, besides the involvement of many

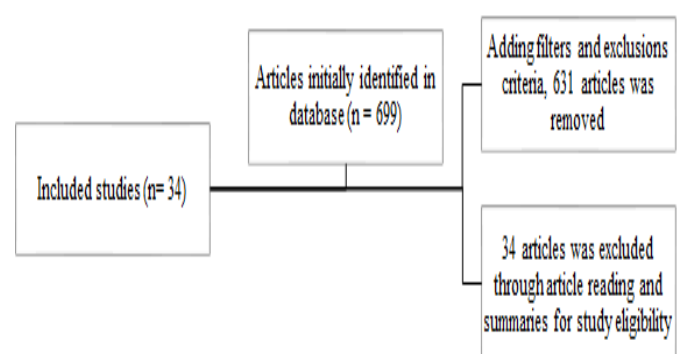
organs or systems leading to sepsis or septic shock with organic disfunction [4]. Beyond the clinical presentation above, big amount of COVID-19 cases had cutaneous manifestations [5]. COVID-19 register of American Academy of Dermatology, a collaboration between American Academy of Dermatology and International League of Dermatologic Societies, observed that among 171 patients with COVID-19 confirmed in the laboratory with cutaneous manifestations of the disease, most prevalent related was morbilliform cutaneous eruptions, acral lesions (pernium), urticaria, macular erythema, vesicular eruptions, papuloescamous eruption and retiform purpura [6]. The mechanism of cutaneous changes in COVID-19 are not well known, but some theories are prevalent. It is believed that viral particles is included in blood vessels of the patients skin with the disease can carry to a linfocitic vasculitis like the ones observed by imune complexes secondary to the huge activation of cytokines, event that could explain the late present of lesions in evolutive phase known as hyperinflammation phase [7]. It also can be justified by keratinocytes attack secondary to Langerhans cells activation in pathophysiology's disease by immune answer to the infection, resulting in development of vasodilatation [7]. Other theories justify the show up lesions in livedoreticular form or even necrosis, by the gathering of microthrombs originated in other organs, which may reduce the blood flux in cutaneous microvascular system or even because of thrombogenic vasculopathy with complement deposition [7]. Laboratorial diagnosis is made by polymerase DNA exam, which uses the enzyme chain reaction to identify the genetic material in the blood and breathing samples [8]. Then, considering the knowledge importance about clinical manifestations of COVID-19, the main goal of this systematic review is approach the prevalence of main dermatological manifestations and their anatomical location.

Body text:

This article is a systematic review about dermatological manifestations in SARS-CoV-2

infection. To make this study possible is necessary to follow some steps: defining the main question, how to choose the database, descriptions and filters used during this study in addition to defining the inclusion and exclusion criteria. After that, must analyze and evaluate critically these studies to choose which ones will be part of this review [9]. The database used for this research was: PubMed Central® (PMC), Literature Latino-Americana e do Caribe em Ciências da Saúde (LILACS) e Scientific Electronic Library Online (SciELO). The descriptors chose was “manifestations”, “cutaneous” and “COVID-19”, with Boolean operator “AND” been applied. To find a better way to reduce the amount of articles that have been found, some search filters was applied: articles published on 2020, descriptors only in the title or summary and full texts. In the same way, only observation studies, case and serial cases reports was included on this research. It was excluded the ones that did not broach about this theme or contemplate the specific objective of this research. Otherwise, filters to restrain another language were not used in order to allow bigger data as this theme is so recent. It was found 699 articles in the beginning of research with Boolean descriptor already been used, with no results in LILACS database and just two in SciELO. Filters been used with exclusion criteria mentioned above, it was excluded the amount of 631, resulting in 68 articles to be read and analyzed. After that, 34 articles were selected to this study database, which is visible in the flowchart, picture 1.

Picture 1: Flowchart of the process realized to select the articles



Source: Research database, 2020.

