Coding Long COVID: Characterizing a new disease through an ICD-10 lens

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Abstract

Background: Naming a newly discovered disease is a difficult process; in the context of the COVID-19 pandemic and the existence of post-acute sequelae of SARS-CoV-2 infection (PASC), which includes Long COVID, it has proven especially challenging. Disease definitions and assignment of a diagnosis code are often asynchronous and iterative. The clinical definition and our understanding of the underlying mechanisms of Long COVID are still in flux, and the deployment of an ICD-10-CM code for Long COVID in the US took nearly two years after patients had begun to describe their condition. Here we leverage the largest publicly available HIPAA-limited dataset about patients with COVID-19 in the US to examine the heterogeneity of adoption and use of U09.9, the ICD-10-CM code for “Post COVID-19 condition, unspecified.”

Methods: We undertook a number of analyses to characterize the N3C population with a U09.9 diagnosis code (*n* = 21,072), including assessing person-level demographics and a number of area-level social determinants of health; diagnoses commonly co-occurring with U09.9, clustered using the Louvain algorithm; and quantifying medications and procedures recorded within 60 days of U09.9 diagnosis. We stratified all analyses by age group in order to discern differing patterns of care across the lifespan.

Results: We established the diagnoses most commonly co-occurring with U09.9, and algorithmically clustered them into four major categories: cardiopulmonary, neurological, gastrointestinal, and comorbid conditions. Importantly, we discovered that the population of patients diagnosed with U09.9 is demographically skewed toward female, White, non-Hispanic individuals, as well as individuals living in areas with low poverty, high education, and high access to medical care. Our results also include a characterization of common procedures and medications associated with U09.9-coded patients.

Conclusions: This work offers insight into potential subtypes and current practice patterns around Long COVID, and speaks to the existence of disparities in the diagnosis of patients with Long COVID. This latter finding in particular requires further research and urgent remediation.

Keywords: Long COVID, electronic health records, health disparities

Background

Naming diseases is an ever present challenge, and there is no shortage of efforts that aim to better standardize, disambiguate, and keep track of disease nomenclature and definitions[1–4]. Disease naming has long been controversial–for example, there are more than 400 names for syphilis dating back to the 15th century[5]. Naming a disease requires defining it, and assigning a standard code to the disease facilitates research, care, and patient engagement due to ease of patient classification and knowledge exchange. However, naming and coding a disease does not mean the disease did not exist prior to its naming or coding. For instance, although “SARS-CoV-2” and “COVID-19” were both coined February 11, 2020, by the International Committee on the Taxonomy of Viruses and the WHO, respectively[6, 7], we know that cases of COVID-19 began to surface in Wuhan, China in late December 2019[8]. In the US, most diagnostic coding uses the ICD-10-CM terminology; however the ICD-10-CM code for COVID-19, U07.1, was not made available for use until April 1, 2020. The implications of this naming delay are wide-ranging. To this day, US COVID-19 cases prior to April 1, 2020 are difficult to retrospectively ascertain. Even after that date, use of U07.1 for COVID-19 phenotyping came with caveats–use of the new code was inconsistent and of variable sensitivity and specificity, and studies have shown both underuse and overuse of U07.1 in different contexts and health systems[9–11].

Long COVID, which is included in the more general term of post-acute sequelae of SARS CoV-2 infection (PASC), is also subject to the effects of delayed naming. By Spring of 2020, patients suffering from Long COVID had coined various terms to describe the condition, including the COVID-19 long tail, long-haul COVID, and Long COVID[12–14]. Long COVID is defined by ongoing, relapsing, or new symptoms or other health effects occurring after the acute phase of SARS-CoV-2 infection (i.e., present four or more weeks after the acute infection). Heterogeneous symptoms may include, but are not limited to, fatigue, difficulty breathing, brain fog, insomnia, joint pain, and cardiac issues[15–17]. As the impact of Long COVID on health and quality of life became increasingly clear at a population level, patients worldwide came together to urge healthcare systems and policymakers to acknowledge this condition[18, 19].

Despite the relatively early recognition of this condition, an ICD-10-CM code (U09.9, “Post COVID-19 condition, unspecified”) was not made available for use in the clinical setting until October 2021. Moreover, this single code may prove insufficient: considering the phenotypic and severity variation seen in Long COVID patients, it is likely that subtypes of Long COVID exist, and such subtypes may correlate with specific underlying mechanisms that should be targeted by different interventions.

Regardless, the fact remains that there is more naming to be done, and a particular need to define and refine computable phenotypes for Long COVID and its subtypes. As can be seen by the widely differing estimates of long COVID prevalence across many studies, a lack of definitional consistency is affecting the accuracy and

reproducibility of otherwise robust research.[20] Among other advantages, refined definitions will enable us to appropriately define cohorts for clinical studies, provide more precise treatment and clinical decision support, and accurately estimate long COVID's incidence and prevalence. This is a key priority for the parent program for this work, the NIH Researching COVID to Enhance Recovery (RECOVER) Initiative,[21] which seeks to understand, treat, and prevent PASC through a wide variety of research modalities, including electronic health record (EHR) and real-world data.

In response to the COVID-19 pandemic, the US informatics and clinical community harmonized an enormous amount of EHR data to reveal candidate risk factors and therapies associated with COVID-19. The NIH's National COVID Cohort Collaborative (N3C) is now the largest publicly available HIPAA limited EHR dataset in U.S. history, with over 14 million patients, and is a testament to the partnership of over 290 organizations. Due to the scale and demographic and geographic diversity of data within the N3C, it is uniquely well-suited to characterize the early use of the new Long COVID ICD-10-CM code. Here, we seek to characterize both (1) the early clinical use patterns of U09.9 and (2) the patients receiving that code from a provider. These characterizations reveal interesting patterns that may enable us to glean a better understanding of rough subtypes of Long COVID, current clinical practices for diagnosis and treatment of Long COVID, and potential racial and social disparities affecting who seeks and receives care for Long COVID. Ultimately, identifying patients with Long COVID based upon multiple means of inquiry (including U09.9) is critically important to recruit participants for research studies, assess the public health burden, and support nimble analytics across our heterogenous health care systems.

Methods

To characterize the use of the U09.9 code, we used EHR data integrated and harmonized inside the NIH-hosted N3C Secure Data Enclave to identify clinical features co-occurring around the time of patients' U09.9 index date. The methods for patient identification, data acquisition, ingestion, and harmonization into the N3C Enclave have been described previously[22–24]. Briefly, N3C contains EHR data for patients (1) who tested positive for SARS-CoV-2 infection; (2) who have a diagnosis code for COVID-19 (U07.1), multisystem inflammatory syndrome (MIS-C, M35.81), or Long COVID (U09.9); (3) whose symptoms are consistent with a COVID-19 diagnosis; or (4) are demographically matched controls who have tested negative for SARS-CoV-2 infection (and have never tested or been diagnosed as positive) to support comparative studies. Lookback data are available from January 2018 forward for each patient.

In this analysis, we defined our initial population (n = 23,744, sourced from 40 different health care systems) as any non-deceased patient with one or more U09.9 diagnosis codes recorded between October 1, 2021 and May 26, 2022. U09.9 codes appearing prior to October 1, 2021 may have been retroactively applied to these patients' records (e.g., as "onset dates" in an EHR Problem List), therefore making it difficult to determine an

index date that reflects the actual date of diagnosis. We excluded patients (*n* = 2,672) whose U09.9 index occurred during an inpatient hospitalization, due to the difficulty of distinguishing co-occurring clinical features related to Long COVID versus the primary reason for their hospitalization. After these exclusions, a base population of 21,072 remained. Note that we did not require patients in our cohort to have a COVID-19 diagnosis code (U07.1) or positive SARS-CoV-2 test on record, as many patients with Long COVID do not have this documentation[19].

Data from 40 of the 74 N3C sites were used for this analysis. The remaining sites either (1) did not use the U09.9 code in their N3C data or had not refreshed data since November 1, 2021, meaning the U09.9 code would not be present even if used at the site (*n* = 25 sites), or (2) did not meet the minimum criteria we set for site data for all RECOVER-related analyses (*n* = 9 sites): (a) >=25% of inpatients with at least one white blood cell count and at least one serum creatinine (to ensure lab measurement completeness); (b) 75% of inpatient visits have valid end dates; and (c) dates must not be shifted by the site more than 30 days. Additional N3C data quality criteria have been described previously, and also apply to this work.[23] The 40 sites used here are diverse in geographic location and institution size, but cannot be specifically named due to N3C governance policies.

We calculated person-level demographics and a number of social determinants of health (SDoH) variables at the area level. These variables are sourced from the Sharecare-Boston University School of Public Health Social Determinants of Health Index[25], and were linked to patients based on the preferred county (majority residence) associated with the patient's 5-digit ZIP code. We then characterized this cohort by examining diagnoses, procedures, and medications that occurred between each patient's U09.9 index date and 60 days after index (hereafter referred to as our "analysis window"). For each variable, values were characterized as high, medium and low based on the distribution of values across all US counties represented in the Sharecare dataset.

Diagnosis Analysis

Our objective in characterizing diagnoses around the U09.9 index date was not only to catalog conditions and symptoms that tend to co-occur with the U09.9 diagnosis, but also to determine which of those conditions and symptoms tend to co-occur with each other. In doing so, we begin to see clusters of conditions that are more likely to occur together within a single patient's record. First, we extracted all conditions in each patient's record within the analysis window, and identified the most frequently occurring conditions in the study population. We then constructed an adjacency matrix for the top 30 conditions, with values indicating the frequency of co-occurrence between two conditions in the study population. From this matrix, we constructed a weighted network with nodes representing individual diagnoses, edges between nodes representing co-occurrence, and edge weights corresponding to the count of patients with both conditions. In order to detect conditions that are more likely to co-occur in our study population than at random, we tested the Louvain [26], Walktrap,[27] and

Girvan-Newman[28] algorithms for community detection. We selected the Louvain algorithm in our final model, as it maximized modularity while retaining a reasonable resolution of detection. For further subgroup analyses, we present clusters detected within age-stratified condition co-occurrence networks. Additional details on community detection, network stability and subgroup analyses are available in **Supplemental Methods**.

Procedure Analysis

Characterizing common procedures around the time of U09.9 allowed us to assess current practice patterns (i.e., diagnostics and treatments) for patients receiving the code. We defined a "procedure" as any medical diagnostics or treatments rendered by a healthcare provider. We excluded non-informative records that simply reflect that an encounter took place (e.g., CPT 99212, "Office or other outpatient visit"), despite their technical classification as "procedure codes." We then aggregated remaining procedures into high-level categories (e.g., "radiography," "physical therapy") in order to discern the diagnostics and treatments that occurred within each patient's analysis window.

Medication Analysis

As with diagnoses and procedures, we extracted all medication records occurring within each patient's analysis window, in order to characterize newly prescribed medications that may be used to treat symptoms of Long COVID. In order to focus on newly prescribed medications and not long-standing prescriptions, we excluded medications for each patient for which there were records prior to the patient's U09.9 index. Medications were categorized using the third level of the Anatomical Therapeutic Chemical (ATC) classification system[29]. Results of this analysis are shown in **Supplemental Figure 2**.

Results

Greater severity of acute SARS-CoV-2 infection does not appear to have an outsize influence in determining which patients end up with a U09.9 code; 2,542 of the U09.9 patients (12.1%) were hospitalized during a prior acute SARS-CoV-2 infection. This proportion of hospitalized patients is even lower than that cited in a recent FAIR Health white paper, which noted that 25% of patients with a U09.9 code recorded in claims data had been hospitalized with acute COVID-19.[30] Also notable is the fact that 6,806 (32.3%) of the U09.9 patients did not have a COVID index date available in N3C's records, suggesting that these patients' acute SARS-CoV-2 infection was indicated by a test at home, at an external health care system, or at a testing site not connected to a health system (e.g., drugstore, airport, workplace). **Table 1** shows the breakdown of the study cohort by person-level demographics and area-level social determinants of health.

	Age <21	21-45	46-65	66+
	n = 1490	*n* = 7263	*n* = 8600	*n* = 3719
Person-level variables				

Sex (%)				
female	863 (57.9)	5284 (72.7) +/-5	5606 (65.2) +/-5	2205 (59.3)
male	627 (42.1)	1978 (27.2) +/-5	2992 (34.8) +/-5	1514 (40.7)
unknown	0 (0.0)	<20	<20	0 (0.0)
Race (%)				
Asian	36 (2.3) +/-5	199 (2.7)	143 (1.7)	43 (1.2) +/-5
Black	217 (14.6) +/-5	1109 (15.3)	1233 (14.4)	380 (10.3) +/-5
Hawaiian/Pac Isldr.	<20	27 (0.4)	21 (0.2)	<20
White	975 (65.4) +/-5	4957 (68.4)	6285 (73.4)	2984 (80.8) +/-5
Other	47 (3.2)	81 (1.1)	83 (1.0)	31 (0.8)
Unknown	215 (14.4)	869 (12.0)	794 (9.3)	251 (6.8)
Ethnicity (%)				
Hispanic/Latino	192 (12.9)	694 (9.6)	630 (7.3)	193 (5.2)
Not Hispanic/Latino	1102 (74.0)	5748 (79.1)	7001 (81.4)	3211 (86.3)
Unknown	196 (13.2)	821 (11.3)	969 (11.3)	315 (8.5)
Area-level social determinants of health (county level)				
Households with Income below poverty (%)				
High (>18%)	205 (13.8)	971 (13.4)	1278 (14.9)	483 (13.0)
Medium (13-18%)	383 (25.7)	2158 (29.7)	2615 (30.4)	1172 (31.5)
Low (<13%)	636 (42.7)	2792 (38.4)	3093 (36.0)	1320 (35.5)
Missing	266 (17.9)	1342 (18.5)	1614 (18.8)	744 (20.0)
Residents with college degree (%)				
High (>15%)	957 (64.2)	4793 (66.0)	5392 (62.7)	2277 (61.2)
Medium (11-15%)	202 (13.6)	776 (10.7)	1013 (11.8)	453 (12.2)
Low (<11%)	65 (4.4)	352 (4.8)	581 (6.8)	245 (6.6)
Missing	266 (17.9)	1342 (18.5)	1614 (18.8)	744 (20.0)
Residents 19-64 with public health insurance (%)				
High (>21%)	237 (15.9)	853 (11.7)	1070 (12.4)	445 (12.0)
Medium (14-21%)	433 (29.1)	2603 (35.8)	3126 (36.3)	1342 (36.1)
Low (<13%)	554 (37.2)	2465 (33.9)	2790 (32.4)	1188 (31.9)
Missing	266 (17.9)	1342 (18.5)	1614 (18.8)	744 (20.0)
MDs per 1000 residents (%)				
High (>1.12)	1032 (69.3)	5022 (69.1)	5742 (66.8)	2402 (64.6)
Medium (0.49-1.12)	140 (9.4)	611 (8.4)	881 (10.2)	403 (10.8)
Low (<0.49)	52 (3.5)	288 (4.0)	363 (4.2)	170 (4.6)
Missing	266 (17.9)	1342 (18.5)	1614 (18.8)	744 (20.0)

Table 1. Demographic breakdown of patients in N3C with a U09.9 diagnosis code. In addition to person-level demographics, we have included a number of social determinants of health variables at the *area* level (see Methods). In accordance with the N3C download policy, for demographics where small cell sizes (<20 patients) could be derived from context, we have shifted the counts +/- by a random number between 1 and 5. The accompanying percentages reflect the shifted number. All shifted counts are labeled as such, e.g. +/- 5.

There are distinct trends among the area-level SDoH metrics. Post-hoc analysis showed that the U09.9 cohort had significantly lower representation in socially deprived counties than all COVID-19 patients in the N3C Enclave. We used the g-test of independence to compare rates in area-level SDoH across all age groups. The U09.9 patient cohort had fewer patients in the "high" category for households with income below the poverty rate compared to all COVID-19 patients (13.9% vs. 15.8%; p-value <0.01). The former cohort had a higher percentage of patients in the "high" category for residents with a college degree (63.7% vs. 51.4%; p-value <0.01), residents 19-64 with public health insurance (12.4% vs. 9.9%; p-value <0.01), and MDs per 1000 residents (67.4% vs. 60.3%; p-value <0.01).

We also analyzed uptake of the U09.9 code itself, among sites using the code. There is a rapid increase in use of U09.9 by sites following the code's release (**Figure 1**). Usage of U09.9 post-release is compared with usage of B94.8 ("Sequelae of other specified infectious and parasitic diseases"); some sites used B94.8 at the CDC's initial recommendation[31] as a placeholder code prior to U09.9's release. Once U09.9 became available, it quickly supplanted B94.8.

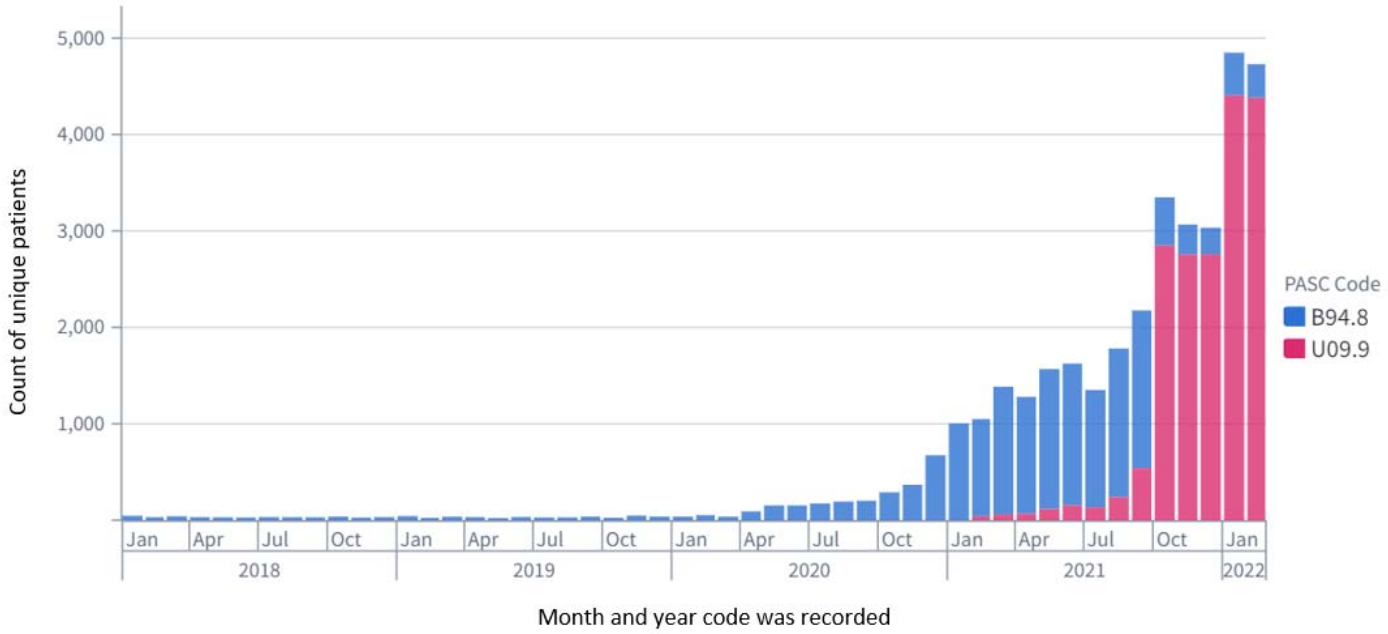
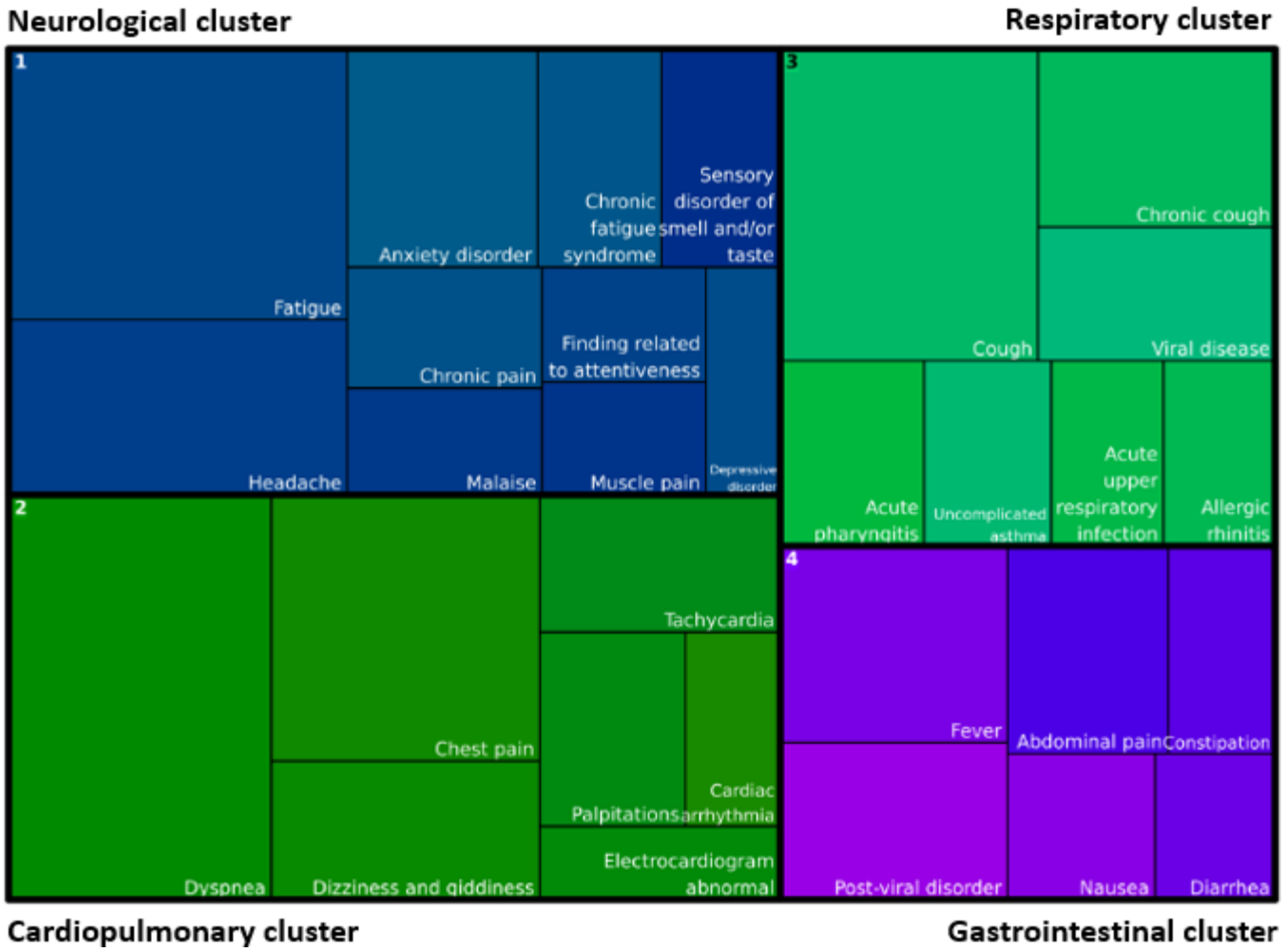


Figure 1. Clinical use of B94.8 decreases as U09.9 becomes available. Prior to U09.9's release, the CDC recommended use of B94.8 ("Sequelae of other specified infectious and parasitic diseases") as a placeholder code to signify Long COVID. As this code is not specific to sequelae of COVID-19, the figure above shows consistent but infrequent use during two pre-pandemic years. Use of B94.8 ramps up in Spring of 2020, suggesting increased recognition of Long COVID by providers. However, upon its release in October 2021, U09.9 supplants B94.8 in terms of usage frequency.