The selected articles through the research were choose by two independent reviewers (ML e TC), in order to make the Kappa index apply possible, and to evaluate the selection agreement between them (Table 1). In case of disagreement, a third reviewer (LT) was supposed to define the inclusion of discordance articles between the two reviewers from before. The index obtained, 0.7774 value, presents strong concordance [10], being essential to the next steps of the research (Table 1).

Table 1: kappa index.

	Category 1*	Category 2**
Kappa category	0.7774	0.7774
Standard mistake of Kappa category	0.055	0.0539
Interval trust of 95% from Kappa category	Sup: 0.8852 Inf: 0.6696	Sup: 0.883 Inf: 0.6718

*Articles included in the study **Articles excluded in the study

Source: Research database, 2020.

Results and discussion:

Tables 2 e 4 show the included studies details as author's name, sample number, type of study and place where the study was made, besides the percentual of dermatological manifestations and age group that was found in the samples. In the end, it was noticed that 1.231 total cases related these manifestations.

Table 2: Data about the Chose Articles and Study Sample.

Article	Sam ple (n)	Sample with dermatol ogical manifesta tions	Plac e	Age group	Study type
GC Casas <i>et al</i> [11]	375 cases	375 cases (100%)	Spai n	No restrict ions	Observat ional
S Recalc	88 cases	18 cases (20,45%)	Italy	Not related	Observat ional

ati [12]					
A Tammaro <i>et al</i> [13]	279 cases	32 cases (11,5%)	Spai n e Italy	Not related	Observat ional
WJ Guan <i>et al</i> [14]	1009 cases	6 cases (0,6%)	Chin a	35 a 58 years	Observat ional
A Dalal <i>et al</i> [15]	102 cases	13 cases (12,7)	Indi a	39,3 years average	Observat ional
O Askin <i>et al</i> [16]	210 cases	52 cases (24%)	Turk ey	18 to > 85 years	Observat ional and prospecti ve
C Guarneri <i>et al</i> [17]	125 cases	13 cases (10,4%)	Italy	71,9 years average	Observat ional and prospecti ve
V Giorgi <i>et al</i> [18]	678 cases	53 cases (7,8%)	Chin a e Italy	28 a 69 years	Observat ional and cross sectional
A Reymundo <i>et al</i> [19]	7 cases	7 cases (100%)	Spai n	66,5 years average	Retrospe ctive
R Pangti <i>et al</i> [20]	138 cases	10 cases (7,25%)	Indi a	Sem restriçõ es	Prospecti ve
MGL Martín ez <i>et al</i> [21]	26 cases	26 cases (100%)	Spai n	28 years average	Case series
CAR Muniz <i>et al</i> [22]	34 cases	34 cases (100%)	Spai n	53 years average	Case series
EE Freeman <i>et al</i> [23]	716 cases	171 cases (23,9%)	Unit ed Stat es	28 a 61 years	Case series
EE Freeman <i>et al</i> [24]	505 cases	318 cases (63%)	Unit ed Stat es	17 a 38 years	Case series

Source: Research database, 2020.

The Table 3 presents the dermatological manifestations mentioned in the case report articles and the perceptual (when mentioned) in the patients. It can be observed that urticaria is the

most frequent manifestation, existing in 10 articles (71,4%) of 14 evaluated, followed by maculopapular eruptions, mentioned in 6 articles (42,8%), and itching, related in 5 articles (35,7%). Analyzing the most prevalent manifestations accord the number of cases (not considering the articles that did not mentioned it) the erythematous is related in 489 cases, followed by chilblains, mentioned in 447 cases.

Table 3: Prevalence of Dermatological Manifestations in Articles.

Dermatological manifestations	Mentioned in articles	Samples with manifestations
Acrocyanosis	C Guarneri <i>et al</i> [17]	
Erythema with vesicles or pustules in the acral area (Pseudo-chilblains)	GC Casas <i>et al</i> [11] MGL Martínez <i>et al</i> [21]	19% (71 cases) 73% (19 cases)
Peeling	R Pangti <i>et al</i> [20]	-
Enantema e estomatitis aphous	O Askin <i>et al</i> [16]	5,8% (12 cases)
Chilblains	EE Freeman <i>et al</i> [24] EE Freeman <i>et al</i> [23]	63% (318 cases) 18% (129 cases)
Macular erythema	EE Freeman <i>et al</i> [23] R Pangti <i>et al</i> [20]	13% (93 cases) -
Rash	WJ Guan <i>et al</i> [14]	-
Erythema eruptions	S Recalti [12] V Giorgi <i>et al</i> [18] A Tammaro <i>et al</i> [13] C Guarneri <i>et al</i> [17]	15,9% (14 cases) 70% (475 cases) - -
Squamous erythema eruptions	O Askin <i>et al</i> [16]	32,7% (69 cases)
Maculopapular eruptions	GC Casas <i>et al</i> [11] A Dalal <i>et al</i> [15] O Askin <i>et</i>	47% (177 cases) 2,9% (3 cases) 23% (48 cases) 100% (7 cases) 15,4% (4 cases)

	al [16] A Reymundo <i>et al</i> [19] MGL Martínez <i>et al</i> [21] CAR Muniz <i>et al</i> [22]	14,7% (10 cases)
Petechial purpuric eruption	O Askin <i>et al</i> [16]	7,7% (16 cases)
Vesicular eruptions	GC Casas <i>et al</i> [11]	9% (34 cases)
Target lesions	CAR Muniz <i>et al</i> [22]	14,7% (5 cases)
Chilblains-like lesions (COVID fingers)	C Guarneri <i>et al</i> [17] R Pangti <i>et al</i> [20]	- -
Livedo or necrosis	GC Casas <i>et al</i> [11] O Askin <i>et al</i> [16] CAR Muniz <i>et al</i> [22]	6% (23 cases) 7,7% (16 cases) 29,4% (10 cases)
Morbilliform	EE Freeman <i>et al</i> [23]	22% (157 cases)
Herpes simplex oral reactivation	C Guarneri <i>et al</i> [17]	-
Papulosquamous	EE Freeman <i>et al</i> [23]	9,9% (71 cases)
Panniculitis	C Guarneri <i>et al</i> [17]	-
Pernio	O Askin <i>et al</i> [16] R Pangti <i>et al</i> [20]	1,9% (4 cases) -
Petechial	V Giorgi <i>et al</i> [18] R Pangti <i>et al</i> [20]	- -
Itching	A Dalal <i>et al</i> [15] O Askin <i>et al</i> [16] MGL Martínez <i>et al</i> [21] A Tammaro <i>et al</i> [13]	7,8% (8 cases) 1,9% (4 cases) 50% (13 cases) - -

	V Giorgi <i>et al</i> [18]	
Purpura	EE Freeman <i>et al</i> [23] CAR Muniz <i>et al</i> [22] R Pangti <i>et al</i> [20] V Giorgi <i>et al</i> [18]	6,4% (46 cases) 11,8% (4 cases) 1,5% (2 cases) -
Aphthous ulcers	R Pangti <i>et al</i> [20]	-
Urticaria	V Giorgi <i>et al</i> [18] GC Casas <i>et al</i> [11] S Recalti [12] A Dalal <i>et al</i> [15] O Askin <i>et al</i> [16] MGL Martínez <i>et al</i> [21] EE Freeman <i>et al</i> [23] CAR Muniz <i>et al</i> [22] C Guarneri <i>et al</i> [17] A Tammaro <i>et al</i> [13]	26% (177 cases) 19% (72 cases) 3,4% (3 cases) 1,9% (2 cases) 13,5% (29 cases) 7,7% (2 cases) 16% (114 cases) 11,8% (4 cases) - -
Vesicular	EE Freeman <i>et al</i> [23] S Recalti [12] A Tammaro <i>et al</i> [13]	11% (79 cases) 1,1% (1 case) -
Varicella-like vesicles	V Giorgi <i>et al</i> [18] MGL Martínez <i>et al</i> [21] A Tammaro <i>et al</i> [13]	0,3% (2 cases) 3,8% (1 case) -
Weals	R Pangti <i>et al</i> [20]	2,2% (3 cases)

Source: Research database, 2020.