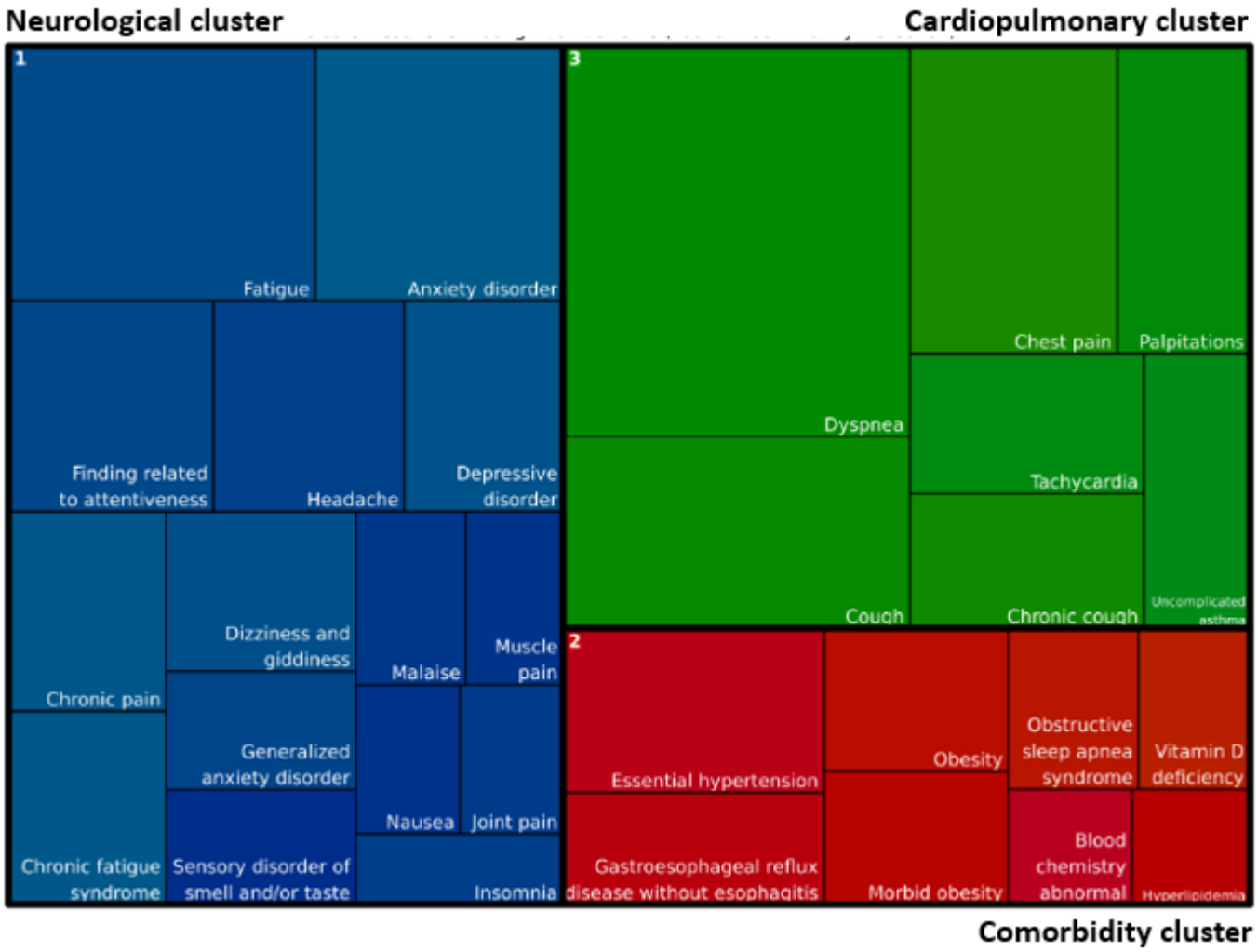
The definition of Long COVID[32] includes a wide-ranging list of symptoms and clinical features. Many of those features appear below in **Figure 2**, a visualization of diagnoses that commonly co-occur with U09.9, and each other. As shown, the mix of co-occurring diagnoses as well as the clusters produced by the Louvain algorithm change when the cohort is subset into age groups. A full accounting of diagnoses co-occurring with U09.9 (i.e., within the analysis window) in at least 20 patients from our cohort is included as **Supplemental Figure 1**.

Figure 2. **Age-stratified clusters of co-occurring diagnoses among patients with a U09.9 code.** When the Louvain algorithm is applied to the top 30 most frequent pairs of co-occurring diagnoses for U09.9 patients (i.e., diagnoses co-occurring in the same patient 0 through 60 days from U09.9 diagnosis date), distinct clusters emerge. These clusters may represent rough subtypes of Long COVID presentations, and differ among age groups. The size of each box within a cluster reflects the frequency of that diagnosis relative to others in the diagram. Condition names are derived from the SNOMED CT terminology, mapped from their ICD-10-CM equivalents. Similar clusters share the same color across all four diagrams.

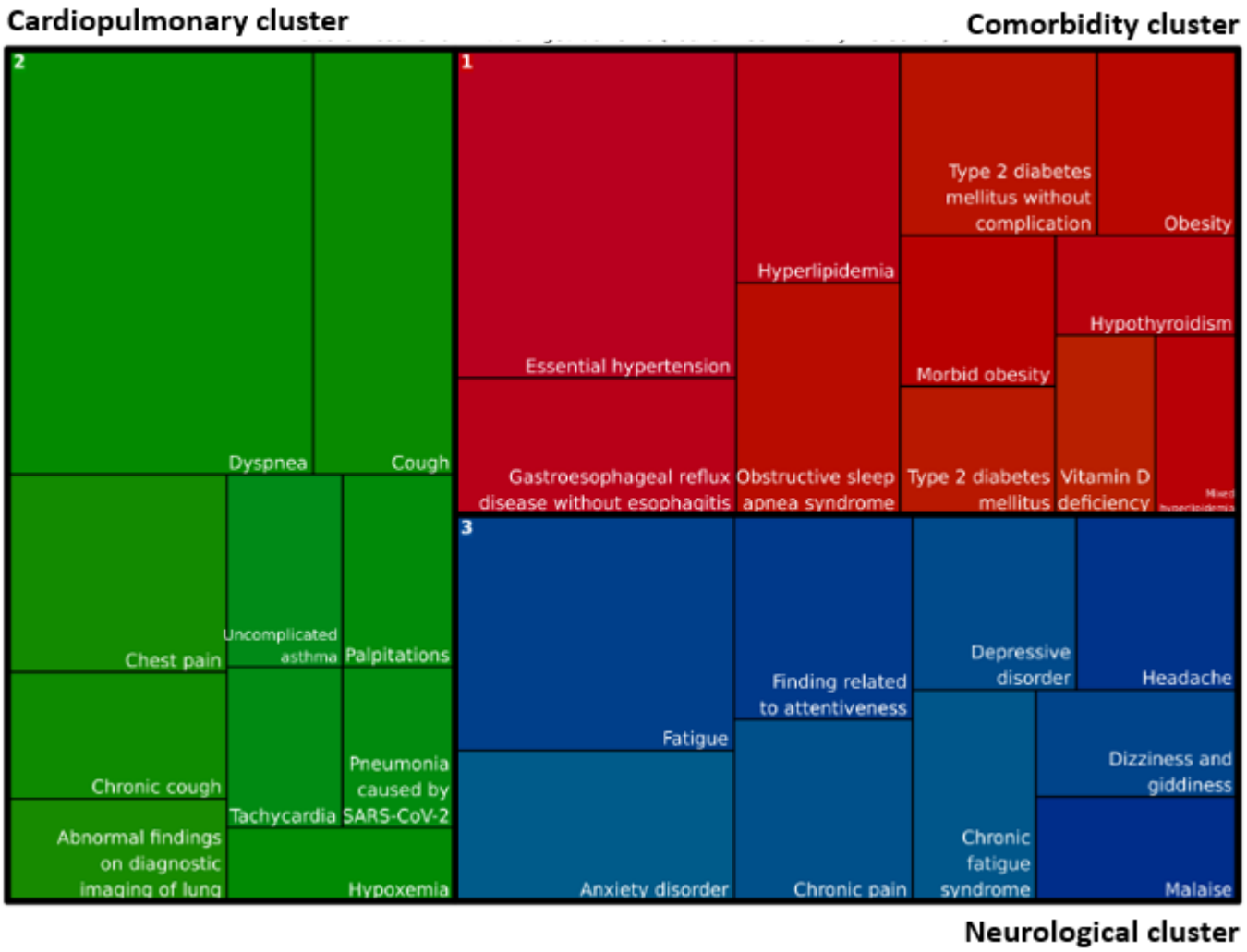
a. U09.9 patients <21 years of age



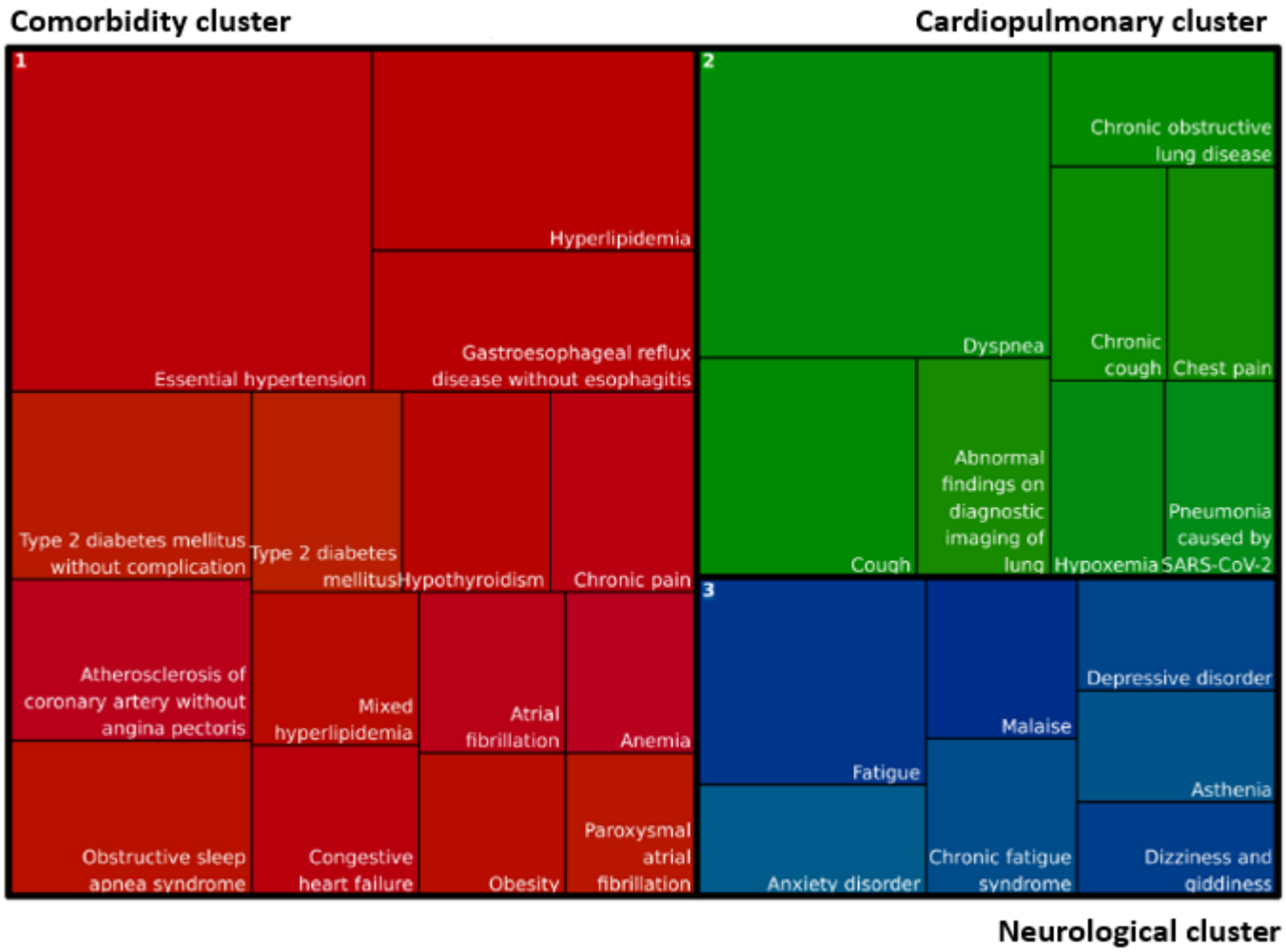
b. U09.9 patients 21-45 years of age



c. U09.9 patients 46-65 years of age



d. U09.9 patients 66+ years of age



Our findings suggest that Long COVID symptoms and associated functional disability may present differently depending on the patient, but commonly fall into clusters. Conditions within a single cluster are more likely to co-occur within a single patient than conditions appearing in different clusters, allowing us to roughly subtype clinical presentations of Long COVID. When stratified by age, the conditions within each cluster change somewhat, though the themes remain consistent.

N3C data also enables us to examine procedures and medications that occur in each patient's analysis window, as shown in **Figure 3** and **Supplemental Figure 2**, respectively.

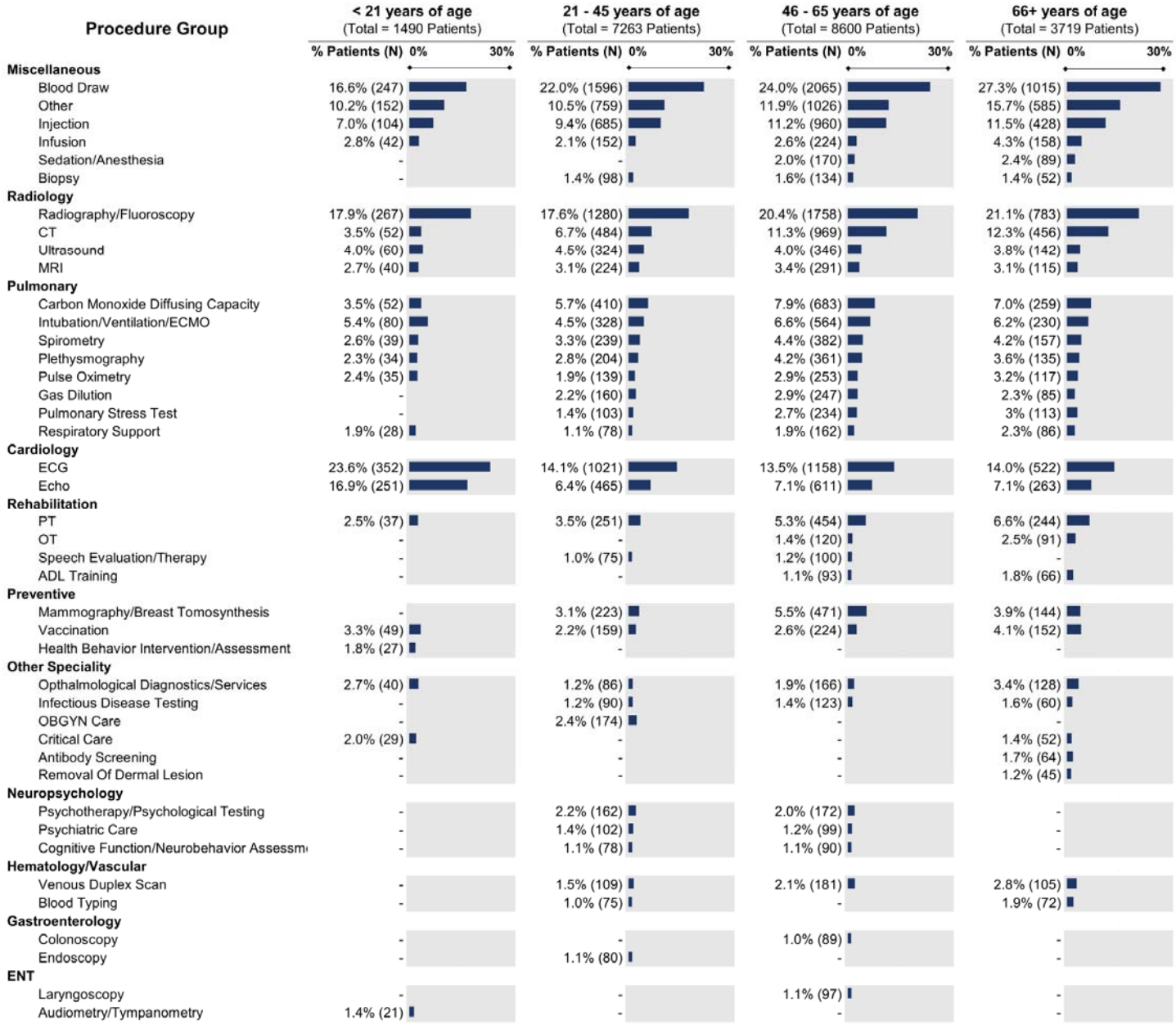


Figure 3. Common procedures among patients with a U09.9 code. Procedures shown occur within 60 days after a patient's U09.9 diagnosis. Procedure records that simply reflect that an encounter took place (e.g., CPT 99212, "Office or other outpatient visit") are excluded. Category totals represent unique patient - procedure pairs, not necessarily unique individuals. Procedure classes associated with fewer than 20 patients or less than 1.0% of the age-stratified cohort size are not shown, per N3C download policy. Percentages in each column are shown relative to the total *n* in that column.

Discussion

Diagnosis codes are frequently used as criteria to define patient populations. While diagnosis codes alone may not define a cohort with perfect accuracy, they are a useful mechanism to narrow a population from "everyone in the EHR" to a cohort highly enriched with the condition of interest. Our analysis of U09.9 shows that this code may serve in a similar capacity to identify Long COVID patients. However, temporality and rate of uptake by providers are critical issues that must be considered. U09.9 was released for use nearly two years into the

COVID-19 pandemic, resulting in potentially millions of patients with Long COVID who "missed out" on being assigned the code. Our findings must thus be interpreted through this lens of partial and incremental adoption. More work is needed to understand clinical variability and barriers to uptake by providers.

We investigated whether the use of non-specific coding such as B94.8 ("Sequelae of other specified infectious and parasitic diseases") could be used as a proxy for early case identification. Our findings show B94.8 use increasing among COVID patients from April 2021 to October 2021, indicating a potential shift in clinical practice patterns to code for Long COVID presentation as guided by the Centers for Disease Control[31]. While B94.8 can be used for Long COVID ascertainment in EHRs prior to October 2021, it should be noted that B94.8 is used to code for any sequelae of *any* infectious disease. For this reason, it may not be specific enough to rely on for highly precise Long COVID case ascertainment without applying additional logic (e.g., requiring a positive COVID test prior to B94.8). Even still, it is likely the most reliable structured variable in the EHR to identify potential Long COVID patients prior to October 1, 2021.

Our diagnosis clusters suggest that Long COVID is not a single phenotype, but rather a collection of sub-phenotypes that may benefit from different diagnostics and treatments. Each of these clusters contains conditions and symptoms reported in existing Long COVID literature[33], clearly suggests that the definition of Long COVID is more expansive than lingering respiratory symptoms[34], and illustrates that Long COVID can manifest differently among patients in different age groups. Overall, the clusters can be summarized as neurological (in blue), cardiopulmonary (in shades of green), gastrointestinal (in purple), and comorbid conditions (in red). The clustering for the youngest patients (<21 years of age, **Figure 2a**) is the most unique, with distinct respiratory and gastrointestinal clusters that are not seen in other age groups. Patients aged 65+ (**Figure 2d**) are also unique, in that they present with more chronic diseases associated with aging (e.g. congestive heart failure, atherosclerosis, atrial fibrillation) in addition to Long COVID symptoms. The comorbid conditions cluster is unique in that it likely does not represent symptoms of Long COVID, but rather a collection of comorbid conditions that increase in incidence as patients age. The impact of these comorbid conditions on risk and outcomes of Long COVID requires further study.

Also noteworthy is the fact that the neurological cluster appears more prominently in younger groups, especially patients 21-45 years of age. Of particular note is the appearance of myalgic encephalomyelitis (listed in SNOMED CT as "chronic fatigue syndrome," a non-preferred term)–a disease which parallels Long COVID in many ways[35–37]–in the neurological cluster across all age groups, suggesting not only frequent co-occurrence with a U09.9 diagnosis, but also co-occurrence with other neurological symptoms. The cluster differences we see among age groups make a case for age stratification when studying U09.9, and Long COVID in general. Regardless, given Long COVID's heterogeneity in presentation, course, and outcome, the

clustering of symptoms may prove informative for future development of classification and diagnostic criteria.[38]

The common procedures around the time of U09.9 index provide insight into diagnostics and treatments currently used by providers for patients presenting with Long COVID, for which treatment guidelines remain under development[39–42]. For new diseases where consensus is lacking, care is often ad hoc and informed by both the symptoms that patients present with and the available diagnostics and treatments that providers can offer. The identification and characterization of care patterns is an important step in designing future research to assess the efficacy and outcomes of these interventions. Radiographic imaging is a common occurrence across all age groups, with an average of 19.3% of patients with at least one imaging procedure in the analysis window. Electrocardiography (ECG) and echocardiography are also relatively common across all age groups, though patients younger than 21 years of age have the highest proportion (23.6% and 16.9% for ECG and echo, respectively, compared with an average of 13.9% and 6.9% across the other age groups). Pulmonary function testing shows a slight increase in frequency with more advanced age. Also of interest is the fact that some patients are receiving rehabilitation services in the 60 days after diagnosis, such as physical and occupational therapy, which lends insight into the burden of functional disability for patients with Long COVID. The proportion of patients receiving rehabilitation services also rises with patient age.

Differences across age groups were less apparent in the medication analysis (**Supplemental Figure 2**), though the youngest patients appear slightly more likely to be prescribed medications for gastrointestinal, cardiac, and neurological indications. Perhaps unsurprisingly, respiratory system drugs were the most commonly prescribed across all age groups. Interestingly, antibacterials were also used frequently across all age groups; it is unclear whether patients with Long COVID are more susceptible to bacterial infections, or if there may be overuse of antibiotics in the setting of fluctuating respiratory Long COVID symptoms or viral infections [43, 44]. Corticosteroids were also commonly used, presumably to treat persistent inflammation as a possible mechanism mediating Long COVID symptoms. The variety of medication categories seen in our analysis reflect the potential multi-system organ involvement and symptom clusters in Long COVID that we see in the analysis of conditions.

We also investigated how demographics and SDoH contribute to variation in diagnosis with U09.9. When evaluating the U09.9 cohort across age groups and SDoH variables, distinct trends can be observed (see **Table 1**). Patients with a U09.9 diagnosis code are more likely to live in counties with a high percentage of residents with college degrees and a high number of doctors per 1000 residents. Patients living in counties with a high level of poverty and/or a high percentage of residents using public insurance make up the smallest share of the U09.9 cohort. In contrast, research shows that socially deprived areas have higher rates of COVID-19 cases and deaths.[45],[46] Given the higher rates of COVID-19, lower rates of Long COVID seem

unlikely. Rather, patients in deprived areas may be less likely to be treated for Long COVID. Moreover, a large majority of the U09.9 cohort identifies as female, White, and non-Hispanic. These trends are unlikely to be an accurate reflection of the true population with Long COVID, but may instead illustrate racial and social disparities in access to and experience with healthcare in the US. Clearly, the role of access to providers and the economic means to afford Long COVID care should continue to be studied for their role as contributors to disparate care and outcomes, as well as sources of research and algorithmic bias.

Limitations

All EHR data is limited in that patients with lower access or barriers to care are less likely to be represented. EHR heterogeneity across sites may mean that a U09.9 code at one site does not quite equate to a U09.9 code at another. Moreover, we are not able to know what type of provider issued the U09.9 diagnosis (i.e., specialty), and different clinical organizations have different coding practices.

As the U09.9 code is still quite new and our sample size is limited, we cannot yet confidently label these clusters as clear “Long COVID subtypes.” Rather, these clusters are intended to be hypothesis generating, with additional work underway by the RECOVER consortium to further develop and validate these clusters. It should also be noted that many symptoms are not coded in the EHR (and may, for example, be more likely to appear in free-text notes rather than diagnosis code lists). Future work will incorporate these non-structured sources of symptoms for use in our clustering methodology.

Given the variable uptake of the U09.9 code, it is challenging to accurately identify comparator groups for this population–i.e., the absence of a U09.9 code cannot, at this time, be interpreted as the absence of Long COVID. This will continue to be an issue in future research, especially when evaluating the effect of PASC on patient morbidity and utilization of diagnostic testing and treatments.

Conclusions

The recent release of ICD-10-CM code U09.9 to codify Long COVID will undoubtedly assist with future case ascertainment and computable phenotyping. However, a large number of patients who developed Long COVID prior to October 1, 2021 continue to be burdened with symptoms, and must also be included in data-driven cohort identification efforts for trial recruitment and retrospective analyses. Considering the caveats around rate of uptake among clinicians and late timing of the code’s release, we recommend that when characterizing Long COVID using EHRs, U09.9 should not be used alone, but rather in combination with other strategies such as more complex computable phenotypes[47]. Our findings from the characterization of patients with the U09.9 diagnosis may be of use in refining phenotypes to identify pre-U09.9 patients that might have Long COVID. There is clear utility to the characterization of early use of U09.9, as it represents the first “hook” in EHR data that can be used to identify and assess current diagnostic and treatment patterns at scale. Moreover, given the

heterogeneous presentation of Long COVID, clustering of co-existing conditions and potential symptoms may be valuable in informing future development of more detailed criteria for diagnosis of Long COVID and its subtypes.

Declarations

Ethics approval

The N3C data transfer to NCATS is performed under a Johns Hopkins University Reliance Protocol # IRB00249128 or individual site agreements with NIH. The N3C Data Enclave is managed under the authority of the NIH; information can be found at https://ncats.nih.gov/n3c/resources. The work was performed under DUR RP-5677B5.

Consent for publication

Not applicable

Availability of data and materials

The N3C Data Enclave is managed under the authority of the NIH; information can be found at ncats.nih.gov/n3c/resources. Enclave data is protected, and can be accessed for COVID-related research with an approved (1) IRB protocol and (2) Data Use Request (DUR). A detailed accounting of data protections and access tiers is found in [1]. Enclave and data access instructions can be found at https://covid.cd2h.org/for-researchers; all code used to produce the analyses in this manuscript is available within the N3C Enclave to users with valid login credentials to support reproducibility.

Competing interests

Author ATG is an employee of Palantir Technologies. MAH and JAM are co-founders of Pryzm Health.

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Data Partners with Released Data

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Additional Data Partners Who Have Signed a DTA and Whose Data Release is Pending

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- data curation, integration, and quality assurance: ERP, AB, KK, EH, JL, RM, CGC
- clinical subject matter expertise: JMB, RW, TDB, HD
- statistical analysis: ERP, CMB, AB, AG
- data visualization: CMB, AB, JAM, AG
- project management: LK
- governance/regulatory oversight: MH, JAM, CGC
- manuscript drafting: ERP, CMB, JMC, AB, HD, AG, EH, LK, KK, JL, JAM, RW, TDB, RM, CGC, MH
- critical revision of the manuscript for important intellectual content: ERP, CMB, JMC, AB, HD, AG, EH, LK, KK, JL, JAM, RW, TDB, RM, CGC, MH

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Diagnostic value of skin manifestation of SARS-CoV-2 infection

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Abstract

SARS-CoV-2 causes multiple immune-related reactions at various stages of the disease. The wide variety of skin presentations has delayed linking these to the virus. Previous studies had attempted to look at the prevalence and timing of SARS-COV-2 rashes but were based on mostly hospitalized severe cases and had little follow up. Using data collected on a subset of 336,847 eligible UK users of the COVID Symptom Study app, we observed that 8.8% of the swab positive cases (total: 2,021 subjects) reported either a body rash or an acral rash, compared to 5.4% of those with a negative swab test (total: 25,136). Together, these two skin presentations showed an odds ratio (OR) of 1.67 (95% confidence interval [CI]: 1.41-1.96) for being swab positive. Skin rashes were also predictive in the larger untested group of symptomatic app users (N=54,652), as 8.2% of those who had reported at least one classical COVID-19 symptom, *i.e.*, fever, persistent cough, and/or anosmia, also reported a rash. Data from an independent online survey of 11,546 respondents with a rash showed that in 17% of swab positive cases, the rash was the initial presentation. Furthermore, in 21%, the rash was the only clinical sign. Skin rashes cluster with other COVID-19 symptoms, are predictive of a positive swab test and occur in a significant number of cases, either alone or before other classical symptoms. Recognising rashes is important in identifying new and earlier COVID-19 cases.

Introduction

During the COVID-19 pandemic, it became clear that the SARS-CoV-2 virus, whilst mainly targeting the lungs, also affected multiple other organs, including the heart, kidneys, and brain[1]. Skin manifestations were slower to be reported, possibly because in patients in critical conditions the need for documenting skin changes was less pressing, and because the virus causes a wide variety of skin symptoms that delayed recognising their link with COVID-19[2]. The first cases of COVID-19 affecting the skin were documented in China, but the prevalence was very low at 0.2% in 1,099 hospital cases[3]. Italy then reported that 20% of the patients on a COVID-19 ward (N=88) had skin signs[4]. A large series of 375 patients from Spain as well as from other groups[2,5,6] have described urticarial, dengue fever-like, chickenpox-like rashes as well as less frequent cases of chilblains affecting fingers or toes (acral rash), thought to be due to minor thrombotic events or damage to the endothelial walls of small distal vessels of the digits.

Here, using a population approach, we investigated the diagnostic value of body and acral rashes for SARS-CoV-2 infections using data from 336,847 users of the COVID Symptom Study app[7], and from an independent survey on COVID-19 related skin symptoms in 11,546 subjects, 2,328 of whom also shared photos of their skin complaints.

Results

Among 336,847 UK users of the COVID Symptom Study app who registered between May 7th and June 22nd 2020, 6,403 reported the presence of skin signs and symptoms (**Table 1**). Most of the users included in this study were white European (94.0%), and ethnicity, smoking status, chronic diseases, and medications are summarised in **Supplementary Table 1**. Results for SARS-CoV-2 swab tests were provided by 27,157 users (8.1%), 2,021 of whom (7.4%) were positive. Among users who were not tested for SARS-CoV-2, 54,652 were symptomatic (*i.e.*, reported at least one of the 16 collected symptoms), including 17,371 individuals presenting with at least one of the three main symptoms of COVID-19 (*i.e.*, fever, persistent cough, and/or anosmia) whose presence, as suggested by the NHS guidelines, would require isolation and testing for SARS-CoV-2 infection.

Skin-related symptoms were reported by 1,534 users who had a swab test, and by 3,672 untested symptomatic users. Among the 2,021 users who tested positive on swab test, 178 users (8.8%) reported skin related changes. Of those, 138 (6.8%) reported body rashes and 62 (3.1%) acral rashes (**Table 1).** Only 22 (1.1%) of them reported both body and acral skin-related symptoms. Infected individuals reporting acral rashes were slightly older (mean age = 50.2) than those who did not report this skin symptom (mean age = 43.7; Wilcoxon's test $P = 6.27 \times 10^{-3}$). In addition, body rashes prevalence was

slightly higher among females (odds ratio [OR] = 1.60, 95% Confidence Interval [CI] = 1.08-2.44, P = 0.02). We did not observe any age differences for body rashes or sex differences for acral rash prevalence (P > 0.05).

Similar skin symptoms were also seen in symptomatic untested users: 1,429 (8.2%) of users who did not have a swab test but reported any of the three classical COVID-19 symptoms also reported a rash, compared to 6.0% for those whom were not tested and did not report any of the three classical COVID-19 symptoms (OR = 1.40, 95% CI = 1.31-1.50, $P < 2.2x10^{-16}$). We could not assess whether ethnicity affected the prevalence of skin symptoms as the number of non-European users with skin symptoms was too low (**Supplementary Table 1**).

Association analysis highlighted higher prevalence of either body or acral rashes among individuals who tested positive for SARS-CoV-2 compared to those who tested negative (OR=1.67, 95% CI=1.41-1.96, $P=1.45x10^{-9}$). The subtypes were similar. Body rashes were associated with SARS-CoV-2 positive swab with an OR of 1.65 (95% CI =1.37-1.99, $P=1.30x10^{-7}$), whereas the OR for acral rashes was 1.73 (95% CI=1.32-2.27, $P=7.25x10^{-5}$; see **Methods)**. Sensitivity analyses are reported in **Supplementary Table 2.** The comparison between 17,371 symptomatic untested users who reported at least one of the classical COVID-19 symptoms and those who did not report any of the three yielded an OR of 1.46 (95% CI=1.35-1.58, $P=2.92x10^{-20}$) for body rash, while the association with the rarer acral rash was not significant (P = 0.22). In comparison, the odd ratio for fever was 1.47 (95% CI= 1.31-1.65, $p=5.77x10^{-7}$).

To better investigate the duration of these skin rashes and their timing in relation to other COVID-19 symptoms, we collected data from 11,546 individuals who responded to an independent on-line survey on possible COVID-19 related skin rashes. Median age [1^{st}-3^{rd} quartile] was 53 years old [41-63], 77% of whom were female. Among them, 694 surveyees reported a positive SARS-CoV-2 swab or antibody test, and 3,109 were not tested but reported to have had one of the three classical COVID-19 symptoms. Photos of rashes were shared by 2,328 surveyees, and 365 photos were randomly selected across sexes and age ranges. These were assessed by an experienced dermatologist and divided in three categories (see **Methods**). Of these, 56 photos were removed because of bad quality and 42 were judged not attributable to SARS-CoV-2 infection (13.6%). The three most common presentations were papular rashes (including erythemato-papular and erythemato-vesicular types, 41%), urticaria (28%), and acral lesions (23%). The average duration of symptoms was 24 days for acral lesions, 18 days for papular, and 10 days for urticaria (significantly shorter duration; Wilcoxon's $P < 1.3x10^{-3}$; **Figure 1**). We did not observe significant differences in either age or sex distribution between the three types of rashes.

The 694 surveyees that declared to have been tested positive to SARS-CoV-2 *via* a swab or antibody test, with skin signs, also reported other classical COVID-19 related symptoms: fatigue (11%), headaches

(9%), loss of smell (9%), fever (7%), muscle pain (6%), shortness of breath (6%) and persistent cough (6%) being the most common. Interestingly, while most surveyees declared skin changes to appear at the same time as other COVID-19 symptoms (47%) or afterwards (35%), in 17% of the cases skin symptoms appeared before any other symptoms, and in 21% of the cases they were the only symptom. Similar estimates were obtained when focusing on the 3,109 untested subjects presenting with at least one of the classic COVID-19 symptoms, where 47%, 39%, and 15% surveyees declared to have had skin symptoms during, after, and before any other symptoms, respectively.

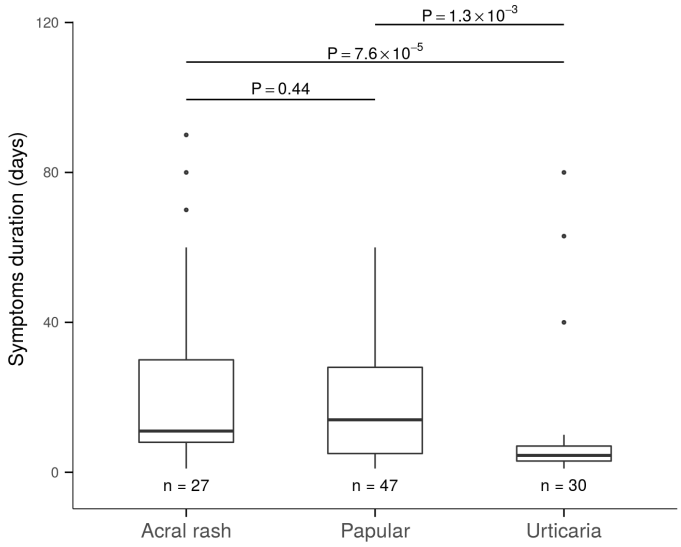

Figure 1. Distribution of duration of symptoms for the three most common skin symptoms diagnosed from the photos of 267 users of our survey.

Table 1. Sample characteristics. Categorical values are reported as number and percentage, and compared using Pearson's χ^2 test. Continuous values are reported as mean ± standard deviation and compared using Wilcoxon's test. Associations P values with body and acral rash are from logistic regression, and with BMI from linear regression, adjusted for the relevant covariates (see **Methods**). "Users tested" refers to individuals self-reporting a positive or negative swab test result. "Symptomatic untested users" refers to individuals who reported at least one of the 16 collected symptoms, did not believe that they had already had COVID-19 when first registering with the app, had not yet been tested for SARS-CoV-2. "Classic symptoms" refers to those included in the NHS guidelines (*i.e.*, fever, persistent cough, and/or anosmia).

	All users	**Users tested for SARS-CoV-2**				**Symptomatic untested users**			
		All	**Positive**	**Negative**	**P value**	**All**	**With classic symptoms**	**Without classic symptoms**	**P value**
N	336,847	27,157	2,021	25,136	-	54,652	17,371	37,281	-
Females (%)	188,118 (55.8%)	16,474 (60.7%)	1,376 (68.1%)	15,098 (60.1%)	1.47×10^{-12}	34,789 (63.7%)	10,684 (61.5%)	24,105 (64.7%)	1.03×10^{-12}
Age	43.9±19.7	43.9±17.5	43.9±15.6	43.9±17.7	0.09	41.4±18.5	38.2±19.4	42.9±17.8	1.51×10^{-145}
BMI	26.2±6.4	27.0±6.5	28.2±6.8	26.9±6.5	$<2.20 \times 10^{-16}$	26.6±6.7	26.7±7.2	26.5±6.4	$<2.20 \times 10^{-16}$
Healthcare workers (%)	31,915 (9.5%)	7,494 (27.6%)	1190 (58.9%)	6,304 (25.1%)	2.94×10^{-234}	5,344 (9.8%)	1,541 (8.9%)	3,803 (10.2%)	1.18×10^{-6}
Body rash (%)	4,812 (1.4%)	1,177 (4.3%)	138 (6.8%)	1,039 (4.1%)	1.30×10^{-7}	2,729 (5.0%)	1,128 (6.5%)	1,601 (4.3%)	2.92×10^{-20}
Acral rash (%)	2,188 (0.6%)	520 (1.9%)	62 (3.1%)	458 (1.8%)	7.25×10^{-5}	1,210 (2.2%)	419 (2.4%)	791 (2.1%)	0.22

Discussion

COVID-19 is now known to have varied clinical manifestations and to target multiple organs, including the skin[1,3]. COVID-19 rashes may present in many forms and at different stages of the disease. The heterogeneous presentations, the time delay, as well as the focus on severely ill patients during the early phases of the pandemic, led to the skin being overlooked as an important target organ for COVID-19.

In this community-based study, 8.8% of positive COVID-19 cases *via* swab tests and 8.2% of users who were not tested but reported at least one of the classic COVID-19 symptoms, based on NHS guidelines, also reported skin rashes. Our data suggest that skin rashes are valuable predictors for COVID-19 positivity, with an odds ratio of 1.67 for any type of rashes in users tested for SARS-CoV-2. When looking at types of rashes, body rashes were more frequent than acral lesions (6.8% *vs* 3.1%) although their predictive value was equivalent (OR=1.65 *vs* 1.73, respectively). The odd ratio for both types of rash was greater than for fever (1.47) and fever has been used widely to screen for COVID. Reports of cases with both body rashes and acral lesions were rare, and this suggests different pathogenesis with the former caused by immunological reactions to the virus whilst acral rashes are more likely to be explained by delayed small thrombotic occlusions or damage to vessel walls[2].

The use of the COVID Symptom Study app by UK citizens has been valuable to document the presence of many different types of COVID-19 symptoms in the community [8]. However, data on skin symptoms were only recently collected, and this hindered our ability to identify at which stage of the disease they appear and how long they last. An independent survey was therefore carried out to capture more details on the types of rashes, their duration, timing, results from SARS-CoV-2 swab/antibody test, and co-occurring symptoms. The prevalence of the three types of rashes was assessed with photos by a dermatologist. This showed that papular rashes were the most frequent, acral lesions the longest lasting, while urticaria was short lived. The survey also showed that 17% of the SARS-CoV-2 positive users and 15% of the untested users with at least one of the classical COVID-19 symptoms may not have any other concomitant symptoms when they first become unwell, and, as a result, might miss out on early diagnosis. When additional symptoms co-occurred in infected individuals, the most frequent were the most classical COVID-19 symptoms such as fever, persistent cough, and anosmia. Furthermore, 21% of the SARS-CoV-2 positive surveyees presented with skin symptoms alone, and would have been missed if using the NHS classic symptoms alone. The Spanish study[5] had attempted to investigate the timing and duration of rashes but the cases, as well as those from previous studies, were mostly more severe hospitalized patients and there was little follow up for late skin manifestations.

A major limitation of the current study is the self-reported nature of the data. However, we believe that the presence of a rash, especially if symptomatic, is less subjective and more specific than symptoms such as fatigue, headaches, or chronic cough. About 13.6% of the photos uploaded by the surveyees which were assessed represented likely non-CoVID-19 related dermatological conditions, thus suggesting that the overall number of self-reported rashes may have been overestimated. However, the large number of users of both our COVID Symptom Study app and the survey in this study makes it unlikely that such reporting errors may have significantly affected our estimates. On the other hand, many of the COVID Symptom Study app users may have failed to realise the relevance of skin symptoms and not have reported them if not accompanied by other more known COVID-19 symptoms. Second, our study sample is not fully representative of the general population, as it represents a self-selected group of individuals, and also because of the uneven access to SARS-CoV-2 testing in the early stages of the pandemic, with tested subjects encompassing a mixture of healthcare workers, at-risk subjects with chronic diseases, elderly people, etc. Third, although COVID-19 rashes can be divided into three main types, *i.e.*, urticarial on the face or body, erythemato-papular/vesicular usually present on central body, and chilblains/perniosis on acral sites, the app only classified them into two categories, with the urticarial rash and erythemato-papular/vesicular rashes together, as both tend to be itchy and the users may not be able to differentiate between them.

The NHS in UK lists three main classical symptoms suspicious of COVID-19 (www.nhs.uk/conditions/coronavirus-covid-19/symptoms), whilst the CDC in the USA lists five (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html). However, these do not currently include skin-related symptoms, although they can be easily spotted by patients.

This study strongly supports the inclusion of skin rashes in the list of suspicious COVID-19 symptoms. Although, it is less prevalent than fever, it is more specific of COVID-19 and last longer. An increased awareness from the public and healthcare professionals regarding COVID-19 skin changes will allow more efficient identification of new and earlier clusters of the disease.

Methods

The COVID Symptom Study app

The COVID Symptom Study app was developed by Zoe Global Limited, supported by physicians and scientists at King's College London and Massachusetts General Hospital, Boston. The COVID Symptom Study app has been described in detail previously[7]. The app collects, on sign up, data on sex, age, ethnicity, and core health risk factors, including height, weight, and common disease (*e.g.*, cancer,

diabetes, heart, kidney, and lung disease) status, the use of a set of medications (*e.g.*, corticosteroids, immunosuppressants, and blood pressure medications), and whether the individual is a healthcare worker. Since May 7th, 2020, the app also prompts users to self-report detailed information, also retrospectively, regarding whether they have ever had a SARS-CoV-2 test, and, for each test, how this was performed (*e.g.*, nose/throat swab, antibody testing), and the test result. By using the app, users can provide updates on their daily health status by answering the question "How do you feel right now?". If they feel unwell, the app further collected self-reported presence of 14 COVID-19-related symptoms, namely: abdominal pain, chest pain, delirium, diarrhoea, fatigue, fever, headache, hoarse voice, loss of smell, persistent cough, shortness of breath, skipped meals, sore throat, and unusual muscle pains. From April 29th, 2020, skin manifestations of the disease were added: raised, red, itchy wheals on the face or body or sudden swelling of the face or lips (body rash), and red/purple sores or blisters on the feet or toes (acral rash). Asking the participants to differentiate between a transient urticarial rash and a fixed erythemato-papular/vesicular rash was problematic, so the body rashes were collected together, and the second skin question only covered the more specific acral rash. Marzano *et al* also divided the many different types of rashes in two broad categories: inflammatory/exanthematous rashes for the various body rashes, and vasculopathic rashes for the fingers or toes[2].

Study population

This study included residents in the UK from 1 to 90 years who downloaded the app and entered regular data between May 7th and June 22nd, 2020, either themselves or *via* proxy. In this study, we excluded individuals with body mass index (BMI) outside the range of 15 to 55 kg/m^2 (for individuals 16 years old or older), or outside two standard deviation from the sample's mean for each age (for individuals younger than 16 years old), pregnant women, and individuals who did not report their sex. When users failed to report other pieces of information (*e.g.*, the presence of a symptom or disease) we considered them as absent. We removed inconsistent daily assessments, such as those with a logged body temperature outside the range of 35 to 43° C, or where individuals reported feeling unwell but had no symptoms. This resulted in 336,847 individuals, 17,407 of whom also provided valid (*i.e.*, positive or negative) results for SARS-CoV-2 swab tests. We further selected 54,652 symptomatic users (*i.e.*, users reporting at least one of the 16 collected symptoms during their daily log history) who did not believe of having already been infected when first registering with the app and had not yet been tested for SARS-CoV-2 *via* nose/throat swab. These users were divided in two groups: those reporting at least one of the of the three main symptoms of COVID-19 (*i.e.*, fever, persistent cough, and/or anosmia) either at the time or logging or retrospectively, and who, according to the NHS guidelines, would require isolation and testing for SARS-CoV-2 infection, and those that did not. Sample characteristics are summarised in **Table 1 and Supplementary Table 1**.

The study has been approved by the King's College London Research Ethics Committee REMAS ID 18210, review reference LRS-19/20-18210 and all subscribers provided informed consent.

The skin rash survey

To further collect more detailed information on body and acral rush duration and timing with respect to other COVID-19 symptoms, and to create a repository of photos for COVID-19 related skin symptoms, Zoe Global Limited delivered an on-line questionnaire *via* Survey Monkey asking whether the rash was the only symptom, how many days it lasted, and, if other COVID-19 related symptoms were present, whether the rash started before, during or after the other symptoms. The questionnaire was open from 12th to 17th June, 2020. We removed 895 surveyees reporting more than six weeks duration of their skin symptoms, as well as those not reporting age, or reporting a number outside the 1-90 years old range. We selected 365 photos from individuals having a positive SARS-CoV-2 test, or reporting at least one of the three classic COVID-19 symptoms used in the UK, from both sexes to be assessed and categorised independently by an experienced dermatologist. The categories were papular, urticarial, vasculitic body and acral lesions.

Statistical analyses

Statistical analyses were carried out using R (v. 3.6.1). Comparisons between categorical and continuous values were carried out using logistic regression and Wilcoxon's test, respectively. Associations between the presence/absence of self-reported skin-related symptoms and, in tested individuals, SARS-CoV-2 test results, and, in symptomatic untested individuals, the presence/absence of the three classic COVID-19 symptoms, were carried out through multivariate logistic regression, and the following variables were included as covariates: sex, age, BMI, ethnicity (namely: Asian, Black, Chinese, Middle Eastern, White, or mixed), smoking status (namely: never, ex, current), common disease status (namely: cancer, diabetes, lung, heart, or kidney disease) and whether corticosteroids, immunosuppressants, or blood pressure medications were administered.

Contributors

VB, AV, TDS, and MF conceived the study. JW, CS, and TDS conceived COVID Symptom Study app. VB, AB, TDS conceived the survey. AV, NR, BM, and SO curated the COVID Symptom Study app data. AV, NR, and MF curated the survey data. VB assessed and categorised the photos. VB, AV, and MF drafted the manuscript. All authors read and approved the final version of the manuscript.

Declaration of interests

AB and JW are employees of Zoe Global Limited. TDS is a consultant to Zoe Global Ltd. The other authors have no conflict of interest to declare.

Data availability

Data collected in the app are being shared with other health researchers through the NHS-funded Health Data Research UK (HDRUK)/SAIL consortium, housed in the UK Secure e-Research Platform (UKSeRP) in Swansea. Anonymized data collected by the symptom tracker app can be shared with *bonafide* researchers *via* HDRUK, provided the request is made according to their protocols and is in the public interest (see https://healthdatagateway.org/detail/9b604483-9cdc-41b2-b82c-14ee3dd705f6). Data updates can be found at https://covid.joinzoe.com. The app code is publicly available from https://github.com/zoe/covid-tracker-react-native. The main data cleaning script is publicly available from https://github.com/KCL-BMEIS/zoe-data-prep.

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Long COVID in the skin: a registry analysis of COVID-19 dermatological duration

Since the start of the COVID-19 pandemic, multiple studies have reported that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with dermatological manifestations.[1] However, data on duration of signs and symptoms for the myriad dermatological manifestations of COVID-19 are lacking. Patients infected with SARS-CoV-2 who experience prolonged symptoms have been termed "long-haulers"[2] or are said to have "long Covid",[3] with studies reporting that 66–87% of patients continued to have one or more COVID-19 symptoms 60 days after PCR positivity.[4–6] Using an international registry of COVID-19 dermatological manifestations, we evaluated the duration of dermatological signs and symptoms of COVID-19 and assessed the presence of patients with persistent skin manifestations.

In collaboration with the International League of Dermatological Societies and the American Academy of Dermatology, we established an international registry for COVID-19 dermatological manifestations in April, 2020.[7] Physicians and other health-care providers entered information on confirmed or suspected COVID-19 cases with dermatological manifestations, including PCR test results, antibody test results, and total sign and symptom duration when known. Additionally, providers were contacted in June and August to update COVID-19 laboratory test results and COVID-19 dermatological sign and symptom duration. Laboratory tests for SARS-CoV-2, including nasopharyngeal swab PCRs and serum antibody tests (IgM, IgG, and IgA), were reported when available. We defined long-haulers as patients with dermatological signs of COVID-19 that persisted for more than 60 days.[4] Data were analysed descriptively with medians and IQRs using Stata (version 16). Duration of skin signs was calculated separately for each dermatological condition and plotted using a boxplot to illustrate IQRs and outliers.

From Apr 8, 2020, to Oct 8, 2020, 1030 total cases and 331 laboratory-confirmed or suspected COVID-19 cases with dermatological manifestations were reported in the registry from 41 countries. Of these cases, 234 total cases and 96 laboratory-confirmed cases reported data for dermatological sign and symptom duration (appendix p 1). Median duration of signs was 13 days (IQR 7–21) for all patients, and 7 days (IQR 5–14) for the subset of patients with laboratory-confirmed disease (appendix p 2). Morbilliform lasted a median of 7 days (IQR 5–10) and urticarial eruptions lasted a median of 4 days (IQR 2–10) among patients with laboratory-confirmed COVID-19, with a maximum duration of 28 days. Papulosquamous eruptions lasted 20 days (IQR 14–28) in laboratory-confirmed cases, with one case having a confirmed long-hauler eruption lasting 70 days. Pernio lasted a median of 15 days (IQR 10–30) in patients with suspected COVID-19, and 12 days (IQR 7–23) in laboratory-confirmed cases.