20 case reports have been analyzed, as this theme is so recent, the inclusion in this type of study would increase the data about the main theme related here (Table 4).

Table 4: Case Report Articles and Their Samples Main Features.

Article	Sample (n)	Place	Age group	Study type
OU Olisova <i>et al</i> [25]	1 case	Russia	12 years	Case report
P Suter <i>et al</i> [26]	1 case	Switzerland	42 years	Case report
K Hassan [27]	1 case	Scotland	46 years	Case report
R Beaupre <i>et al</i> [28]	1 case	United States	42 years	Case report
G Paolino <i>et al</i> [29]	1 case	Italy	37 years	Case report
N Aghazadeh <i>et al</i> [30]	1 case	Iran	9 years	Case report
N Patel <i>et al</i> [31]	1 case	United Kingdom	78 years	Case report
N Spifle <i>et al</i> [32]	1 case	United States	54 years	Case report
BE Putra <i>et al</i> [33]	1 case	Indonesia	29 years	Case report
SAA Elhag <i>et al</i> [34]	1 case	United Arab Emirates	40 years	Case report
GM Iancu <i>et al</i> [35]	1 case	Romenia	41 years	Case report
S Farouk [36]	1 case	Egypt	33 years	Case report
MR Navaeifar <i>et al</i> [37]	1 case	Iran	12 meses	Case report
A Estebanez <i>et al</i> [38]	1 case	Spain	28 years	Case report
MM Olive <i>et al</i> [39]	2 cases	Spain	2 meses e 6 years	Case reports
JJ Cauhe <i>et al</i> [40]	4 cases	Spain	58 a 77 years	Case reports
M Sachdeva <i>et al</i> [41]	3 cases	Italy	71 a 77 years	Case reports
I Chaabane <i>et al</i> [42]	3 cases	Tunisia	20 a 36 years	Case reports
RC Valdes <i>et al</i> [43]	5 cases	Mexico	Not related	Case reports
S Young <i>et al</i> [44]	2 cases	United States	68 e 39 years	Case reports

Source: Research database, 2020.

Table 5 presents the dermatological manifestations described in report cases. It is possible to notice bigger prevalence of maculopapular lesions, mentioned in 8 case reports (40%), and urticaria, described in 7 reports (35%), it is visible that manifestations with bigger incidences was the same observed after analysis in Table 3.

Table 5: Dermatological Manifestations Presented In Case Reports.

Article (Case reports)	Dermatological manifestations
OU Olisova <i>et al</i> [25]	Cutaneous eruption e hairy tongue
P Suter <i>et al</i> [26]	Erythema nodosum
K Hassan [27]	Itching and whitening eruption, swelled lips and urtiation
R Beaupre <i>et al</i> [28]	Maculopapular and purpuric eruption
G Paolino <i>et al</i> [29]	Maculopapular erythema lesions (urticaria-like)
N Aghazadeh <i>et al</i> [30]	Vesicular oral eruptions, erythematous acral papules and erythematous plaques
N Patel <i>et al</i> [31]	Maculopapular erythematous eruption and non-itching, vesicles and urticaria
N Spifle <i>et al</i> [32]	Erythema nodosum and itching
BE Putra <i>et al</i> [33]	Papules
SAA Elhag <i>et al</i> [34]	Cutaneous eruptions, itching, urticaria and angioedema
GM Iancu <i>et al</i> [35]	Cutaneous erythematous and maculopapular eruptions, itching and macula
S Farouk [36]	Cutaneous eruptions, erythematous rash, urticariform lesions, itching and petechial
MR Navaeifar <i>et al</i> [37]	Cutaneous eruptions, petechial, maculopapular erythema and edema
A Estebanez <i>et al</i> [38]	Itching lesions, papules, erythematous spots, urticaria and hidradenitis
MM Olive <i>et al</i> [39]	Erythematous maculopapular rash and itching urticaria
JJ Cauhe <i>et al</i> [40]	Cutaneous eruptions, palliative and petechial macules. erythematous papules transform in violaceous erythematous plaques with dark center and pseudovesicle in the middle. Typical target lesions of multiform erythema.
M Sachdeva <i>et al</i>	Maculopapular itching eruptions,