Seven (6·8%) of the 103 cases with pernio were long-haulers with pernio lasting for more than 60 days, of whom two cases were laboratory-confirmed. One long-hauler patient who presented with 20 days of cough and fatigue and 13 days of pernio lesions initially tested negative for COVID-19 by SARS-CoV-2 nasopharyngeal PCR, serum IgM, and IgG. The patient seroconverted to anti-SARS-CoV-2 IgM positivity within 6 weeks after pernio onset, and continued to experience severe pernio and fatigue for over 133 days (detailed case timeline is shown on appendix p 2). Additional ELISA-based testing of banked serum drawn 24 days after symptom onset showed IgA reactivity to SARS-CoV-2 full spike protein and spike protein receptor binding domain, consistent with reported IgA immunoreactivity detected in other COVID-19-associated cohorts of patients with pernio (appendix p 3).[8,9] This finding increases our confidence that this patient had a true SARS-CoV-2 infection. Another long-hauler patient who developed pernio and livedo reticularis 1 month after exposure to a SARS-CoV-2 nasopharyngeal PCR-positive family member tested positive for SARS-CoV-2 serum IgG 1 month after pernio lesion onset, and continued to experience pernio and livedo reticularis lesions for over 150 days.

A limitation of this registry-based study is that providers might have entered data at only one timepoint, often soon after seeing the patient, when the full-time course of disease had not yet been observed.

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See Online for appendix

We attempted to overcome this issue by proactively requesting case updates. This challenge probably biased our results towards inclusion of cases with a shorter duration of dermatological signs and symptoms. Indeed, 58% of providers reported that patients had ongoing COVID-19 dermatological manifestations at the time of case entry. Therefore, the duration of dermatological manifestations reported here probably underestimates both average duration and the number of long-hauler patients.

Since the onset of the COVID-19 pandemic, appreciation for persistent morbidity beyond the acute phase of disease has increased.[4,10] To our knowledge, our data represent the largest dataset to date on persistent skin signs and symptoms of COVID-19 and the duration for several distinct skin manifestations. Urticarial and morbilliform eruptions were relatively ephemeral, whereas papulosquamous eruptions, and particularly pernio, were longer-lasting. Our analysis revealed a previously unreported subset of patients who experience long-hauler symptoms in dermatology-dominant COVID-19, raising questions about persistent inflammation even in patients who initially experienced relatively mild COVID-19.

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Long Covid: where we stand and challenges ahead

Alberto Mantovani[1,2,3]✉, Maria Concetta Morrone[4,5], Carlo Patrono[6], M. Gabriella Santoro[7,8], Stefano Schiaffino[9], Giuseppe Remuzzi[10], Giovanni Bussolati[11,12]✉ and On behalf of the Covid-19 Commission of the Accademia Nazionale dei Lincei*

Post-acute sequelae of SARS-CoV-2 (PASC), also known as Post-Covid Syndrome, and colloquially as Long Covid, has been defined as a constellation of signs and symptoms which persist for weeks or months after the initial SARS-CoV-2 infection. PASC affects a wide range of diverse organs and systems, with manifestations involving lungs, brain, the cardiovascular system and other organs such as kidney and the neuromuscular system. The pathogenesis of PASC is complex and multifactorial. Evidence suggests that seeding and persistence of SARS-CoV-2 in different organs, reactivation, and response to unrelated viruses such as EBV, autoimmunity, and uncontrolled inflammation are major drivers of PASC. The relative importance of pathogenetic pathways may differ in different tissue and organ contexts. Evidence suggests that vaccination, in addition to protecting against disease, reduces PASC after breakthrough infection although its actual impact remains to be defined. PASC represents a formidable challenge for health care systems and dissecting pathogenetic mechanisms may pave the way to targeted preventive and therapeutic approaches.

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FACTS

- PASC is a frequent legacy of acute SARS-CoV-2 infection, affecting over 10% of patients with different signs and symptoms across a wide range of organs and systems.
- The most frequent manifestations of PASC, in addition to compromised lung functions, include: neurocognitive alterations; alterations of cardiovascular functions and increased risk of acute events; fatigue.
- The SARS-CoV-2 virus seeds and persists in different organs and tissues.
- The pathogenesis of PASC is multifactorial and includes: virus seeding and persistence in different organs; activation and response to unrelated viruses (e.g., EBV); autoimmunity; uncontrolled inflammation.
- Biomarkers of clinical PASC include levels of IgG, cytokines, chemokines, PTX3, and interferons.
- Vaccination reduces PASC after breakthrough infection.

OPEN QUESTIONS

- Occurrence, mechanism, and significance of SARS-CoV-2 persistence in different organs.
- Mechanisms, targets, and significance of autommune reactions.
- Role of other viruses.
- Impact of host genetics and microbiome.
- Actual impact of vaccination in people who get breakthrough infections and its duration.
- Occurrence and severity of PASC after infection with future variants.
- Preventive and therapeutic approaches.

INTRODUCTION

The colloquial terms Long Covid and Post-Covid syndrome (PCS) have been extensively used to identify a wide variety of symptoms occurring for several weeks up to two years following the diagnosis of Covid-19 or symptoms that were consistent with SARS-CoV-2 infection. The syndrome, now formally known as Post-Acute Sequelae of SARS-CoV-2 (PASC), mainly includes neurological and cognitive impairment; fatigue; pain manifestations; cardio-pulmonary symptoms; anosmia-dysgeusia; and headache [1]. The British National Institute for Health and Care Excellence (NICE) defines PASC as "signs and symptoms that develop during or after an infection consistent with Covid-19, continue for more than 12 weeks and are not explained by an alternative diagnosis".

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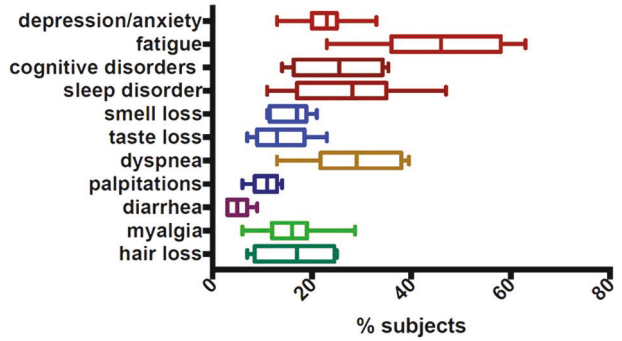

Fig. 1 The frequency of the most common symptoms four week or more after the acute Covid-19 infection. Data presented in meta-analyses, selected on the basis of homogeneous reporting criteria [10–20].

The WHO has crystallized the following clinical case definition of PASC: "it occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of Covid-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis" [2].

Women and men were affected differently from the Covid-19 pandemic. Women did show less severe complications in the short-term while suffering from worse long-term ones such as depression, impaired physical activity impacting also on lifestyle habits, increasing the cardio-vascular risk [3, 4]. The impact of COVID-related long-time imbalances affecting the general population should not be under-estimated [5]. In fact, the incidence of people reporting COVID-related symptoms varies extensively, being related to sex, age, and severity of symptoms during the acute phase. In UK, epidemiological analyses conducted by February 2021 estimated that from 1 up to 2 million people reported at least one COVID-related symptom which lasted for 12 or more weeks [6]. According to a metanalysis conducted in UK, the main symptoms still present 1 year after the acute disease included cognitive and mental health disorders, such as depression, anxiety, memory loss, concentration difficulties and insomnia, fatigue, dyspnea, muscle, and joint pain [7]. A higher risk of diabetes has also been observed [8]. Female sex and severe COVID-19 disease were associated with higher risk of experiencing symptoms of PASC [8]. In a large population study in Southern Germany (EPILOC cohort, age 18–65), the three most frequent clusters of symptoms were fatigue, neurocognitive, and chest/cardiorespiratory, with at least moderate impairment (>20%) of general health and working capacity in 26% of the subjects (age and sex standardized), including young and middle-aged subjects [9]. Numerous reports have dealt with the frequency of symptoms related to SARS-CoV-2 and present several weeks or months following the acute phase. Most reports are limited in number and meta-analyses can provide more extensive and reliable values. Frequencies collected from 11 meta-analyses reporting homogeneous information [10–20] allow to present reliable data (Fig. 1). Information on the presence of Covid 19-related symptoms over 12 months from the acute infection are limited [8, 10] but confirm the possibly of persistence of symptoms (especially fatigue and cognitive disorders) for long time.

Symptoms, related pathological findings, pathogenetic data, and prognostic prospects are different in different organs, which implies separate analytical reports of patterns involving lung, cardio-vascular system, neuro-muscolar system, and brain. Other organs can also be affected. Besides the already mentioned higher frequency of diabetes, kidney imbalances have been reported. Adult patients who survived Covid-19 beyond the first 30 days of infection exhibited increased risk (and burden) of acute kidney insufficiency, eGFR (estimated Glomerular Filtration Rate) decline, End Stage Kidney Disease, and major adverse kidney events [21]. The risk (and burdens) of kidney outcomes increased according to the severity of the acute infection.

Here we will review the current understanding of the main manifestations and organ involvement by PASC. Underlying cellular and molecular mechanisms will be discussed with emphasis on the contribution of viral persistence and immune responses.

ORGANS AND SYSTEMS INVOLVED

Lung

Persistent dyspnea, frequently associated with fatigue, chest pain, and cough affect ~20% of patients 3 months after the acute SARS-CoV-2 infection [22]. Lung involvement by PASC is generally related to the disease severity, but there is no strict relationship between dyspnea and the degree of initial disease [23]. In most cases, dyspnea progressively improves over time even if a subgroup of patients experiences persistent dyspnea up to 1 year after Covid-19. Interestingly, among Survivors of Covid-19 experiencing long-term symptoms, increased breathlessness, and reduced quality of life were observed in young, previously healthy working age adults and frequently younger females [24].

After hospital discharge, fatigue, dyspnea, chest pain, and cough are the most prevalent respiratory symptoms found in 52%, 37%, 16%, and 14% of patients between 3 weeks and 3 months. The pathogenesis of persistent COVID-related symptoms is likely multifactorial, but evidence indicates that pulmonary endotheliopathy and pro-thrombotic changes, as well as inflammatory cytokine production could be involved [22, 25, 26]. Abnormalities in alveolar diffusion capacity, revealed by diffusing lung capacity for carbon monoxide (DPCO) tests persist for long periods and are likely related to interstitial pneumonia, which might evolve into pulmonary fibrosis. A long-term evolution towards pulmonary fibrosis is a possible occurrence, strictly related to the severity of pulmonary inflammation during the acute phase and affecting which higher frequency patients which required mechanical ventilation. Radiological data are important in the management of Covid-19 patients and in the follow-up after the acute phase. Interstital fibrosis leads to abnormalities at high-resolution CT-scans: reticulations and traction bronchiectasis can reveal the severity of the process, months after the acute infection. McGroder and Coworkers [27] observed that such radiological abnormalities were related with cough and pulmonary function degradation. Furthermore, these Authors reported that fibrotic-like radiological abnormalities correlated with shorter blood leukocyte length. The respiratory outcome of patients who required hospitalization during the acute phase tends to improve over time, as assessed by radiological exams and pulmonary function tests such as DLCO (diffuse capacity of the lungs for carbon monoxide) but in a fraction of patients changes persisted up to 1 year [28].

Diffuse alveolar damage in the proliferative phase and collagen deposition were observed in a series of autopsies performed on patient died over 65 days after infection. Pulmonary tissue damage can be amplified by concomitant bacterial superinfection, aspergillosis, thromboembolism, and hemorrhage [29].

A study on immuno-fibrotic drivers of impaired lung function in PASC reports that circulating factors associated with acute neutrophil activation, fibrosis signaling, and alveolar epithelial repair remain elevated in survivors of acute Covid-19 infection and may predict the impairment of pulmonary function [30].

A meta-analysis including a total of 4478 Covid-19 patients from 16 cohort studies reports that fatigue or weakness (47%) were the most prevalent physical effects of post-acute Covid-19 syndrome. In recovering patients, defective lung functionality as revealed for instance by diffusion capacity for carbon Monoxide (DLCO < 80%) persisted for long time. Decreased lung function and joint pain were more frequently observed in patients with severe disease [16].

Cardio-vascular system

Myocardial injury associated or not with the multisystemic inflammatory syndrome [31] occurs frequently in patients with acute Covid-19 infection (as revealed also by high serum Troponin levels) and is associated with increased mortality during hospitalization. In the general population, an incidence of Covid-19-associated myocarditis of ~150 cases per 100,000 was observed [32]. In patients who survive, the incremental mortality at 6 months and 1 year was seen to be low [33]. Some evidence indicates that males between 12 and 17 years of age most likely developed myocarditis within 3 months of SARS-CoV-2 infection [34].

An accurate statistical analysis estimated the risks and 12-month burdens of pre-specified cardiovascular outcomes confirming that they are substantial and span several cardiovascular disease categories (ischemic and non-ischemic heart disease, dysrhythmias, and others). Symptoms may include chest pain, shortness of breath, fatigue, and autonomic manifestations such as postural orthostatic tachycardia which are common and associated with significant disability, heightened anxiety, and public awareness [35–37]. The risks and burdens of cardiovascular disease were evident even among patients who did not necessitate hospitalization for acute Covid-19 disease [38]. Patients with PASC frequently experience Inappropriate Sinus Tachycardia (IST), possibly sustained by a cardiac autonomic nervous system imbalance with decreased parasympathetic activity [39]. Most cardiac abnormalities were seen to alleviate with time, but some of them, especially diastolic dysfunction, may persist, raising the presumption of a chronic alteration [40].

The pathogenesis for post-acute cardiac damage is still not fully elucidated. Possibly, a chronic inflammatory response evoked by persistent viral reservoirs in the heart after acute infection might be the explanation, with underlying mechanisms suggested for post-acute Covid disease affecting other organs (see below). Moreover, another putative mechanism for delayed damage is an autoimmune response to cardiac antigens through molecular mimicry, and some evidence has been presented in favor of this hypothesis [41].

Neuromuscular system

Muscle weakness, fatigue, and exercise intolerance are among the most frequent symptoms of PASC. Myalgia is also observed in several patients and the symptoms may persist for several weeks or months [42]. This condition, which is more frequent in patients who were hospitalized for Covid-19, but is also seen in non-hospitalized patients, is similar to the chronic fatigue syndrome (CFS), also called myalgic encephalomyelitis (ME) or ME/CFS that may occur following different viral infections, thus also referred to as post-viral fatigue syndrome (PVFS). The pathogenesis of all these conditions is unclear. To dissect the causes of muscle fatigue in PASC, it is useful to consider the pathogenesis of neuromuscular symptoms also during the acute phase of severe Covid-19.

Muscle wasting in Covid-19 patients admitted to ICU. Intensive-care patients with severe Covid-19 show dramatic muscle wasting and weakness, a condition related to the Critical Illness Myopathy due to immobilization and mechanical ventilation seen in many patients admitted to ICU, independently of the cause of the disease [43]. This condition is followed, for those who survive, by sustained physical disability and requires a long rehabilitation process. Both myogenic mechanisms, with loss of myosin from the muscle fibers, and neurogenic factors, with slowing of nerve conduction velocities and axonal degeneration, may contribute to the Critical Illness Myopathy seen in patients with severe Covid-19 [42]. In addition, other factors, including systemic inflammation with increased cytokine levels (cytokine storm), hypoxemia, which is present in all patients with severe disease, malnutrition due to loss of appetite, loss of smell, and alteration in taste, likely contribute to promote muscle wasting.

Viral infection of skeletal muscles. It is not clear whether viral infection of muscles is involved in muscle changes during and after Covid-19. Evidence for myositis has been reported in deceased patients with Covid-19. However, detection of viral load was low or negative in most skeletal muscles, and probably attributable to circulating viral RNA rather than direct infection of muscle cells [44].

Peripheral neuropathy during or after SARS-CoV-2 infection. Several Covid-19 patients show symptoms of peripheral neuropathy, such as painful paresthesia (numbness and tingling) either during or after SARS-CoV-2 infection [45]. In some of these patients, a diagnosis of small fiber neuropathy was supported by skin biopsy, and autonomic dysfunction was demonstrated by autonomic function testing. Combined involvement of motor and sensory nerves was seen only in occasional patients, for example patients showing bifacial weakness and paresthesia [46]. These cases are consistent with conditions related to various forms of Guillain-Barré syndrome (GBS), probably caused by autoimmunity, thus different from other sensory disfunctions seen in Covid-19, such as anosmia and dysgeusia, which seem to reflect a direct viral infiltration of the nervous system.

Nervous system

It is now clear that many brain functions are affected for a long time after Covid-19 infection, in patients both with severe and mild symptomatology [47, 48]. PASC includes cognitive, neurological and psychiatric diseases, and distressing symptoms such as memory loss, fatigue, anosmia, and dysgeusia. The peculiar sensory deficits, anosmia/dysgeusia, that characterized the early symptoms of Covid-19 were manifested in more than 40% of Covid-19 patients infected with Delta or previous variants. It affected patients of all ages and the impairment lasted on average for 2–3 months after the end of the infection. However, even in young adults with no severe Covid, loss of taste and/or smell (about 28% of prevalence) were present at 6 months post infection. These sensory deficits are amongst the brain function deficits with a faster recovery in PASC [49, 50].

Cognitive dysfunction in PASC is very broad, affecting attention, executive function, problem solving, and decision making. The most prevalent dysfunction concerns memory, affecting up to 73% (in an interview study on 2739 patients), inducing both short-term and long-term memory loss [50]. The time course of the loss and of the possible recovery of the many affected brain functions are variable: cognitive dysfunction increased over the first three months post infection, then decreased slightly in the following 7 months. The probability of experiencing memory symptoms increased over the first few months, with 56% reporting memory symptoms at month 4 and 50% at month 7. While age is an important factor in cognitive and memory disfunction, it is worrying that non-hospitalized, young people (16–30 years old) suffer potentially severe symptoms, such as concentration and memory problems, half a year after infection [47, 50].

The study of the anatomical or functional imaging of brain alterations in PASC shows consistent changes in many brain areas, including the somatosensory cortex, rectal/orbital gyrus (including the olfactory system), temporal lobe (including the amygdala, piriform cortex, and the hippocampus), hypothalamus/thalamus, brainstem, and cerebellum [51]. 18F-FDG brain PET studies in Covid-19 patients have shown prominent hypometabolism in many of the above areas. However, during the PASC phase, a reversibility of the decreased neocortical glucose metabolism is evident, which importantly is associated with an improvement in cognitive function. Interestingly, the spatial covariance pattern of the hypometabolism correlates with the cognitive impairment [52].

The preliminary evidence of brain alterations has been corroborated by a larger study that could compare in the single patient (55–75 years of age) brain anatomy before and about

Table 1. Mechanisms of pathogenesis of PASC.

Mechanisms	Details	Selected refs.
Persistence of SARS-CoV-2 and/or fragments	High RNAmia at the time of diagnosis is a risk factor	[49]
	SARS-CoV-2 presence in different organs	[62, 85]
	Viral persistence in the GI tract	[63]
Activation of other viruses	Circulating EBV	[49]
	CMV reactive T cells	[49]
Innate immunity, inflammation	Myeloid cell activation, cytokines (IFN, IL-6), PTX3	[73, 74]
	Glial cell disregulation; TNF, IL-6, CCL11; brain fog	[83]
Adaptive immunity	Antibodies (IgG/IgM signature, T cell activation)	[49, 72]
Autoimmunity	Autoantibodies, autoreactive T cells	[70, 71]
Microclots	Endothelial cell and virus triggered microthrombi	[61]

5 months after the Covid-19 infection [53]. Again, this study recruited patients in 2020 and early 2021, and hence does not include infections with omicron variants. Both gray and white matter of many brain areas change. The changes are subtle but are consistent across individuals and highly significant. Gray matter, evaluated by cortical thickness, is reduced in many regions of the orbito/frontal cortex and limbic system that include olfactory cortex, piriform cortex, amygdala, parahippocampal and hippocampal cortex, and insula. The changes are consistent with the white matter alterations, measured with mean diffusivity, in regions functionally connected with the piriform cortex, olfactory tubercle, and anterior olfactory nucleus. These altered structures participate in the perception of taste, smell, emotion, memory, and spatial navigation, functions that are strongly compromised during PASC.

The correspondence between the major cognitive and neurological dysfunction in PASC and the neuronal substrate that mediates these functions suggest that the observed symptoms result from insults, although small, to the brain in consequence of the infection. The mechanism that generates the insults is still to be defined (see below).

A pronounced loss of gray matter was also observed in crus II, part of the cognitive, and olfactory-related lobule VII of the cerebellum. Interestingly, the amount of gray matter loss correlated well with the patient individual performance in a spatial attention task widely used as a neuropsychological test. Again this demonstrates a causal link between brain alterations and behavioral deficits. Despite these highly localized deficits, there is also an increase in Cerebro Spinal Fluid (CSF) volume and decrease of whole brain volume respect to the controls, suggesting an additional diffuse loss of gray matter. The anatomical deficits increase with age between 60 and 75 and are likely to be modest in the age group of 55. This reinforces neuropsychological data that showed Covid-19 as a risk factor to develop dementia, neurodegenerative diseases and mild cognitive impairments even in 50-year-old adults [54].

Metabolic dysfunctions and diabetes

Metabolic dysfunctions, such as obesity and insulin resistance, and metabolic diseases, such as diabetes, were recognized as predisposing risk factors for severe acute Covid-19 since the early stages of the pandemic. Now emerging evidence supports the notion that these conditions also predispose to Long Covid (PASC). For example, lipid metabolism disorders and obesity were found to be age-independent risk factors for the development of PASC, as shown in a retrospective study involving more than 50.000 patients with a confirmed diagnosis of Covid-19 treated by general practitioners in Germany [55].

Type 2 diabetes is a well-established PASC-anticipating risk factor [49] and several reports now support the notion that the incidence of diabetes is increased after Covid-19 [56]. Abnormalities in glycometabolic control, insulin resistance, and beta cell function were detected in patients with Covid-19 without any pre-existing history or diagnosis of diabetes and persist even after recovery [57].

The study by Xie and Al-Aly [7] stands out for its large sample size. A cohort of more than 180,000 participants who had a positive COVID-19 test were followed up for about 1 year. Compared to a non-infected contemporary and a historical control group (both > 4 M subjects) cohort members were observed to have an increased risk of incident diabetes [7]. The risk was found to increase according to the severity of disease during the acute phase of the infection, Comparing three groups of patients (non-hospitalized, hospitalized, and admitted to intensive care), the risk was found to be related to disease severity but also present in the non-hospitalized group. The excess burden of diabetes among non-hospitalized individuals (8.3 per 1000 people at 12 months) points to the magnitude of the problems that health systems might face, considering the hundreds of millions of people infected globally. Given the importance of this major risk of Long Covid, it will be important to support the conclusion of these reports with prospective epidemiological studies [58]. An immediate implication of the studies is the necessity of screening for hyperglycemia not only during the acute phase of Covid-19 but also during the follow-up.

PATHOGENESIS AND BIOMARKERS

Understanding fundamental mechanisms underlying the pathogenesis of Long Covid is in its infancy and represents a major challenge. Candidate mechanisms of pathogenesis can be classified along five major lines: persistence of SARS-CoV-2; reactivation of other viruses, in particular Epstein-Barr virus (EBV); autoimmunity triggered by the virus; persistent tissue damage and immunity-triggered inflammation [59, 60]; formation of microthrombi in the vascular bed of different tissues [61] (Table 1; Fig. 2).

Persistence of the virus and viral fragments has been proposed to represent a driver sustaining long-term sequelae of PASC (see below) [62]. Gastrointestinal (GI) viral shedding has been associated in some patients with persistent disease following the acute phase of the disease [63]. Consistent with the view of an important role of virus persistence are preliminary observations of vaccination of Long Covid patients being associated with resolution [64, 65]. PASC occurs in the aftermath of a complex interplay between the virus and the host immune system (see for review [60, 66]). Intriguingly, a mechanism of subversion of immunity by SARS-CoV-2 includes syncityum-mediated lymphocyte elimination [67, 68].

Consistent with an important role of the virus itself, SARS-CoV-2 RNAmia was recently identified as a risk factor for PASC at the time of initial diagnosis [49]. In this longitudinal cohort of 209 patients investigated using a multi-omic approach, additional risk factors included diabetes, circulating EBV, and auto-antibodies. The EBV

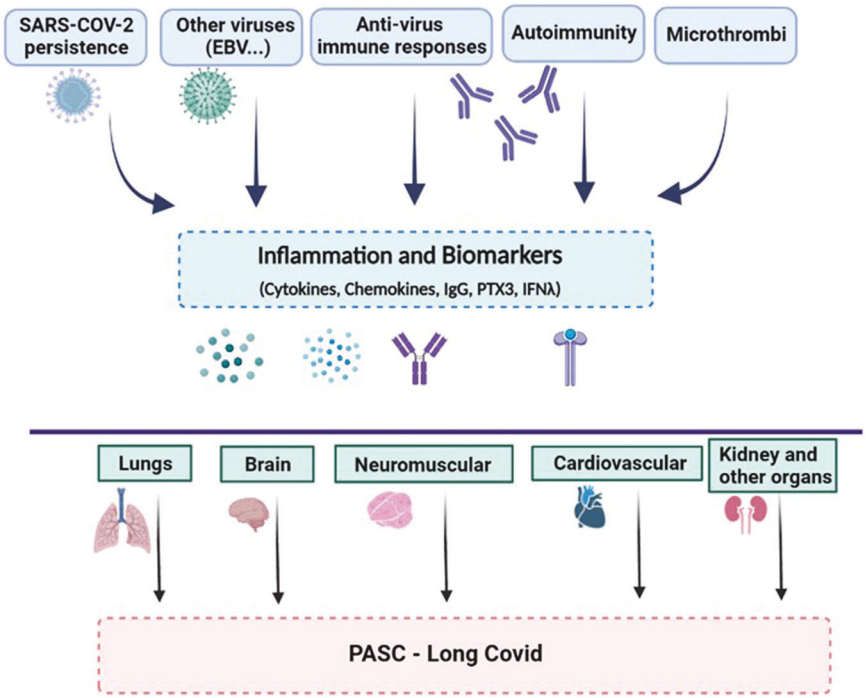

Fig. 2 A schematic representation of the pathogenic mechanisms and main targets of PASC. The drivers, effector molecules, biomarkers, and affected organs are presented in a schematic form, as discussed in the text. The inset suggesting that the host genetics and microbiome may affect the development of Long Covid is based on current evidence on determinants of severe Covid-19. Type 2 diabetes has been shown to increase the risk of developing PASC.

data suggest that viral reactivation may contribute to the pathogenesis.

Immune activation and autoimmunity have long been associated with PASC [69]. Indeed, autoantibodies have been shown to contribute to severe Covid-19 disease [70]. Activation of autoreactive T cells has been observed in infection settings including Covid-19 [71]. In a recent study, GI-PASC was found to correlate with newly expanded cytotoxic CD8+ and CD4+ T-cell populations. These new populations include SARS-CoV-2 reactive clones and their activation occurred during convalescence from acute disease. Concomitantly, non-specific activation of CMV-specific T cells was observed in subjects with GI-PASC [49].

A limited number of prospective studies with validation cohorts have been conducted to investigate pathogenesis and prediction of evolution to PASC. In a study involving 215 subjects and a 395 individuals validation cohort [72], an antibody signature (IgM and IgG3) together with a set of clinical variables was able to predict PASC. A study conducted on 147 patients in addition to normal subjects, included controls who had been infected with prevalent coronaviruses other than SARS-CoV-2 [73]. Eight months following mild-to-moderate SARS-CoV-2 infection profound perturbations were found in Covid-19 patients. Myeloid cells showed an activated phenotype and alterations of naive T cells were observed. A combination of analyses was associated with PASC with a 78–81% accuracy. This set of biomarkers included cytokines (IFN-β, IFN-γ, IFN-λ, and IL-6) and the fluid phase pattern recognition molecule PTX3 [74].

Covid-19 has been associated with microvascular thrombosis [75–80] and microthrombi have been suggested to play a role in PASC [61]. Different mechanisms may contribute to formation of microclots. Endothelial cell activation and activation of the lectin pathway can facilitate thrombus formation [61, 75–81]. Fibrinogen in platelet-poor plasma of PASC patients has been shown to clot in an anomalous "amyloid" form of fibrin resistant to fibrinolisis. A propensity to develop microthrombi in PASC has obvious implications for the pathogenesis of cardiovascular problems discussed above. Intriguingly, it has been suggested that the SARS-CoV-2 proteome includes amyloidogeneic peptides which may contribute to neurological symptoms [82].

Brain fog is a prominent feature of PASC and a recent study identified a cytokine/chemokine cascade as a driver of its pathogenesis [83]. In mice, mild respiratory Covid triggered microglial reactivity with loss of neurogenesis and of myelinated axons. Neuroinflammation was sustained by cytokines (TNF and IL-6) and a chemokine (CCL11). In agreement with these data in mice, humans with lasting cognitive symptoms after Covid-19 showed elevated levels of CCL11.

Thus, the pathogenesis of PASC is complex, at the interception between virus persistence, activation of, and response to, endogenous viruses (EBV and possibly others), activation of antiviral and autoimmune responses, sustained inflammation. Given the diversity and pleiomorphic nature of PASC manifestations, it is tempting to speculate that the relative importance of different pathogenic components may vary depending on the spectrum of organs involved.

MECHANISMS OF PATHOGENESIS: VIRUS PERSISTENCE

A growing number of studies provide evidence that in some PASC patients, SARS-CoV-2 is capable of persisting in several tissue reservoirs after acute infection. In addition to the respiratory tract, SARS-CoV-2 viral proteins and/or RNA have in fact been detected throughout the cardiac and renal systems, GI tract, muscles as well as in the brain and lymph nodes months after infection (reviewed in [84]) (Fig. 3).

Recently, in one of the most comprehensive analyses to date of SARS-CoV-2 persistence across the body and brain in a diverse autopsy cohort collected in the United States, the authors report that, whereas the most common location in which SARS-CoV-2 RNA tends to linger is the respiratory tract, in more than 50% of the cases the virus was detected also in extrapulmonary tissue, including in the myocardium, lymph nodes and in all sampled

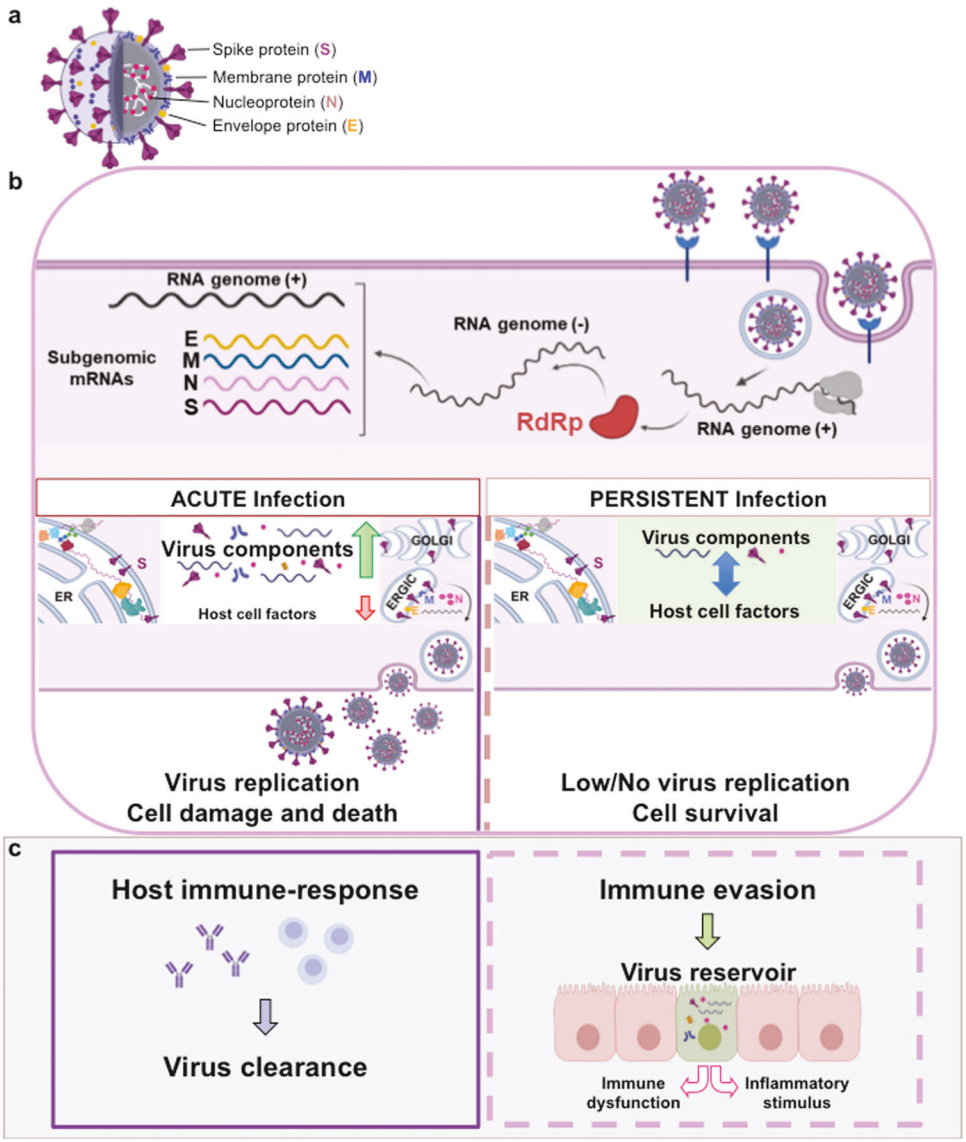

Fig. 3 Schematic representation of SARS-CoV-2 virus infection and its role in PASC. a The SARS-CoV-2 virus lipid bilayer comprising the spike protein (S, violet), the membrane protein (M, blue) and the envelope protein (E, orange), and the viral RNA (white) associated with the nucleocapsid protein (N, pink) are shown. **b** Different steps of SARS-CoV-2 replication cycle are illustrated in the cartoon, including binding to the ACE2 receptor (blue), virus entry, viral RNA replication, sub-genomic RNA transcription and translation, virus assembly, and exit from the host cell. RdRp, RNA-dependent RNA polymerase. ER endoplasmic reticulum, ERGIC ER-Golgi intermediate compartment. During acute infection (right), the virus hijacks the host cell transcriptional/translational machinery to make large amounts of viral proteins and RNA (green arrow), while shutting down cellular protein synthesis (red arrow), resulting in infectious virus progeny production, and host cell damage and death. The host immune-response eventually leads to virus clearance (gray box, **c**). The mechanisms at the basis of virus persistence in the host cell are currently unknown. In the hypothetical model of persistent infection (left) concurrence of molecular and immunological events may allow a metastable equilibrium between SARS-CoV-2 and the host cell (blue arrow), where a virus-directed transcriptional program enables a long-lasting virus-host interaction and cell survival. Evasion of the host immune response may allow the establishment of virus reservoirs (gray box, **c**). In persistently infected cells viral RNA and/or selected viral proteins might act as constant stimuli causing chronic immune system dysregulation and inflammation (**c**, left panel).

areas of the brain, except the dura mater [85]. The data also indicate that SARS-CoV-2 can replicate within different tissues for over 3 months after infection. In some individuals, viral RNA could be detected in multiple compartments for up to 230 days after primary infection [85]. The authors suggest that the persistence of viral genomic and subgenomic RNA may represent infection with defective virus, which has been described in persistent infection with other viruses, including the measles virus.

In addition to autopsy findings, persistence of SARS-CoV-2 RNA was detected in intestinal enterocytes of 5 out of 14 intestinal biopsies obtained from asymptomatic individuals at 4 months after the onset of Covid-19 [86]. Interestingly, a recent study also revealed the presence of virus transcripts and of SARS-CoV-2–infected cells in the olfactory mucosa of patients with long-term persistence of Covid-19–associated anosmia who were negative to nasopharyngeal swab SARS-CoV-2 RNA tests [87].

Persistence of SARS-CoV-2 in some Covid-19 patients is not unexpected. Several studies have shown that coronaviruses are capable of establishing persistent infections in vitro as well as in vivo. Starting from the initial studies on the beta-coronavirus MHV (murine hepatitis virus) that was extensively investigated for its ability to cause persistent infection in the central nervous

system also in primates, in some cases associated with demyelination [88, 89], several studies have shown that persistent infection of FCoV (feline coronavirus) can often occur in cats [90]. Regarding human coronaviruses (HCoV), the ability of establishing persistent infection in cell cultures has been demonstrated for the seasonal coronaviruses HCoV-OC43 and HCoV-229E [91, 92], as well as for the SARS-CoV-2 phylogenetically related SARS-CoV and MERS-CoV [93, 94]. In the case of these two highly pathogenic coronaviruses, it should be noted that a subset of individuals who survived SARS or MERS were reported to experience, in addition to persistent impairment of pulmonary function, protracted neuropsychiatric symptoms, sleep abnormalities, fatigue, myalgias and functional disabilities reminiscent of Long Covid (reviewed in [84]).

In the case of SARS-CoV-2, it has been recently shown that the virus can establish a long-term, non-productive persistent infection in different types of cells [95, 96].

The molecular mechanisms governing the establishment of RNA virus persistent infections have attracted considerable attention, but remain elusive. In the case of SARS-CoV-2, during acute infection the virus hijacks the host cell transcriptional/translational machinery to make large amounts of viral proteins and RNA, while shutting down host messenger RNA translation [97, 98], resulting in infectious virus progeny production and cell death; during persistent infection it is hypothesized that concurrence of molecular and immunological events is required to allow the virus to direct a transcriptional program enabling a long-lasting virus-host interaction, by regulating its replication without killing the host cell and by evading the immune response (Fig. 3). Establishment of SARS-CoV-2 persistent infection has been associated with immunosuppression [99, 100], reduced expression of ribosomal proteins [100] and possible integration of selected SARS-CoV-2 sequences into the genome of infected cells [101].

Another intriguing hypothesis to be considered is that, due to the high cell–cell fusion activity of its spike protein [102, 103], the SARS-CoV-2 virion or some of the virus components may spread through cell–cell contact. This insidious strategy, which is adopted by other RNA viruses, including the respiratory syncytial virus, the measles virus [104] and the human immunodeficiency virus [105], allows the pathogen to spread in a particle-independent way, promoting immune evasion [106]. Cell-to-cell transmission of SARS-CoV-2 has been recently demonstrated in human cells [107].

Contribution of SARS-CoV-2 persistence to PASC pathogenesis is not currently understood, but it could be hypothesized that viral RNA and/or selected viral proteins might act as constant stimuli that maintain an inflammatory condition contributing to pathogenesis until viral clearance is achieved (see above). This possibility is supported by reports of improved clinical symptoms after administration of anti-SARS-CoV-2 vaccines in PASC patients [65].

PROTECTION BY VACCINATION

A preliminary patient-led observational study has suggested that PASC symptoms might be diminished through vaccination [108]. Among 900 people affected by Long Covid, 56.7% of the vaccinated saw an overall improvement, 18.7% a deterioration, and 24.6% were unchanged post-vaccination. A different survey (Covid symptom app study) [109] showed that the odds of experiencing symptoms more than 28 days post-vaccination, were halved by two vaccinations ($n = 906$). It has been suggested that an increased viral clearance and a muted chronic inflammatory response could explain the reduction of symptoms after vaccination [110]. Early evidence was obtained in Israel that childhood vaccination against Covid-19 protects against both, the direct acute and the long-term effects of Covid-19 disease [111].

Three recent studies have investigated the impact of vaccination on PASC following breakthrough infection (BTI). In a large study conducted on the US Department of Veterans Affairs database it was observed that vaccination with a single dose of the Ad26.CoV2.S or two doses of a mRNA vaccine conferred only limited, but significant, protection against Long Covid after BTI [112]. Limitations of this study include the time window of observation (January through October 2021), the low number of females (<10%), the suboptimal vaccine schedule. A longitudinal study involving a carefully controlled hospital personnel cohort conducted in Italy covering the omicron sustained wave in spring 2022 indicated strong protection against PASC after BTI by vaccination with mRNA vaccines [113]. The observation time included the spring 2022 wave and protection was dependent on the number of jabs, requiring two or three shots. Protection by vaccination against PASC after BTI was also observed in a survey on Long Covid [114] conducted in Israel.

Assessment of protection against PASC after BTI poses methodological challenges with limitations which are inherent to longitudinal versus case-control studies, usage of different vaccines or number of jabs, representation of different prevailing virus variants. However, in spite of these limitations, available information obtained using different approaches strongly suggests that full vaccination with mRNA vaccines confers protection against the development of PASC after BTI. The duration of protection and its significance to future variants remains to be defined.

CONCLUDING REMARKS AND PERSPECTIVE

Progress has been made in defining key cardinal aspects of PASC (neurocognitive, cardiorespiratory, fatigue, etc.) and its prevalence, but important aspects remain undefined. These include the actual boundaries of the PASC symptom constellation, its similarity and peculiarities in relation to other viral diseases, its actual frequency and relevance in the pediatric population.

Some of the symptoms and imbalances characteristic of PASC tend to last up to months, but are ultimately going to disappear, although in a minority of patients, anosmia, brain "fog", DPCO, and dyspnea can persist after one year even among young and middle-aged adults after mild acute SARS-CoV-2 infection and impact on general health and working capacity [115–117]. Females showed significantly more neurocognitive symptoms than males. It has been observed that among patients symptomatic after 2 months, 85% still reported symptoms one year after their symptom onset, while evolution of symptoms showed a decreasing prevalence over time for 27/53 symptoms (e.g., loss of taste/smell); a stable prevalence over time for 18/53 symptoms (e.g., dyspnea), and an increasing prevalence over time for 8/53 symptoms (e.g., paresthesia) [118]. Of major concern are the reported increase in incidence, following Covid-19 infection, of Diabetes and cerebrovascular events, notably acute ischemic strokes. In addition, Covid-19 is a risk factor for deep vein thrombosis, pulmonary embolism, and bleeding [119] and coagulopathies (dysfunctions of the blood coagulation system), possibly related to fibrin amyloid microclots [61], that persist long after the initial infection. Alterations (reduction in thickness) of the brain cortex as a sequel of Covid-19 infection was observed in specific areas, mainly related to olfact sensibility, but it is not known if such derangements are going to persist in time. Recent data (May 2022) from Wuhan indicate that Covid-19 survivors still had more prevalent symptoms and more problems in pain or discomfort, as well as anxiety or depression, at 2 years than did controls [120].

Most of the reported observations on the sequels to Covid-19 infections are related to early variants of the virus: we do not know and only time will tell if the now prevailing omicron variants induce similar effects [9, 120]. It is tempting to speculate that the lower intrinsic pathogenicity of omicron and the dramatic impact on disease severity of vaccination will translate in lower risk of PASC at the individual level. Recent results suggest that early omicron variants are associated with approximately a 50% reduction in the risk of developing PASC compared to delta

[121]. However, given the increase in transmission of omicron variants, including children, the potential PASC disease burden at the population/society level should not be underestimated and deserves careful assessment.

Current understanding of pathogenesis is in its infancy. Evidence suggests that persistence of Covid-19, reactivation of other viruses, autoimmunity, and uncontrolled inflammation are major determinants of PASC. Given the diversity of organ involvement and manifestations, it is tempting to speculate that the relative importance of pathogenic mechanisms may vary in different tissue and organ contexts. A better understanding of the PASC disease spectrum and underlying mechanisms may pave the way to better prevention and therapeutic strategies. It is reasonable to assume that prevention via vaccination and early treatment of the acute phase of Covid-19 represent invaluable assets to address the challenge of PASC at the level of individuals and society.

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GB and AM coordinated the design and finalization of the review. MCM, CP, MGS, SS, and GR contributed to specific sections of the review. In particular MGS was responsible for the virological part of the review.

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

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ON BEHALF OF THE COVID-19 COMMISSION OF THE ACCADEMIA NAZIONALE DEI LINCEI

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Unavoidable Pressure Injury during COVID-19 Pandemic:

A Position Paper from the National Pressure Injury Advisory Panel

The purposes of this National Pressure Injury Advisory Panel (NPIAP) Position Paper are to:

1. Summarize the current NPIAP position regarding unavoidable pressure injuries.
2. Examine the effects of the COVID-19 crisis on the scope of what is considered an unavoidable pressure injury.
3. State the position of the NPIAP regarding determinations of unavoidable pressure injuries during the COVID-19 crisis.
4. Renew the NPIAP call to collaborate on the development of criteria for the determination of unavoidable pressure injuries in acute care.

Background

The initial definitions of *avoidable and unavoidable pressure ulcers* originated from The Centers for Medicaid and Medicare Services (CMS) as part of its inspection of long-term care facilities. *Avoidable pressure injury* has been defined by CMS as those pressure injuries that develop in [patients] for whom the [healthcare provider(s)] did not do one or more of the following: [properly] evaluate the [patient's] clinical condition and pressure injury risk factors; define and implement interventions that were consistent with [patient's] needs, goals for care, and recognized standards of practice; monitor and evaluate the outcome of the interventions; and/or revise the interventions as appropriate.[1] *Unavoidable pressure injury* occurs when the [healthcare provider(s)] "had [properly] evaluated the [patient's] clinical condition and pressure injury risk factors; defined and implemented interventions that were consistent with the [patient's] needs, goals, and recognized standards of practice; monitored and evaluated the outcome of the interventions; and/or revised the approaches as appropriate" and a pressure injury developed despite reasonable care.[1]

In 2010, National Pressure Injury Advisory Panel (NPIAP)[a] expanded the clinical circumstances it included in the consideration of the formation of pressure injury deemed unavoidable to include situations in acute care that rendered the delivery of pressure injury prevention clinically unsafe. Unsafe clinical situations are those in which harm may come to the patient by doing the preventive care, particularly turning and repositioning. Clinical situations involving cognitively intact patients' refusal of preventive care (despite counseling of the risks of refusal) were also addressed.[2]

In 2014, NPIAP addressed how comorbid conditions can contribute to an unavoidable pressure injury.[3] Many comorbid conditions (e.g., peripheral vascular disease, shock states) constitute risk factors for

[a]Previously the National Pressure Ulcer Advisory Panel (NPUAP)

pressure injury development that are either non-modifiable or extremely difficult to modify. In some cases, treatments designed to stabilize physiologically unstable patients may add to pressure injury risk (e.g., vasopressors, medical devices). NPIAP concluded that some cases of pressure injury are unavoidable because the magnitude and severity of risk are overpoweringly high and/or preventive measures are either contraindicated or inadequate to overcome the magnitude and severity of non-modifiable risk.

The magnitude and severity of non-modifiable risk factors can undoubtedly play a major role in pressure injury outcomes but should not be the sole determinant of unavoidability. Any determination of unavoidability requires an honest and thorough review of the documentation, the appropriateness and the adequacy of the evidence-based preventive measures[4] that were implemented.

Unavoidable pressure injuries have long been recognized in long-term care settings. However, there has never been a mechanism for determining unavoidability of pressure injuries in acute care. Establishing the criteria applicable in acute care settings for determining whether a pressure injury is unavoidable is long overdue and has become a critical priority in the current environment of the COVID-19 pandemic.

During the COVID-19 Pandemic

The COVID-19 crisis has dramatically changed significant aspects of pressure injury prevention in acute care hospitals. The first aspect focuses on the intrinsic condition of the patient and the second aspect addresses the extrinsic conditions in the environment of care.

Intrinsic Factors

1. The virus itself creates a systemic coagulopathy including hypercoagulation and microvascular occlusion which has led to ischemic stroke, myocardial infarction, venous thromboembolism, acute limb ischemia and pulmonary embolism.[5-9] While the overall mechanism of this hypercoagulable state is still not completely understood at this time, it does involve the skin. The changes in the skin with COVID-19 have been addressed by NPIAP in a separate paper.[10] These skin changes appear purpuric and quickly become necrotic. They mimic the appearance of deep tissue pressure injury (DTPI), especially when they occur over tissue exposed to pressure and/or shear stress (e.g., sacrum, buttocks, heels) or under medical devices. If the vessels are significantly or fully occluded, then adequate reperfusion is not achievable even in the presence of reasonable repositioning and turning of the patient and the use of appropriate support surfaces. In addition, there are reports of true pressure injuries that underwent rapid deterioration presumably from microvascular thrombosis caused by the COVID-19 virus, although the full pathophysiology of their rapid deterioration is yet to be identified.

   The NPIAP's evolving understanding of the pathophysiology of COVID-19 leads to these conclusions:

   - Purple skin discoloration on tissue not exposed to pressure and/or shear stress are not pressure injuries; In patients with COVID-19, a differential diagnosis should include consideration of whether these areas were precipitated by the virus and should be more accurately characterized as COVID-19 skin manifestations, and
   - The microvascular occlusions of COVID-19 on tissue exposed to pressure and/or shear stress may increase the magnitude and severity of non-modifiable risk to a level that is unable to be overcome even with reasonable efforts at pressure injury prevention.

2. During COVID-19 infection, microvascular occlusion also impairs other organs contributing to multiple organ dysfunction. Multiple organ dysfunction may be the result of various other pathophysiologic mechanisms in critically ill patients; however, COVID-19-initiated microvascular occlusion probably exacerbates this process. Additionally, the attempt to provide more optimal functioning for one organ often predisposes another organ to dysfunction. The effect of treatment for the lungs on the kidneys is an example. While the pathologic relationship between these two organs occurs for various reasons,[12-13] one particular issue is the fluid overload in the lungs due to inflammatory responses. In attempts to reduce the fluid overload and improve oxygenation, fluids are restricted rather than balanced and lead to compromised renal function due to restricted fluid volume. Ultimately, the skin as an organ is affected by fluid shifting that may be the result of other organs trying to obtain homeostasis. In particular, a state of interstitial fluid overload (edema) can deprive the skin of adequate circulation and the needed nutrients, thus diminishing the skin's ability to protect and be more resilient to injuries and trauma including pressure injury formation.[4]

3. Nutrition is paramount to the prevention of pressure injuries[4] and has a significant role in the critically ill. It is well known that infections, such as COVID-19, lead to a hypermetabolic state and place patients at a higher risk of nutritional deficiency.[13] Of particular importance is the need for increased protein intake, either via oral nutritional supplements or enteral/parenteral nutrition.[14-16] As a result, it is recommended that patients should be started on enteral nutrition within 12 hours of intubation or 24-36 hours after admission to critical care if the patient is hemodynamically stable.[17-18] However, many COVID-19 patients arrive at the hospital in acute respiratory distress requiring immediate intubation or rapidly deteriorate into hemodynamic instability after admission, and therefore, the provision of nutrition is necessarily delayed. Also problematic to nutritional support is the need to place the patient in the prone position to improve ventilation and perfusion. Patients in the prone position often receive large amounts of sedation and paralytic agents which slow digestive function. This results in decreased absorption of nutrients and occasional holding of enteral feedings due to large residual volumes of formula in the stomach and risk of aspiration. Another issue in tube fed patients is the development of diarrhea which can damage the skin, create incontinence associated dermatitis (IAD), and further increase the risk for pressure injury. Some patients ultimately require fecal incontinence devices which can lead to medical device related pressure injury in the perineum and anus. Shortages of enteral feeding pumps/tubing also created challenges with the delivery of continuous tube feedings, which lead to the need for alternative feeding methods such as bolus feedings in some clinical settings.