[41]	morbiliform and macular hemorrhagic eruptions, papulovesicular itching eruptions
I Chaabane <i>et al</i> [42]	Maculopapular itching lesions, itching eruptions, (erythema nodosum-like eruption)
RC Valdes <i>et al</i> [43]	Urticarial eruptions
S Young <i>et al</i> [44]	Cutaneous eruptions, Chillbains, purpura, ulcer, rash, urticaria

Source: Research database, 2020.

About the most affected parts by dermatological manifestations, stands out chest area, presented in 29 studies (85,3%), extremities, presented in 21 studies (61,8%), face, presented in 16 studies (47%) and oropharyngeal, presented in 10 studies (29,4%). Dermatological manifestations are atypical in COVID-19 with low prevalence. However, like in other viral infections it can be presented and it is extremely important that health professionals be aware to act in advance, avoid wrong diagnosis and prevent transmissions through warning measures [45]. The most common manifestations are erythematous papules, followed by generalized urticaria and varicella-like vesicles [46], they can appear in much pathology, including viral. This way, it is essential identify different diagnosis with other diseases, like dengue, because there is not a specific feature to differ them [11]. The average age of the patients with cutaneous manifestations was 53 years, being 38,9% in men and 27,8% in women. Chest lesions are more common than extremities (66,7% against 19,4%), even though, hands and feet have a meaning prevalence [47]. The evolving time of the lesion may vary, in the examined cases, 12,5% of patients presents lesions before other common symptoms appear, while 69,4% of patients presents lesions after the beginning of common symptoms like respiratory or COVID diagnosed. However, all patients had healed in 10 days [48]. As there some relates that cutaneous manifestations precede respiratory symptoms, it's not known if cutaneous symptoms are consequence of respiratory infections or skin primary infection; probably, should have a combination of these factors. Likewise, in cases when cutaneous symptoms show up after the

diagnosis, there is a possibility of being side effects of the medication [7]. The pathophysiological mechanism isn't clear, yet some aspects have been identified. Sars-Cov 2 promotes deposits in complement system, like C5b-9 (membrane attack complex, MAC), C4d and serine protease associated to mannose binding lectin (MBL) (MASP) 2 in microvasculature. Besides, there was co-localization of peak glycoproteins COVID-19 with C4d and C5b-9 in septal microvasculature of some examined cases. This way, these activities may produce a trombogenic vasculopathy pauci-inflammatory in the skin, the purpuric skin lesions [49]. In conclusion, in some cases, COVID-19 may develop microvascular lesion syndrome through complement system activation and pro-coagulant state associated. The activation mechanisms with coagulation system are still being in discussion [49].

Conclusion:

Therefore, it still does not have concrete and conclusive information about cutaneous manifestations as atypical symptom of COVID-19. However, there is a particular interest in this theme since a dermatological manifestation, before a fever or any respiratory symptom, may indicate a new pathophysiological knowledge about this virus with so much impact nowadays. This way, bigger studies are needed about cutaneous lesions, even because the available article about this correlation is case report form. Furthermore, is necessary spread the data described to promote the recognize potential between health professionals about possible dermatological manifestations of COVID-19 and considerate about the possibility, including some cases in advance, helping with preventive methods and potential repressive transmission.

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