4. In the context of the critically ill COVID-19 patient, there is a greater potential of being unable to safely turn the patient due to the profound hypoxia and/or hemodynamic instability. Turning critically ill patients from side-to-side is within the standard of care when it can be done without causing harm to the patient. For example, in certain situations it is not only challenging but sometimes not possible to reach an angle allowing adequate reperfusion of skin and soft tissue while maintaining adequate oxygenation, hemodynamic status and a safe airway for patients. For the COVID-19 patient with acute respiratory distress syndrome, prone positioning is often used for many hours and/or days and "turning" is limited to microshifts and changing the position of the head, arms and upper body according to "swimmer position" protocols.[19]

5. Survivors of severe cases of COVID-19 often undergo prolonged recoveries of weeks to months. These patients are often malnourished, severely debilitated or chronically critically ill and require intensive care and rehabilitation. The risk of pressure injuries remains high and continued vigilance in pressure injury prevention is required, particularly in relation to device related injuries from tracheostomy tubes, feeding tubes and oxygen delivery devices.

Extrinsic Factors

1. The standard of care for critically ill patients includes support surfaces designed to redistribute pressure, reduce shear forces and manage humidity on the skin and soft tissues. Support surfaces that offer pressure redistribution and humidity management, such as alternating pressure and low air loss, aide in keeping the skin intact during times when the patient cannot be safely turned or repositioned. The unique complexities of the COVID-19 patient, combined with the rapid volume of their admissions outpacing the available critical care support surfaces, places the COVID-19 patient at heightened risk for the development of unavoidable pressure injury.

2. As the COVID-19 pandemic peaked in various "hotspots" throughout the country, hospitals were forced to change and change rapidly. As discussed throughout this position paper, there was an overwhelming influx of patients admitted with COVID-19 that inundated our hospitals and depleted the equipment that would customarily be available for patient care. This included everything from support surfaces to tube feeding systems. In certain situations, the high volume of patients required repurposing the general patient care units, that previously had no need for support surfaces used for the critically ill, and the influx of patients across the country limited the availability of obtaining any upgraded support surfaces. Patients placed in these repurposed units were often necessarily placed on support surfaces designed for lower risk patients despite their heightened risk due to COVID-19. Unfortunately, in certain situations, the equipment supply was so strained and volume of patients so high, that some patients had to be placed on a gurney or medical cot.

3. The unprecedented need to supplement staffing with nurses from other specialties as well as agency and travelling nurses further contributed to care challenges. Hospitals were also left with little to no information about training the staff on COVID-19, and they had limited time for cross-training on what was known, such as the critical care competencies of ventilator management, vasopressor titration, and pressure injury prevention with limited equipment and prone positioning.

4. The COVID-19 crisis also forced providers into unknown territory and crisis care mode. At the onset of the COVID-19 pandemic, providers were not able to access evidence-based guidelines; there were no studies on COVID-19 pathophysiology or treatment; there was little known about prevention and no known cure. While treating COVID-19, providers themselves were at risk of acquiring the virus. Health care workers have also experienced moral distress, anxiety, sleeplessness, and other emotional responses because of battling an unknown disease without the supplies, time, and information they normally would have had to combat a known disease process. The lack of information about this rapidly evolving disease process amplified the already complex care of these critically ill patients. The complex care needed by many, many patients combined with resource and personnel shortages and

the emotional toll faced by these health care providers inevitably and understandably affected the ability to prevent skin injury.

Nurses have a time-honored duty to implement evidence-based practices at the bedside, but this duty depends on the expectation that their health systems are adequately prepared to supply the materials and resources that support these practices. The overwhelming time commitment to handle COVID-19 patient surges in combination with the distraction from fundamental practices and the lack of resources to support the care of these acute patients' needs or best practices has resulted in an abnormal level of moral distress for many healthcare providers. "Moral outrage" emerged as the crisis continued without adequate material and personnel support to ensure patient needs (and professional standards designed to address those needs) were being met. This moral outrage is distracting to pressure injury prevention as it comes in direct competition with basic support and resources necessary for caregivers to provide appropriate evidence-based practice.[20]

Position Statements

Although the NPIAP does not consider this time the "new normal," we need to recognize that the preventive measures possible in pre-COVID-19 times may not have been feasible in the middle of the COVID-19 crisis. Pressure injury prevention was challenged during the early part of the COVID-19 crisis in some hotspots and the demand for appropriate equipment (support surfaces, mattresses, heel offloading devices, pressure redistribution cushions and positioners) and the skin and wound care products required may have been difficult to obtain. Additionally**,** despite reasonable attempts made to incorporate prevention strategies into the critically ill COVID-19 patient's care, the COVID-19 crisis rendered some of them impossible to achieve and pressure injury formation was unavoidable. Our hope is that we have learned from our experiences and can be better prepared for future waves of COVID-19 with better information, improved equipment, and adequate quantities of equipment, supplies and personnel to maximize our ability to prevent pressure injury formation in future COVID-19 patients.

The NPIAP takes the following positions on the development of pressure injury during COVID-19 crisis situations.

1. Before any decision is made about the avoidability or unavoidability of a pressure injury that developed during the COVID-19 crisis, all factors should be considered on a case-by-case basis, including both the intrinsic issues in the critically ill patient and the extrinsic issues in the health care facility at the time of the injury.
2. Before labeling purpuric skin manifestations in COVID-19 patients, consider that the skin manifestations of COVID-19 may mimic the appearance of pressure injuries and should be considered in the differential diagnosis.
3. Areas of skin discoloration or tissue injury on non-loaded anatomic locations (i.e. no history of pressure and/or shear stress, no use of a medical device) are most likely not pressure injuries.
4. When pressure injuries occur on anatomical locations likely subjected to pressure and/or shear stress in patients with COVID-19, the pressure injury may be unavoidable IF:
    a. Microvascular occlusions from COVID-19 increased the magnitude and severity of non-modifiable risk to a level that preventive interventions were not able to be overcome despite reasonable efforts at prevention;

b. Multiorgan dysfunction issues from critical illness ultimately affected the skin's normal abilities to protect the body and remain resilient to injuries and trauma including pressure injuries; and,
c. All reasonable efforts to provide evidence-based preventive care were attempted within the context of a health care system determined to be at crisis capacity.

Conclusions

The NPIAP remains fully committed to its mission to improve patient outcomes in pressure injury prevention and management through education, public policy, and research. Every reasonable effort should be taken to prevent pressure injuries. The mere diagnosis of COVID-19 does not make a pressure injury inevitable or unavoidable. However, some pressure injuries are unavoidable. Intrinsic factors with the COVID-19 virus pathophysiology and extrinsic factors during the COVID-19 pandemic associated with its propensity to overwhelm health care systems should be taken into consideration when determining whether a pressure injury was unavoidable. It is imperative that we prepare for future pandemics with adequate supplies of functioning equipment, supply chain management to ensure timely and appropriate distribution of supplies[21-22] and pressure injury prevention protocols designed to be effective in crisis situations. Criteria for unavoidable pressure injury determinations require clarification for all patients with pressure injuries, whether or not they are affected by the COVID-19 crisis.

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Disclaimers

This document is intended for educational and informational purposes only. It does not constitute medical advice. Follow institutional policies, manufacturer recommendations and principles of sound clinical judgment.

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REVIEW ARTICLE

DERMATOLOGIC THERAPY WILEY

Oral manifestations of COVID-19 disease: A review article

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Abstract

Dysgeusia is the first recognized oral symptom of novel coronavirus disease (COVID-19). In this review article, we described oral lesions of COVID-19 patients. We searched PubMed library and Google Scholar for published literature since December 2019 until September 2020. Finally, we selected 35 articles including case reports, case series and letters to editor. Oral manifestations included ulcer, erosion, bulla, vesicle, pustule, fissured or depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, hemorrhagic crust, necrosis, petechiae, swelling, erythema, and spontaneous bleeding. The most common sites of involvement in descending order were tongue (38%), labial mucosa (26%), and palate (22%). Suggested diagnoses of the lesions were aphthous stomatitis, herpetiform lesions, candidiasis, vasculitis, Kawasaki-like, EM-like, mucositis, drug eruption, necrotizing periodontal disease, angina bullosa-like, angular cheilitis, atypical Sweet syndrome, and Melkerson-Rosenthal syndrome. Oral lesions were symptomatic in 68% of the cases. Oral lesions were nearly equal in both genders (49% female and 51% male). Patients with older age and higher severity of COVID-19 disease had more widespread and sever oral lesions. Lack of oral hygiene, opportunistic infections, stress, immunosuppression, vasculitis, and hyper-inflammatory response secondary to COVID-19 are the most important predisposing factors for onset of oral lesions in COVID-19 patients.

KEYWORDS
aphthous, COVID-19, gingivostomatitis, manifestation, oral

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-chain RNA virus that is the cause of novel coronavirus disease known as COVID-19. The most common clinical symptoms are fever, headache, sore throat, dyspnea, dry cough, abdominal pain, vomiting, and diarrhea. Angiotensin converting enzyme 2 (ACE 2) receptor is a known receptor for SARS-CoV-2 that is found in the lung, liver, kidney, gastrointestinal (GI) and even on the epithelial surfaces of sweet glands and on the endothelia of dermal papillary vessels. Todate, various cutaneous manifestations of COVID-19 disease have been described including varicelliform lesions, pseudochilblain, erythema multiforme (EM)-liker lesions, urticaria form, maculopapular, petechiae and purpura, mottling, and livedo reticularis-like lesions.[1,2]

At the beginning of COVID-19 pandemic, it was assumed that lack of oral involvement is a differentiating feature of COVID-19 exanthema relative to other viral exanthemas. Recently, SARS-CoV-2 has been detected from saliva of the patients and it has been demonstrated that reverse transcriptase-polymerase chain reaction (RT-PCR) from saliva can even be a more sensitive test in comparison with nasopharyngeal test. Furthermore, ACE2 has been found in oral mucosa, especially with more density on dorsum of tongue and salivary glands relative to buccal mucosa or palates. To date, there is only one systematic review that described oral manifestations of COVID-19 disease; however, it mostly focused on impairment of taste. Dysgeusia is the first recognized oral symptom of COVID-19 reported in 38% of patients, mostly in North Americans and Europeans, females, and patients with mild-moderate disease severity.[1] In this review article, we described oral lesions of COVID-19 patients.

TABLE 1 Clinical and laboratory characteristics of patients with oral manifestations

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Verdoni[28]	7/5 (2/9-16)Y	M = 7 F = 3	–	MP Acral swelling	NA	–	Lip Oral cavity (80%)	–	Fever Diarrhea Conjunctivitis Meningeal sign lymphadenopathy		20% + (PCR) 80% (IgG) 30% (IgM)	Kawasaki-like	–	–
Jones[29]	6 M	F	–	MP Acral swelling	Cracked lip Prominent papilla in tongue	–	Lip Tongue	–	Fever Conjunctivitis Tachypnea	2	+ (PCR)	Kawasaki-like	IVIG ASA	Increased levels of CRP, ESR Hypoalbuminemia
Pouletty[30]	10 (4/7-12/5)Y	M = 8 F = 8	Over weight Asthma	Rash	Cracked lip (87%)	–	Lip	–	Fever Respiratory & GI symptom Anosmia	–	69% + (PCR)	Kawasaki-like	IVIG CS ANTI IL1, IL6 HCH	Increased levels of cardiac markers Increased levels of CRP, ESR Lymphocytopenia
Singh[19]	44Y	M	DM HTN	Non blanch able erythema Necrosis	Extensive mucosal damage	–	Lip Tongue	–	Malaise Dyspnea	4		Vascular inflammation Ischemic reperfusion injury		
Chiotos[31]	5Y	F	–		Fissured lip	–	Lip	–	Fever Diarrhea Conjunctivitis	–		Kawasaki-like	IVIG	Thrombocytopenia Increased levels of cardiac marker
Chiotos[31]	9Y	F	–	–	Fissured lip Straw berry tongue	–	Lip Tongue	–	Fever Diarrhea Conjunctivitis	–	+ (PCR)	Kawasaki-like	IVIG ASA CS	Increased levels of CRP, ESR
Chiotos[31]	12Y	M	–	–	Fissured lip	–	Lip	–	Fever Abdominal pain Diarrhea	–	(–) (PCR)	Kawasaki like	IVIG Milrinone	Increased levels of Cardiac marker Increased levels of CRP, ESR
Chiu[32]	10Y	M	–	–	Cracked lip Erythema	–	Lip Oropharynx	–	Fever Cough Diarrhea Conjunctivitis	–	+ (PCR)	Kawasaki-like	Dopamine	Leukocytosis Lymphocytopenia Increased levels of CRP, ESR, D-dimer, Procalcitonin Increased levels of Cardiac markers
Mazzotta[26]	9Y	M	–	Urticaria Angioedema Acral edema	Glossitis Cheilitis	Painful	–	–	Fever Cough Diarrhea Conjunctivitis	28-84	+ (Ig G)	Kawasaki-like	CS	–

TABLE 1 (Continued)

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Indu[13]	NS	M	–	–	Ulcer	Burning Itching Painful	Lip Tongue	10	Fever	–4	+ (PCR)	Zosteriform	–	–
Taşkın[25]	61Y	F	–	Nodules	Minor aphthous ulcer	–	Hard palate Buccal	–	Fever Fatigue Myalgia Arthralgia	–	+ (PCR)	Atypical Sweet syndrome	AZT HCH Oseltamivir Tocilizomab Favipiravir	Increased levels of CRP, ESR, D-dimer Leukocytosis
Taşlıdere[24]	51Y	F	–	–	Swollen lip Fissured tongue	–	Lip Tongue	–	Malaise Unilateral Facial paralysis Facial edema	Coincident	–	MRS	HCH AZT CS	Increased levels of CRP Negative Serology for HSV, CMV,EBV, coxsackie Ground glass opacity in CT scan
Brandão[7]	28Y	M	–	–	Aphthous-like Ageusia	–	Lip Tongue	6	Fever Cough Headache Myalgia Chills Anosmia	8	+ (PCR)	–	Mouthwash	–
Brandão[7]	29Y	M	–	–	Aphthous-like Ageusia	Painful	Tongue	5	Cough Dyspnea Fever Malaise Headache Anosmia	8	+ (PCR)	–	Ipratropium bromide Fenoterol hydrochloride	–
Brandão[7]	35Y	M	–	–	Aphthous-like	–	Tonsil	8	Fever Malaise Sore throat Cough Hyposmia Ageusia Odynophagia	6	+ (PCR)	–	–	–
Brandão[7]	32Y	F	–	–	Aphthous -like	–	Tongue	5	Dysgeusia Fever Cough Headache Anosmia	10	+ (PCR)	–	Dipyrone	–

(Continues)

TABLE 1 (Continued)

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Brandão[7]	72Y	M	HTN DM	–	Aphthous-like Necrosis Hemorrhagic ulcer	painful	Lip	7	Fever Dyspnea	5	+ (PCR)	–	P/T AZT Ceftriaxone Acyclovir PBM	Increased levels of CRP Lymphocytopenia Positive PCR for HSV
Brandão[7]	83Y	F	HTN COPD Obesity Parkinson Pancreatitis	–	Aphthous-like Petechiae Necrosis	painful	Tongue Hard palate	5	–	2	+ (PCR)	–	Ceftriaxone PBMT P/T	Negative PCR for HSV Lymphocytopenia
Brandão[7]	71Y	F	HTN DM CRF Obesity	–	Aphthous-like Hemorrhagic necrosis Ulcer	painful	Tongue Lip	15	Fever Cough Dyspnea	4	+ (PCR	–	AZT Ceftriaxone Acyclovir PBMT	Positive PCR for HSV
Brandão[7]	81Y	M	HTN COPD	–	Aphthous-like Necrosis Hemorrhagic ulcer	painful	Lip Tongue	11	Dry Cough Dyspnea Fever Chills Dysgeusia	5	+ (PCR)	–	AZT Ceftriaxone Acyclovir PBMT	Increased levels of CRP Ground glass opacity in CT scan Positive PCR for HSV
Malih[8]	38Y	M	–	MP	Erythema Aphthous-like	Painful	tonsil	–	Fever Fatigue Myalgia Loss of taste and smell	3	+ (PCR)	–	Acetaminophen	–
Labé[22]	3Y	M	–	Exanthema Palmar edema	Cheilitis Glossitis Stomatitis	–	Lip Tongue Oral cavity	–	Fever Asthenia Cervical LAP	–	–	Kawasaki-like	IVIG	Increased levels of CRP Leukocytosis Ground glass opacity in CT scan
Labé[22]	6Y	M	–	Target lesions	Erosion Cheilitis Hemorrhagic crust	painful	Lip Gingiva	21	Loss of appetite	7	+ (PCR)	EM like	–	Negative serology for mycoplasma Negative PCR for HSV
Aghazadeh[9]	9Y	F	–	Papule Plaque	Vesicles Erosions	–	Lip Tongue Buccal	7	Fever Weakness Loss of appetite Abdominal pain Diarrhea	Coincident	+ (PCR)	Herpetiform	Acetaminophen	Bilateral ground glass opacity

TABLE 1 (Continued)

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Kämmerer[10]	46Y	M	HLP CAD	–	Multiple ulceration covered by yellow gray membrane	Painful	Oral cavity Gingiva	–	Fever Fatigue Dry cough Respiratory distress LAP submandibular	5 days after intubation	+ (PCR)	Secondary herpetic Gingivostomatitis	AZT Meropenem Acyclovir	Increased levels of CRP, IL6, Eosinopenia Positive PCR for HSV Positive serology for HSV(IgM) Bilateral ground glass opacity in CT scan
Cruz Tapia[23]	42Y	M	_	_	Macules	Burning	Hard palate	7	Fever Malaise Dysgeusia Headache	14	+ (PCR)	Mucositis due to vasculitis and thrombosis	Acetaminophen Mouthwash CS	_
Cruz Tapia[23]	55Y	F	–	–	Tongue enlargement Purple blister	–	Tongue	5	Fever Headache Nasal congestion	2	+ (PCR)	Angina bullosa-like	Acetaminophen	–
Cruz Tapia[23]	51Y	F	HTN	_	Vascular-like purple macule nonbleeding Purple plaque	–	Palate	–	Fever Malaise Dysgeusia Arthralgia	–	+ (PCR)	Vascular disorder	CS AZT NSAID	–
Cruz Tapia[23]	41Y	F	_	_	Erythematous blister	–	Hard palate	–	Fever Malaise *Dysgeusia* Hyposmia	–	+ (PCR)	Angina-bullosa-like	Acetaminophen Fexofenadine	–
Díaz Rodríguez[6]	78Y	F	–	–	Dry mouth Atrophy of surface of tongue White & red patches Fissured tongue		Tongue Hard Palate Soft palate Lip	15	–	–	+ (PCR)	Pseudomembranous candidiasis Angular cheilitis due to Stress Immunosuppression	Artificial saliva Nystatin Neomycin CS	–
Díaz Rodríguez[6]	53Y	M	–	–	Angular cheilitis	Burning	Lip	10	Dysgeusia Anosmia	Few days after discharge	+ (PCR)	Cheilitis due to stress and immunosuppression	Nystatin CS Neomycin, Mouthwash	–
Díaz Rodríguez[6]	43Y	F	–	–	Multiple ulcer covered by yellow-gray membrane Lingual depapillation	Burning	Tongue	10	Fever Malaise Dysgeusia Anosmia Diarrhea Pneumonia	14	+ (PCR)	Aphthous-like due to stress and immunosuppression	Mouthwash CS	–

(Continues)

TABLE 1 (Continued)

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Chérif[27]	35Y	F	–	Macule	Chapped lips Ulcer *Hypogeusia*	–	Tongue Lip	10	Fever Myalgia Dyspnea Dry cough Vomiting Diarrhea	–	+ (PCR)	Kawasaki-like	HCH AZT Cefuroxime	Thrombocytopenia Anemia Neutrophilia Lymphopenia Increased levels of liver and cardiac markers Increased levels of CRP,LDH, ferritin
Ansari[18]	75Y	M	HTN	–	Irregular ulcer in erythematous background	Painful	Tongue (anterior)	7	Hypoxia	7	+ (PCR)	Mucosal ulcer due to COVID-19	AZT, Mouthwash	Negative Serology for HSV 1-2
Ansari[18]	56Y	F	DM	–	Irregular ulcer in erythematous background	Painful	Hard palate	7	Fever Dyspnea	4	+ (PCR)	Mucosal ulcer due to COVID-19	Remidisivir AZT	Negative Serology for HSV 1–2
Biadsee[3]	36.25Y	NS	HTN DM Hypothyroidism Asthma	–	Plaque bleeding Swelling Xerostomia Dysgeusia	–	Tongue Palate Gingiva		Fever Cough Myalgia Sore throat Anosmia GI symptoms	–	+ (PCR)	–	–	–
Olisova[11]	12Y	F	–	Purpura Macule	Swollen, Irritated Pronounced lingual papilla	–	Tongue	3	Fever Fatigue Headache	3	+ (PCR)	–	Paracetamol	Increased levels of ESR CRP
Tomo[36]	37Y	F	–	–	Erythema Depapillation of tongue	Painful	Tongue (border)	14	Fever Asthenia Dysgeusia Anosmia	9	+ (PCR)	Mucositis due to hypersensitivity to SARS-CoV-2	CS Dipyrone Mouthwash	–
Ciccarese[17]	19Y	F	–	Macules Papules Petechiae	Erosion Ulcer Hemorrhagic crust Petechial	–	Lip Palatal Gingival Oropharynx	5	Fever Fatigue Hyposmia Sore throat	7	+ (PCR)	Thrombocytopenia due to COVIDS-19 and cefixime	IVIG CS	Thrombocytopenia Leukocytosis Increased levels of liver markers and LDH
Sakaida[16]	52Y	F	–	MP Petechiae	Erosion	–	Lip Buccal	–	Fever Dyspnea Dry cough	–3	+ (PCR)	Drug eruption	NSAID Clarithromycin SAM Levofloxacin Cs	Leukocytosis Lymphopenia Neutrophilia Increased level of CRP

TABLE 1 (Continued)

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Dominguez-Santas[37]	19Y	M	–	–	Minor aphthous	–	Lip	–	Fever Headach Anosmia Malaise dyspnea	0	+ (PCR)	Cytokine storm due to COVID-19	–	Lymphocytopenia Negative PCR for HSV Negative serology for syphilis, HIV, EBV, CMV, HBV, HCV
Dominguez-Santas[37]	37Y	M	–	–	Minor aphthous	–	Tongue	–	–	5	+ (PCR)	Cytokine storm due to COVID-19	–	Lymphocytopenia Negative PCR for HSV Negative serology for syphilis, HIV, EBV, CMV, HBV, HCV
Dominguez-Santas[37]	33Y	M	–	–	Minor aphthous	–	Mucogingivl junction	–	Pneumonia Fever Malaise	3	+ (PCR)	Cytokine storm due to COVID-19	–	Lymphocytopenia Negative PCR for HSV Negative serology for syphilis, HIV, EBV, CMV, HBV, HCV
Dominguez-Santas[37]	43Y	F	–	–	Minor aphthous	–	Buccal	–	Bilateral pneumonia Fever Malaise	4	+ (PCR)	Cytokine storm due to COVID-19	–	Lymphocytopenia Negative PCR for HSV Negative serology for syphilis, HIV, EBV, CMV, HBV, HCV
Putra[5]	29Y	M	_	Papule	Aphthous Stomatitis	–	–	–	Fever Myalgia sore throat Dry cough	6	+ (PCR)	Enanthema due to COVID-19	Paracetamol AZT HCH Oseltamivir Vitamin C Vitamin D	Increase level of CRP
Martín Carreras-Presas[12]	65Y	F	HTN Obesity	Rash	Desquamative gingivitis	Painful	Tongue Gingiva	28	Fever Diarrhea	25	+ (serology)	EM-like	Antibiotic CS HCH HA L/R	–

(Continues)

TABLE 1 (Continued)

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Martín Carreras-Presas[12]	58Y	M	DM HTN	–	Unilateral multiple small ulcers	Painful	Palate	7	–	–	–	Herpetiform	Mouthwash	–
Martín Carreras-Presas[12]	56Y	M	–	–	Dysgeusia, Herpetiform Stomatitis	Painful	Hard Palate	10	Fever Asthenia LAP	2	NP	Herpetiform	Val acyclovir Mouthwash HA	–
Jimenez-Cauhe[21]	60Y	M = 2 F = 4	–	EM-like	Macule Petechiae	–	Palate	–	–	19		Enanthema due to COVID-19	AZT HCH L/R	
Jimenez-Cauhe[21]	40Y			Purpura EM-like	Petechiae Macule Petechiae	–	Palate Palate	–	–	2 24	–	Enanthema due to COVID-19 Enanthema due to COVID-19	L/R HCH AZT T CS L/R HCH AZT Tocilizomab CS	Thrombocytopenia High D-dimer High D-dimer
Jimenez-Cauhe[21]	50Y													
Jimenez-Cauhe[21]	60Y		–	EM-like	Macule Petechiae	–	Palate	–	–	19	+ (PCR)	Enanthema due to COVID-19	L/R HCH AZT	High D-dimer
Jimenez-Cauhe[21]	60Y		–	Papule Vesicle	Petechiae	–	Palate	–	–	–2	+ (PCR)	Enanthema due to COVID-19	L/R HCH AZT	High D-dimer
Jimenez-Cauhe[21]	40Y		–	purpura	Macule	–	Palate	–	–	12	+ (PCR)	Enanthema due to COVID-19	L/R HCH	Thrombocytopenia High D-dimer
Patel[33]	35Y	F	_	_	Bleeding Halitosis Generalized edematous erythematous gingiva Necrosis	Painful	Gingiva	5	Fever LAP submandibular	3	NP	Bacterial co-infection	Metronidazole Mouthwash	_
Chaux-Bodard[14]	45 Y	F	-	Patch	Ulcer	Painful	Tongue (dorsal)	10	Asthenia	–	+ (PCR)	Vasculitis	–	–

TABLE 1 (Continued)

First name author	Age	Sex	Underlying disease	Cutaneous	Oral	Oral Symptom	Site	Duration (days)	Systemic manifestations	Latency (days)	COVID-19	Suggested etiology	Treatment	Lab tests
Soares[15]	42Y	M	DM HTN	Petechiae Vesicle Blister	Ulcer Macules	Painful	Buccal Tongue Lip Hard Palate	21	Fever Cough Dyspnea	–	+ (PCR)	Thrombotic vasculopathy due to SARS –CoV-2	CS Dipyrone	IHC: negative for other viral and trepnema palladium
dos Santos[4]	67Y	M	CAD HTN PCK RT	–	White plaque Multiple yellowish ulcer Geographic tongue Erythema Hypogeusia	–	Tongue Palate Tonsil	14	Fever Diarrhea Dyspnea	24	+ (PCR)	Herpetiform lesions secondary to determination of systemic health and treatment	Mouthwash Fluconazole Nystatin AZT Ceftriaxone HCH Meropenem T/S	Positive Culture for *+Saccharomyces cerevisiae*
Corchuelo[20]	40Y	F	–	–	Petechiae Whitish area Brown pigmentation	Painful	Tongue Lip Gingiva	20	LAP of neck	–	+ (IgG)	Candidiasis Thrombocytopenia due to ibuprofen PIH	Ibuprofen Vitamin D AZT Mouthwash Nystatin	–
Jimenez-Cauhe[35]	66.7(58-77)Y	F = 3	_	EM-like	Petechiae Macule	–	Palate	14-21	_	19.5 (16-24)	_	EM-Like	AZT Ceftriaxone Cs HCH L/R	Increase levels of CRP High D-dimer Lymphocytopenia Negative serology for syphilis, M. Pneumonia and other viral
Cebeci Kahraman[34]	51Y	M	_	_	Large erythematous Petechiae Pustules	Painful	Hard palate Oropharynx Soft palate Ageusia	A few days	Fever Fatigue Dry cough Sore throat Anosmia	10	+ (IgM)	Enanthema due to COVID-19	Clarithromycin	–

Abbreviations: AZT, azithromycin; CAD, chronic arterial disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; DM, diabetes mellitus; HCH, hydroxychloroquine; HLP, hyperlipidemia; HTN, hypertension; L/EX, lower extremity; M, month; MP, maculopapular; MRS, Melkersson-Rosenthal syndrome; P/T, piperacillin/tazobactam; PCK, poly cystic kidney; PIH, postinflammatory hyperpigmentation; RT, renal transplantation; SAM, ampicillin sulbactam; T/S, trimethoprim/sulfamethoxazole; Y, year.

2 | METHODS

We searched PubMed library and Google Scholar for published literature using keywords "COVID-19" or "SARS-CoV-2" or "coronavirus disease 2019" AND "oral" OR "buccal mucosa" in the abstract or title since December 2019 until September 2020. We also searched related articles in the reference lists of the found articles. Finally, we selected 35 articles after deletion of non-English literature and opinion articles.

3 | RESULTS

Oral manifestations included ulcer, erosion, bulla, vesicle, pustule, fissured or depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, hemorrhagic crust, necrosis, petechiae, swelling, erythema, and spontaneous bleeding. The most common sites of involvement in descending order were tongue (38%), labial mucosa (26%), palate (22%), gingiva (8%), buccal mucosa (5%), oropharynx (4%), and tonsil (1%). Suggested diagnoses of the lesions were aphthous stomatitis, herpetiform lesions, candidiasis, vasculitis, Kawasaki-like, EM-like, mucositis, drug eruption, necrotizing periodontal disease, angina bullosa-like, angular cheilitis, atypical Sweet syndrome, and Melkerson-Rosenthal syndrome. Oral lesions were symptomatic (painful, burning sensation, or pruritus) in 68% of the cases. Oral lesions were nearly equal in both genders (49% female, 51% male). Latency time between appearance of systemic symptoms and oral lesions was between 4 days before up to 12 weeks after onset of systemic symptoms. In three cases, oral lesions preceded systemic symptoms and in four cases oral and systemic symptoms appeared simultaneously. The longest latency period belonged to Kawasaki-like lesions. Oral lesions healed between 3 and 28 days after appearance. Different types of therapies including chlorhexine mouthwash, nystatin, oral fluconazole, topical or systemic corticosteroids, systemic antibiotics, systemic acyclovir, artificial saliva, and photobiomodulation therapy (PBMT) were prescribed for oral lesions depends on the etiology[3-37]. The results of literature are summarized in Table 1.

4 | DISCUSSION

Enanthema can develop in various types of viral diseases including dengue fever disease, Ebola virus disease, herpangina, human herpes virus (HHV) infections, measles, and roseola infantum. Infectious diseases, especially of viral etiology, constitute approximately 88% of causes of enanthema. Different types of enanthema such as aphthous-like ulcers, Koplik's spots, Nagayama's spot, petechiae, papulovesicular, or maculopapular lesions, white or red patches, gingival and lip swelling have been reported with various viral infections. Both keratinized (hard palate, gingiva, and dorsum of tongue) and nonkeratinized (labial and buccal) mucosae can be involved.[38] Biadsee and colleagues demonstrated that 7% of the patients with RT-PCR positive test had plaque-like changes on the dorsum of tongue. Also, swelling of oral cavity (including palatal, lingual, and gum) was reported by 8% of the patients. Furthermore, appearance of oral lesions was simultaneously found with loss of taste and smell in the patients and more severe and disseminated oral lesions were reported in older patients and in severe COVID-19.[3] In another study, enanthema was reported in 29% of cases with confirmed COVID-19 and cutaneous exanthema.[35]

4.1 | Aphthous-like lesions

Aphthous-like lesions appeared as multiple shallow ulcers with erythematous halos and yellow-white pseudomemberanes on the both keratinized and nonkeratinized mucosae. In one patient, oral lesions appeared simultaneously with systemic symptoms and in other patients, latency time was between 2 and 10 days. One patient had positive history of recurrent aphthous stomatitis (RAS) and two patients had positive PCR for herpes simplex virus (HSV).[4-8,37] Aphthous-like lesions without necrosis were observed in younger patients with mild infection, whilst aphthous-like lesions with necrosis and hemorrhagic crusts were observed more frequently in older patients with immunosuppression and severe infection. Lesions healed after 5 to 15 days.[7] Regression of oral lesions was in parallel association with improvement of systemic disease. Increased level of tumor necrosis factor (TNF)-α in COVID-19 patients can lead to chemotaxis of neutrophils to oral mucosa and development of aphthous-like lesions. Stress and immunosuppression secondary to COVID-19 infection could be other possible reasons for appearance of such lesions in COVID-19 patients.[4]

4.2 | Herpetiform/zosteriform lesions

Herpetiform lesions presented as multiple painful, unilateral, round yellowish-gray ulcers with an erythematous rim on the both keratinized and nonkeratinized mucosae. Manifestations of these lesions preceded, coincided with, or followed systemic symptoms. In one case, geographic tongue appeared after recovery of herpetiform lesions. Stress and immunosuppression associated with COVID-19 was the suggested cause for appearance of secondary herpetic gingivostomatitis.[4,9,10,12,13]

4.3 | Ulcer and erosion

Ulcerative or erosive lesions appeared as painful lesions with irregular borders on the tongue, hard palate, and labial mucosa. Lesions appeared after a latency time of 4 to 7 days and in one case, lesions appeared 3 days before the onset of systemic symptoms and recovered after 5 to 21 days. In two cases, PCR for HSV-1 and HSV-2 was performed and was negative. Different factors including drug eruption (to NSAID in one case), vasculitis, or thrombotic vasculopathy secondary to COVID-19 were suggested as causes for development of ulcerative and erosive lesions.[14-19]

4.4 | White/red plaques

White and red patches or plaques were reported on dorsum of tongue, gingiva, and palate of patients with confirmed or suspected COVID-19. Candidiasis due to long-term antibiotic therapy, deterioration of general status, and decline in oral hygiene can be the cause of white or red patches or plaques.[4,6,20]

4.5 | EM-like lesions

EM-like lesions appeared as blisters, desquamative gingivitis, erythematous macules, erosions, and painful cheilitis with hemorrhagic crust in patients with cutaneous target lesions in the extremities. Lesions appeared between 7 and 24 days after the onset of systemic symptoms and recovered after 2 to 4 weeks.[12,21,22]

4.6 | Angina bullosa-like lesions

Angina bullosa-like lesions presented as asymptomatic erythematous-purple blisters without spontaneous bleeding on the tongue and hard palate in two confirmed cases of COVID-19.[23]

4.7 | Melkerson-Rosenthal syndrome

There was a report of a 51-year-old woman presenting with complaint of malaise and unilateral lip swelling, fissured tongue and right facial paralysis. She had past history of Melkersson-Rosenthal syndrome since 4 years ago that was spontaneously cured with no relapse. Laboratory data demonstrated an increased level of CRP and computed tomography (CT) scan showed ground-glass opacities in both lungs. The patient cured completely after treatment of COVID-19 disease.[24]

4.8 | Atypical sweet syndrome

There was a report of 61-year-old female who presented complaining of fever, fatigue, arthralgia, myalgia, several erythematous nodules on the scalp, trunk and extremities, and minor aphthous ulcers on the hard palate and buccal mucosa. RT-PCR for COVID-19 was positive. Skin biopsy showed diffuse neutrophilic infiltration in the upper dermis with granulomatous infiltration in the lower dermis and subcutaneous area that was compatible with erythema nodosum-like Sweet syndrome.[25]

4.9 | Kawasaki-like disease

Oral lesions including cheilitis, glossitis, and erythematous and swollen tongue (red strawberry tongue) appeared in COVID-19 patients with Kawasaki-like disease (Kawa-COVID). The long duration of latency between appearance of systemic symptoms (respiratory or gastrointestinal) and onset of oral or cutaneous symptoms could be due to a delayed hyperactivation response of the immune system and secondary release of acute inflammatory cytokines rather than direct effects of virus on the skin and oral mucosa.[22,26-32]

4.10 | Necrotizing periodontal disease

There was a report of a 35-year-old female suspicious for COVID-19 who presented with fever, submandibular lymphadenopathy, halitosis, and oral lesions. Oral lesions included a painful, diffuse erythematous and edematous gingiva with necrosis of inter-papillary areas. The suggested diagnosis was necrotizing periodontal disease due to bacterial coinfections (especially prevotella intermedia) along with COVID-19. The lesions recovered after 5 days.[33]

4.11 | Vesicles and pustules

We found a report of a 9-year-old female presenting with fever, weakness, abdominal pain, and diarrhea that coincided with oral and acral erythematous papular exanthema. Oral lesions included vesicular eruptions and erosions on the tongue and buccal mucosa. PCR test for COVID-19 was positive. Lesions cured after 1 week.[9]

There was also another report on a 51-year-old male presented with fever, fatigue, dry cough, dysgeusia, anosmia, and a positive serology for COVID-19. After 10 days, widespread erythema appeared on hard palate and oropharynx with petechiae and pustules on soft palate border. The suggested diagnosis was enanthema due to COVID-19 and the lesions cured after a few days.[34]

4.12 | Petechiae

In a few studies, Petechiae were reported on the lower lip, palate, and oropharynx mucosa. Latency time for patients with petechiae was shorter compared to the patients with both petechiae and macular lesions. Thrombocytopenia due to COVID-19 infection or the prescribed drug were suggested as possible causes of petechiae.[20,21,34,35]

4.13 | Nonspecific lesions (mucositis)

Erythematous-violaceous macules, patches, papules and plaques on the tongue, lip mucosa, hard palate, and oropharynx were reported in several studies. Thrombotic vasculopathy, vasculitis, hypersensitivity associated to COVID-19 could be the causes of mucositis in patients with COVID-19. Mucosal hypersensitivity secondary to COVID-19, thrombotic vasculopathy, and vasculitis might be the possible causes of mucositis in COVID-19.[8,15,21,23,34-36]

4.14 | Postinflammatory pigmentation

There was one report of pigmentation in the attached and interpapillary gingiva in a 40-year-old female. Increased levels of inflammatory cytokines (including interleukin-1 [IL-1], tumor necrosis factor [TNF]-α) and arachidonic acid metabolites (prostaglandins) secondary to production of stem cell factor (SCF) and basic-fibroblast growth factor (bFGF) from keratinocytes of basal layer lead to postinflammatory pigmentations.[20]

5 | CONCLUSION

Aphthous-like lesions, herpetiform lesions, candidiasis, and oral lesions of Kawasaki-like disease are the most common oral manifestations of COVID-19 disease. An older age and severity of COVID-19 disease seem to be the most common factors that predict severity of oral lesions in these patients. Lack of oral hygiene, opportunistic infections, stress, underling diseases (diabetes mellitus, immunosuppression), trauma (secondary to intubation), vascular compromise, and hyper-inflammatory response secondary to COVID-19 might be are the most important predisposing factors for the development of oral lesions in COVID-19 patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Behzad Iranmanesh, Maryam Khalili, Rezvan Amiri, and Mahin Aflatoonian contributed to the study conception and design. Material preparation, data collection, were performed by Behzad Iranmanesh, Maryam Khalili, Rezvan Amiri, Hamed Zartab, and Mahin Aflatoonian The first draft of the manuscript was written by Behzad Iranmanesh and Mahin Aflatoonian and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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PLOS ONE

RESEARCH ARTICLE

Pathological findings in organs and tissues of patients with COVID-19: A systematic review

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Abstract

Background

Coronavirus disease (COVID-19) is the pandemic caused by SARS-CoV-2 that has caused more than 2.2 million deaths worldwide. We summarize the reported pathologic findings on biopsy and autopsy in patients with severe/fatal COVID-19 and documented the presence and/or effect of SARS-CoV-2 in all organs.

Methods and findings

A systematic search of the PubMed, Embase, MedRxiv, Lilacs and Epistemonikos databases from January to August 2020 for all case reports and case series that reported histopathologic findings of COVID-19 infection at autopsy or tissue biopsy was performed. 603 COVID-19 cases from 75 of 451 screened studies met inclusion criteria. The most common pathologic findings were lungs: diffuse alveolar damage (DAD) (92%) and superimposed acute bronchopneumonia (27%); liver: hepatitis (21%), heart: myocarditis (11.4%). Vasculitis was common only in skin biopsies (25%). Microthrombi were described in the placenta (57.9%), lung (38%), kidney (20%), Central Nervous System (CNS) (18%), and gastrointestinal (GI) tract (2%). Injury of endothelial cells was common in the lung (18%) and heart (4%). Hemodynamic changes such as necrosis due to hypoxia/hypoperfusion, edema and congestion were common in kidney (53%), liver (48%), CNS (31%) and GI tract (18%). SARS-CoV-2 viral particles were demonstrated within organ-specific cells in the trachea, lung, liver, large intestine, kidney, CNS either by electron microscopy, immunofluorescence, or immunohistochemistry. Additional tissues were positive by Polymerase Chain Reaction (PCR) tests only. The included studies were from numerous countries, some were not peer reviewed, and some studies were performed by subspecialists, resulting in variable and inconsistent reporting or over statement of the reported findings.

Conclusions

The main pathologic findings of severe/fatal COVID-19 infection are DAD, changes related to coagulopathy and/or hemodynamic compromise. In addition, according to the observed organ damage myocarditis may be associated with sequelae.

Introduction

On March 11, 2020, the World Health Organization classified the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a pandemic [1, 2]. COVID-19 affects mainly the respiratory system and the clinical presentation ranges from asymptomatic cases to severe manifestations. In individuals with comorbidities and other yet to be characterized host factors, it can cause severe morbidity and mortality, usually in the form of acute respiratory distress syndrome (ARDS) that may progress to multiorgan failure and death. The death toll of COVID-19 is approximately 898,000 worldwide at the time this manuscript was prepared [1, 3, 4].

COVID-19 pathophysiology resembles that of other coronavirus infections [5, 6]; this involves attachment of the SARS-CoV-2 virus to the angiotensin-converting enzyme 2 (ACE2) on target cells, followed by internalization and replication of the virus. ACE2 receptors are highly expressed in upper and lower respiratory tract cells, which determines the highest concentration of viral particles at these sites and explains the high contagiousness of oronasal droplets and aerosols, and the preponderance of respiratory symptoms [7]. However, ACE2 are expressed to a lesser degree in non-respiratory tissues like myocardial cells, renal epithelial cells, enterocytes, and endothelial cells in multiple organs, which may explain some of the extrapulmonary manifestations.

In addition to presumed direct cytopathic viral injury, severe COVID-19 infection is frequently complicated by an infection induced microangiopathy or hypercoagulable state that causes capillary, venous and/or arterial thrombosis [8], and that may lead to end-organ damage due to distant thrombotic or embolic disease [9]. The course of severe COVID-19 disease can be further complicated by pre-existing comorbidities, superinfection with community-acquired or nosocomial organisms, and ventilator-associated lung injury [4, 10].

For epidemiologic analyses of new or emerging diseases, the study of tissue biopsies and autopsy material is a well-established method for researching pathogenetic mechanisms and determining the effects of disease in various tissues and organs, and the cause of death [11]. Recently published systemic reviews on autopsies addressed the pathophysiological timeline [12] or summarized histopathological changes in different organs [13]. We performed a systematic review of biopsy and autopsy findings by a team of anatomic, hematopathology, coagulation and public health specialists to provide relevant clinical-pathologic correlations that may help guide therapeutic and preventive steps to prevent further deaths.

Objectives

- To summarize the reported pathologic findings from biopsies and autopsies of severe COVID-19 cases.
- To document the organs in which the SARS-CoV-2 virus has been detected on tissue specific cells.

- To evaluate whether alterations in affected tissues and organs are the result of direct viral cytopathic injury or of immune/inflammatory-mediated abnormalities leading to microangiopathy and coagulopathy.
- Based on the main pathologic findings identified, clinicopathologic correlations will be attempted to help guide the management of patients with severe COVID-19.

Methods

Search strategy and databases

A structured search was conducted of Embase (Medline included) from January 2020 to 4 August 2020 and in PubMed, MedRxiv, Lilacs and Epistemonikos from January 2020 to 17 June 2020 by two authors (SP and LR). The search terms included MeSH terms and key words in the title, abstract and/or as key words (see S1 Text) with no restrictions on year published, type of publication or language. Studies not in English were translated using automatic translation tools. Forward citation searches and references of all papers identified by the search for inclusion were also performed.

Study selection/ Inclusion and Exclusion criteria

Using PRISMA format, the results of the initial search strategy were first screened by title and abstract, duplicates and studies not meeting the inclusion criteria were excluded by two independent authors.

Inclusion criteria: (1) studies reporting pathologic findings at autopsy from patients with proven COVID-19 infection; (2) Studies reporting pathologic tissue findings of biopsies obtained from proven COVID-19 patients; (3) Case reports and case series including pediatric cases. Peer-reviewed and non-peer reviewed publications were included.

Exclusion criteria (1) lack of pathologic data; (2) patients with other SARS-like illnesses; and (3) In vitro experiments, qualitative and modelling studies.

Data collection process and data items

Data from the full texts were collected using a template with information (excel spreadsheet) by one author (SP). Two other authors (HM and AA) checked the accuracy of the extracted data. Disagreements between the reviewers were resolved by consensus.

Data extracted

Study characteristics: country, author, type of study, sample size, peer-reviewed or not.

Clinical information: demographics, comorbidities, clinical presentation, laboratory test results (e.g., blood type, biomarkers, liver function tests, coagulation parameters), imaging, treatment, and hospitalization days.

Pathology: gross, microscopic, and related ancillary studies by site, including documentation of the presence/absence of virus in the examined tissue.

Methodological quality assessment

The quality assessment was conducted on the domains of selection, ascertainment, causality and reporting [14].

Strategy for data synthesis

A narrative synthesis of the evidence was also undertaken, and summary tables produced per organ system. Meta-analysis was not appropriate as data synthesis was derived from case reports and case series. Ethical approval was not required for this review.

Results

The selection strategy of studies is summarized in Fig 1 and the quality assessment is reported in the (S1 Table).

A total of 75 studies met the inclusion criteria. Mainly the studies originated from USA, China and Germany as seen in Table 1 (S2 Table). The articles described a total of 603 cases: autopsy (66.6%), postmortem biopsy (20.9%), antemortem biopsy (9.3%), and placenta (3.2%). In most cases SARS-CoV-2 infection was diagnosed by nucleic acid testing by polymerase chain reaction (PCR) according to local protocol.

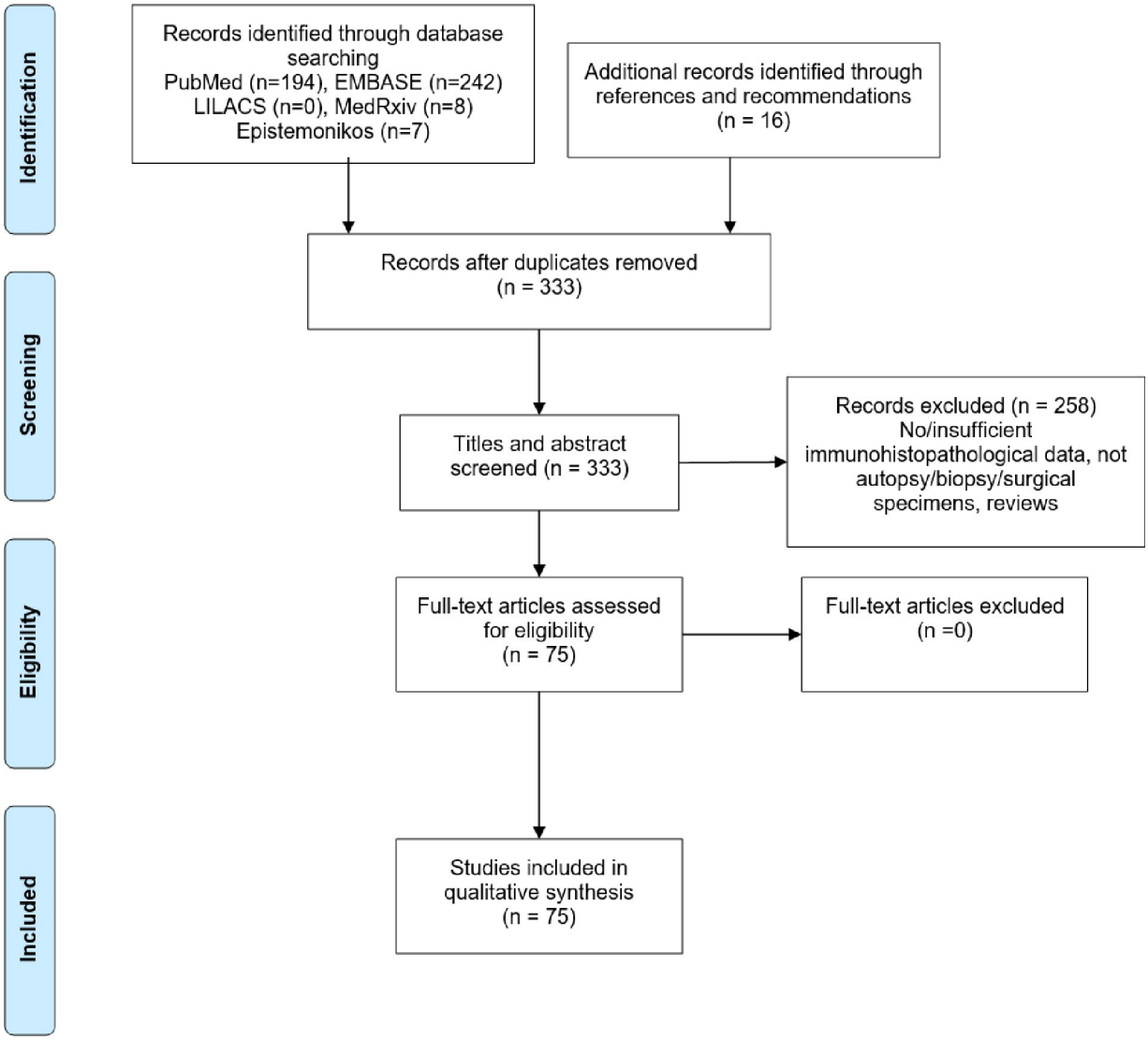

Fig 1. PRISMA flow diagram of literature search and selection process.

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Table 1. Study characteristics.

Characteristics	Number (%)	Characteristics	Number (%)
Country (n = 75)		**Study type (n = 75)**	
United States of America	22 (29.3%)	Case reports	30
China	16 (21.3%)	Case series	45
Germany	9 (12.0%)	**Specimen source (n = 603)**	
Spain	6 (8.0%)	Autopsy	402 (66.6%)
Switzerland	6(8.0%)	Postmortem biopsy	126 (20.9%)
Italy	4 (5.3%)	Antemortem biopsy	56 (9.3%)
Brazil	3 (4.0%)	Placenta biopsy	19 (3.2%)
Belgium	2 (2.6%)	**Sample size (n = 75)**	
Austria	1 (1.3%)	≤5 cases	42 (56.0%)
Finland	1 (1.3%)	6 to ≤10 cases	15 (20.0%)
France	1 (1.3%)	11 to ≤20 cases	10 (13.3%)
Iran	1 (1.3%)	>20 cases	8 (10.7%)
Japan	1 (1.3%)		
Netherlands	1 (1.3%)		
United Kingdom	1 (1.3%)		

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Patient demographics and comorbidities from the 75 studies are shown in Table 2. The median age of adult cases was 68 years (yr.) (range: 28–88), and for pediatric cases the range was 11 to 17 yr. Of 536 cases where gender was reported, 70.9% were male. The four most reported comorbidities were arterial hypertension (40.8%), diabetes mellitus (22.0%), cardiovascular disease (17.2%), and obesity (11.5%).

Table 3 summarizes the radiology, laboratory results and cause of death of severe COVID-19 patients. Radiological assessment of the chest was reported in 313 (51.9%) cases showing unilateral or bilateral lung opacities (54.6%), pulmonary consolidations (32.9%) and

Table 2. Demographics and medical history of the COVID-19 cases.

Demographics	N = 536	% or range
Sex: male*	380/536	70.9%
Median age (Years)**	68	28–88
Comorbidities	**N = 546**	**%**
Hypertension	223/546	40.8
Diabetes Mellitus	120/546	22.0
Cardiovascular Disease	94/546	17.2
Obesity	63/546	11.5
Chronic Kidney disease	47/546	8.6
Tumor	44/546	8.1
Chronic Obstructive Pulmonary Disease	29/546	5.3
Dementia	16/546	2.9
Cardiac arrythmias	19/546	3.5
Dyslipedemia	19/546	3.5
Bronchial Asthma	8/546	1.5

*Data not available n = 48. Does not include the postnatal cases (n = 19)

**Does not include pediatric studies (n = 2), studies with mean age (n = 4) and data not available (n = 4)

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Table 3. Imaging, clinical laboratory and cause of death of COVID-19 patients.

Imaging lung	**n = 313**	**%**
Lung opacities	171	54.6
Lung consolidation	103	32.9
Thromboembolic events	19	6.1
Lung shadows	11	3.5
Lung lesions	2	0.6
Imaging Central Nervous System	**n = 13**	**%**
Infarction/Ischemia	4	30.8
Clinical laboratory	**Abnormal/Total reported**	**%**
C-Reactive Protein	92/101	91.0
Ferritin	30/36	83.3
D-dimer	114/137	83.2
Lactate dehydrogenase	80/100	80.0
Interleukin-6	52/70	74.3
Procalcitonin	14/21	66.7
Aspartate aminotransferase	65/99	65.6
Creatinine	90/148	60.8
Alanine aminotransferase	44/88	50
Creatine Kinase	11/26	42.3
Platelet	19/102	18.6
COVID-19 specified cause of death	**n = 227**	**%**
Respiratory Failure	161	70.9
Multiorgan failure	25	11.0
Cardiac	24	10.6
COVID-19	16	7.0
Pneumonia	15	6.6
Septic shock	7	3.0
Pulmonary Emboli	5	2.2
Gastrointestinal	3	1.3
Cerebral hemorrhage	2	0.9
Liver cirrhosis	1	0.4
Renal failure	1	0.4
Community deaths	**n = 9**	

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thromboembolic events (6.1%). From studies reporting laboratory results, D-dimers were elevated in 83.2%, procalcitonin was elevated in 66.7%, markers of systemic inflammation such as C-reactive protein (CRP), ferritin, interleukin-6 (IL-6) were elevated in 91.0%, 83.3% and 74.3% of the reported cases, respectively.

The reported main cause of death for 227 COVID-19 patients was respiratory failure (70.9%), followed by multiorgan failure (11.0%), cardiac (10.6%), COVID-19 (7.0%) and pneumonia (6.6%).

Table 4 summarizes recurrent pathologic findings in COVID-19 patients. Detailed classification of histopathologic findings in all organs and their relative frequencies are found in S3 Table in the Supplementary Appendix. DAD, the most common lung pathology was found in 315 out of 342 cases (92.1%). 94 cases (27.4%) had superimposed acute focal or diffuse bronchopneumonia. The most common abnormalities in the liver and heart were hepatitis (n = 50, 21.2%) and myocarditis (n = 24, 11.4%) respectively. Encephalitis was observed in 5 (4.6%) brains at autopsy. Vasculitis was commonly observed only in skin biopsies (25.0%).

Table 4. Recurrent pathologic findings by organ/organ-system.

Organ/system	Organ Specific	Microthrombi	Endothelial Injury	TE disease	Vasculitis	Inflammation*	H/D compromise
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Upper airways+	-	-	-	-	-	33/33 (100)	-
Lung	DAD* 315/342 (92.1)	132 (38.6)	61 (17.8)	47 (13.7)	10 (2.9)	21 (6.1) **	27 (7.9)
GI	-	2/83 (2.4)	2 (2.4)	-	-	-	15 (18.1)
Liver	-	-	1/236 (.4)	93 (39.4)	-	59 (25.0)	114 (48.3)
Heart	-	-	8/210 (3.8)	45 (21.4)	-	37 (17.6)	-
Kidney	-	55/276 (19.9)	1 (0.4)	2 (0.7)	-	-	147 (53.3)
CNS	-	20/110 (18.2)	-	9 (8.2)	-	9 (8.2)	34 (30.9)
Hem-Lymph	-	-	-	1/136 (0.7)	-	15 (11.0)	7 (5.2)
Skin	-	13/44 (29.5)	1 (2.3)	-	11 (25.0)	15 (34.1)	-
Placenta	-	11/19 (57.9)	-	-	-	1 (5.3)	-

GI- gastrointestinal, CNS- central nervous system, Hem-lymph- hematolymphoid, DAD- Diffuse alveolar damage, TE- thromboembolic, H/D-hemodynamic.

+Trachea, pharynx, bronchial, mucosa.

* Possible cytopathic effect.

** Inflammation not related to Diffuse Alveolar Damage. Highlighted- most common abnormality by organ-system.

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The presence of microthrombi was documented in the placenta (57.9%), lung (38.6%), kidney (19.9%), CNS (18.2%), and gastrointestinal (GI) tract (2.4%). Injury of endothelial cells was mostly reported in the lung (17.8%) and heart (3.8%). Thromboembolic disease was most common in the liver (39.4%) followed by the heart (21.4%) and lung (13.7%). Changes due to hemodynamic compromise such as coagulative necrosis secondary to hypoxia and/or hypoperfusion, edema and congestion were frequently seen in the kidney (53.3%), liver (48.3%), CNS (30.9%), GI tract (18.1%), lung (8%) and spleen (5.2%).

Viral particles (vp) suggestive of SARS-CoV-2 were demonstrated within specific organ cells in the trachea, lung, liver, colon, kidney, CNS either by electron microscopy (EM), immunohistochemistry (IHC) or immunofluorescence (IF) (Table 5). Among hematolymphoid tissues vp were only observed in monocytes/macrophages. In the lung and kidney vp were observed both within epithelial and endothelial cells. In the skin vp were detected only in endothelial cells. In the pancreas, heart, saphenous vein, tonsils, testes, retina, pleural effusion and placenta, testing was performed only by PCR.

Discussion

The findings presented on this systematic review showed demographic features, comorbidities, clinical manifestations, laboratory, and radiologic findings in line with existing literature on severe COVID-19 infection, indicating that the sample is likely representative of severe COVID-19 disease [15, 16].

Pathologic findings

The predominant findings in fatal COVID-19 cases were DAD, coagulopathy, and hemodynamic compromise. Involvement of non-pulmonary organs was limited to parenchymal inflammation (myocarditis, hepatitis, and encephalitis), which was mostly mild. Direct viral cytopathic injury of extrapulmonary organs in general was not regarded as the cause of organ failure.

Table 5. Detection of SARS-CoV-2 in different organs in COVID-19 patients.

System	Site	Detected (Y/N)	Method (#positive/#tested)			
			PCR	EM	IF	IHC
Upper respiratory	Pharynx	Y	35/39	NA	NA	NA
	Trachea (distal & proximal)	Y	14/14	12/12	NA	1/2
	Epiglottis	Y	1/1	NA	NA	NA
Lower respiratory	Bronchus	Y	22/23	NA	NA	NA
	Lung	Y	94/107	48/87	2/26	21/29
Gastrointestinal	Esophagus	N	0/2	NA	NA	NA
	Stomach	N	0/15	NA	NA	0/3
	Small intestine	N	0/1	NA	NA	NA
	Large intestine	Y	18/25	2/14	NA	0/1
Hepatopancreatobiliary	Liver	Y	22/40	2/2	NA	0/18
	Pancreas	Y	1/4	NA	NA	0/4
	Gallbladder	N	0/4	NA	NA	NA
Cardiovascular	Heart	Y	22/66	0/17	NA	0/5
	Saphenous vein	Y	4/12	NA	NA	NA
Hematolymphoid	Tonsils	Y	1/1	NA	NA	NA
	Lymph nodes	Y	30/30	25/25	NA	0/1
	Spleen	Y	17/ 47	2/24	NA	0/5
	Blood	Y	8/17	NA	NA	NA
	Bone marrow	N	0/3	NA	NA	0/3
Genitourinary	Kidney	Y	41/71	25/54	6/9	2/31
	Bladder	N	0/12	NA	NA	NA
	Vagina	N	0/1	NA	NA	NA
	Testes	Y	22/33	0/3	NA	NA
Endocrine	Adrenal	N	0/2	NA	NA	NA
	Thyroid	N	0/3	NA	NA	0/3
Central Nervous	Brain	Y	41/72	1/1	NA	0/22
	Retina	Y	3/14	NA	NA	NA
Skin	Skin	Y	0/6	1/1	NA	8/11
Soft tissues	Skeletal muscle	N	0/1	NA	NA	NA
Placenta		Y	1/4	NA	NA	NA
Body fluids/excretions	Pleural effusion	Y	10/10	NA	NA	NA
	CSF	N	0/11	NA	NA	NA
	Urine	N	0/2	NA	NA	NA
	Feces	N	0/1	NA	NA	NA

NA- Not Available, Y- Yes, N-No, PCR- Polymerase Chain Reaction, EM- Electron Microscopy, IF- Immunofluorescence, IHC- Immunohistochemistry

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Effects of SARS-CoV-2 in the respiratory tract

The upper respiratory tract is the initial site of viral infection; two proteins critical for the viral entry, ACE2 and TMPRSS2 are highly expressed in nasal goblet cells and ciliated cells of human airways [17]. The S protein of SARS-CoV-2 binds to ACE2 with 10-20-fold greater affinity than that of SARS-CoV-1 [18]. Male gender and smoking have been associated with increased expression of ACE2 in the lower airways and increased severity of infection [19].

The infection is thought to spread to the lower respiratory tract via secretions or leukocytes. CT imaging studies show ground-glass opacities in 93% of pre-symptomatic patients; prominent radiologic abnormalities in patients with no or minimal symptoms appear to be common

[20]. Respiratory function in patients with COVID-19 infection can worsen suddenly, especially around day 9 after initiation of symptoms, leading to intensive care unit (ICU) admission. This worsening is associated with plasma elevations of acute phase reactants such as C-reactive protein, IL-6, and ESR. Procalcitonin, a parameter usually associated with systemic bacterial infection is also frequently elevated, most likely as a result of tissue injury.

Some authors have proposed that the dysregulated inflammatory response is largely restricted to the lungs; this notion is supported by the pathologic findings, which affect primarily the lung. Furthermore, inflammatory mediators such as IL-1β and IL-6 are 100- to 1000-fold higher in respiratory fluids than in serum, and RNA sequencing of bronchoalveolar lavage fluid has shown a marked increase in monocyte-derived macrophage inflammatory phenotype (enhanced transcription of STAT1, STAT2 and multiple IFN regulatory factors) [21].

In contrast with DAD occuring in other clinical contexts, in COVID-19 patients, DAD develops in non-previously critically ill individuals, more commonly in the elderly, but it can also occur in young and/or healthy individuals. In our review, the morphologic findings of COVID-19 related DAD were identical to those seen in DAD of other etiologies [22]. One study describes that the reparative angiogenesis observed in COVID-19 cases is different from that observed in Influenza A (H1N1) induced DAD: in the former the neoangiogenesis occurs predominantly through partition of existing vessels, and in the latter by proliferation (sprouting) of new vessels [23]. These results were obtained on a small sample (n = 7) and the clinical implications of such finding are uncertain.

Per our review, COVID-19 vp have been identified in all main constituents of the alveoli: pneumocytes, capillary endothelial cells, and alveolar macrophages. Endothelial cells and macrophages are major cytokine producing cells; the lung injury is presumably the result of cytopathic viral effect on pneumocytes and endothelial cells, amplified by the inflammatory response and cytokine release elicited by injured endothelial cells and activated macrophages. As the endothelial injury develops, the antithrombotic and anti-inflammatory function of the normal endothelium is lost and the balance shifts to a prothrombotic phenotype. Endothelial dysfunction leads to platelet and complement activation in addition to leukocyte accumulation in the microvasculature, as described in detail by Jackson et al. [24].

The subacute and chronic phases of DAD are primarily the reparative/scarring response to the initial injury and are characterized by an initial amplification of the inflammatory response by recruitment of acute inflammatory cells and proliferation of fibroblasts and vessels, and later by the removal of the damaged tissue by phagocytic cells, apoptosis of granulation tissue; eventually leading to restoration of the normal architecture in most cases. These processes transitorily prevent an effective gas exchange, render the lung susceptible to bacterial superinfection due to disruption of the epithelial barrier, and in a few cases, it may lead to irreversible loss of function [25].

The current management of DAD is primarily supportive, and include lower tidal volumes, optimal level of positive end-expiratory pressure, prone positioning, neuromuscular blockade, extracorporeal membrane oxygenation, corticosteroids, and antibiotic prophylaxis, all of which have been incorporated in the management of COVID-19 related DAD with modest improvements in mortality [26–28].

The acute phase of the disease is the stage most susceptible for therapeutic intervention and failure to improve during the first week of treatment is the most important negative prognostic factor [29]. Addressing the underlying cause of COVID-19 induced DAD implies effective therapy for COVID-19 infection. At present, this includes the use of systematic corticosteroids in severe and critical patients [30]. The use of anticoagulant therapy for thromboprophylaxis in hospitalized patients, to prevent the accumulation of microthrombi in the lung capillaries

and to reduce the progression to systemic coagulopathy that could lead to multiorgan failure have been used with some benefit [31]. Given the known pathophysiology of DAD, the earlier therapies are initiated, the greater the benefit should be [28]. In addition, many other agents including antivirals and immunomodulators for the use in COVID-19 patients are still under investigation [31].

In the subacute phase the emphasis should shift to maintaining adequate oxygenation and hemodynamic support to prevent hypoxia/hypoperfusion/acidosis induced organ damage, adequate nutrition, and prevention of common complications such as ventilator induced lung injury, superimposed pneumonia/sepsis, and thromboembolic events while the tissues heal. Bacterial pneumonia a preventable important common complication of the subacute phase of DAD, was documented in 33% of autopsies in our review.

A prolonged clinical course frequently results in multiorgan failure [32]. In patients who survive, pulmonary function is usually restored within 6 months, although some limitations may persist up to 12 months [25]. Few patients who progressed into the chronic, scarred phase of DAD have undergone lung transplantation [33]. Extent and severity of the long-term respiratory complications in COVID-19 survivors are yet to be confirmed and will require long-term follow-up.

Coagulopathy

In our review, the incidence of pure thromboembolic lesions at autopsy was documented in the lung, liver, and heart 14%, 39% and 21% of cases, respectively; prophylactic anticoagulation was used only in approximately 16% of fatal cases. A recent meta-analysis for the incidence of venous thromboembolism (VTE) found a similarly high incidence of 23% [34]. This high incidence of VTE is due to the connection between coagulation and inflammation, which is referred to as "thromboinflammation or immunothrombosis" to highlight the close association between inflammation and thrombosis. As Foley and Conway [35] point out, the bridge between these pathways is tissue factor (TF), which is present in high levels in lungs and in baseline conditions is expressed in the subendothelium of the vasculature. TF initiates the coagulation process by binding to activated factor VII to generate thrombin, which activates endothelial cells, platelets, leukocytes and able to propagate both microvascular thrombosis and inflammation through protease-activated receptors (PARs). The antithrombotic surface of the endothelium, maintained by nitric oxide, prostaglandin I2, antithrombin, thrombomodulin, protein C and tissue factor pathway inhibitor, becomes a procoagulant surface by expressing TF, leukocyte adhesion molecules (ICAM-1, VCAM-1), and by releasing von Willebrand factor during endothelial cell activation by thrombin. Furthermore, cytokines induce TF expression on circulating monocytes and microparticles during infection which contributes significantly to their procoagulant effect [35].

The increased expression of TF and adhesion molecules combined with release of von Willebrand factor generates microthrombi in the adjacent capillary bed, which can become systemic as the inciting event continues. Endothelial cells express ACE2 receptors [18] and infection of these cells by COVID-19 has been well documented as leading to endothelitis, defined by subendothelial accumulation of monocytes and neutrophils with detachment of endothelial cells [36]. Additionally, neutrophils at the site of infection are able to release some of their nuclear material forming a meshwork of decondensed DNA combined with histones and cytoplasmic content, called neutrophil extracellular traps (NETs) [37]. This process of NETosis is part of the innate immune process and leads to reduced blood flow and thrombus formation through activation of the intrinsic (TF-independent) coagulation pathway. Middleton et al. [38] compared NET formation in plasma of COVID-19 patients with controls and

they found significantly increased plasma NET levels, as well as increased amount of soluble and cellular factors capable of inducing NET development in COVID-19 samples. Importantly, plasma NET levels were correlated with disease severity and were significantly higher in non-survivors compared with survivors and returned to normal in convalescent plasma. In addition, they detected NET-containing microthrombi in pulmonary tissue and they were able to block NET formation by adding inhibitory peptides in vitro to COVID-19 plasma. Their well-designed study supports the role of NETs in the coagulopathy seen in COVID-19 patients.

Studies have stated the frequent occurrence of disseminated intravascular coagulation (DIC) in severe COVID-19 infection associated with increased mortality. However, the laboratory findings in patients with COVID-19 infection do not fit the definition of the earlier phase of DIC, which has been designated as sepsis-induced coagulopathy (SIC) by the International Society of Thrombosis and Haemostasis (ISTH) [39]. In the majority of COVID-19 cases, fibrinogen levels are increased, coagulation tests are normal or minimally prolonged, thrombocytopenia is mild or absent, and morphologic evidence of microangiopathic hemolysis (schistocytes) is not present. The presence of a hypercoagulable state in COVID-19 patients is supported by the presence of markedly increased fibrin degradation products and D-dimers, microthrombosis in different organs and high incidence of thromboembolic events. These changes indicate that the coagulopathy of COVID-19 infection is dominated by hypercoagulability with secondary fibrinolysis. Elevated D-dimer levels of 10 to 20-fold above the upper limit of normal are described in COVID-19 patients, and an association with increased mortality is found in multiple case series [10, 11]. In our review, pathologic evidence of endothelial injury and thromboembolic disease was present in the lung in nearly all cases, while the involvement of other organs was variable, usually in the form of microthrombi or thromboembolic disease, but not hemorrhagic events. Coagulopathy in the context of lung injury is one of the cardinal aspects of DAD [40] and explained by activation of the extrinsic (TF) pathway due to tissue injury, and the intrinsic pathway by NETs. In their review of 83 COVID-19 infected patients, Fogarty et al. [41] hypothesize that a "double-hit" virally induced injury of both the alveolar cells and the capillaries due to their anatomical proximity [42].

The ISTH published interim guidance recommends prophylactic dose of low molecular weight heparin (LMWH) in all patients without active bleeding or platelet count $>$ 25 x 10^9/L, followed by adequate laboratory monitoring [43]. While thromboprophylaxis measures are to be adopted for inpatients with COVID-19 infection [31], some groups advocate for therapeutic instead of prophylactic doses of LMWH [44–46]. The NIH recommends full dose heparin anticoagulation based on the interim results of three international trials including over 1,000 hospitalized patients with moderate COVID-19 symptoms [47] that showed decreased need for life support and improved outcomes in these patients.

Espirito Santo et al. [48] reported microvascular thrombosis *in vivo* by video capillaroscopy in 13 COVID-19 patients on mechanical ventilation while receiving LMWH. The authors concluded that microvascular thrombosis occurs systemically, and that organs with the highest capillary density are most affected. In our review microthrombi were consistent and significant only in the lungs.

Effects of SARS-CoV-2 in non-respiratory organs

EM, IF and IHC allow the detection or direct observation of vp within organ specific cells. PCR is more sensitive than the previous methods but requires homogenized tissue samples precluding the identification of the specific source of the viral RNA. From the 603 cases included in this review, vp were observed in organ specific cells from the trachea, lung, colon,

liver, lymph nodes, spleen, kidney, brain, and skin. Nonetheless, these reports would require additional validation since difficulties in differentiating subcellular structures from vp have been reported recently [49]. In the remaining organs the virus was detected by PCR. Among the hematopoietic organs tested the virus was only observed in monocytes but not lymphocytes or bone marrow cells. Hemophagocytic lymphohistiocytosis (HLH) and hemophagocytosis without HLH have been reported in a number of severe COVID19 infections [50, 51], however available literature does not support a relevant association between these disorders.

Other findings of the hematolymphoid system such as lymphocyte depletion, granulocytic hyperplasia is common in systemic infections and after steroid therapy and expected to be fully reversible [52].

In the GI tract and kidney, ACE2 is involved in amino acid homeostasis, expression of antimicrobial peptides, local innate immunity, and gut ecology [53]. While symptoms such as vomiting, diarrhea and abdominal pain were commonly documented among COVID-19 patients, histopathologic examination of gastrointestinal samples did not show significant infection related tissue damage. Two studies reported cases of ischemic necrosis of the intestine [36, 54] likely due to endothelial/hemodynamic compromise and/or coagulopathy. These changes should be reversible after the infection resolves [55].

Significant hepatic pathology was primarily related to hemodynamic changes and coagulopathy. Mild hepatitis was present in 23% of the cases. Similar abnormalities have been reported with other respiratory viruses and are expected to be fully reversible given the great regenerative capacity of the liver [56].

Significant CNS changes were primarily related to coagulopathy. Mild meningoencephalitis/encephalitis was found in ~10% of the cases; this may explain the reported neurologic symptoms/mental status changes reported in a subset of critically ill patients [57]. Rhodes et al. [58] reports of a neutrophilic microvascular endothelitis present in variable amounts and variably distributed in the examined brains, suggesting a vasculitis with autoimmune features in 10 patients. Long after recovery from the acute illness and when the virus is no longer present, patients may suffer disabling after-effects that may last for weeks or months. These include one or more of the following: fatigue, dyspnea, myalgia, joint pain, chest pain, headaches, palpitations, difficulty concentrating, short term memory loss, persistent loss of smell, and chronic stress. The pathogenesis of this "post-COVID-19 condition" is currently unknown [59], but has been hypothesized to be related to virally induced endothelial damage in the microcirculation [36]. Although recent studies report potential long-term neurological sequelae in COVID-19 patients [60], follow-up of these patients is limited and; in our review, significant infection-associated tissue CNS damage was not identified.

Dysregulation of the renin-angiotensin-system (RAS) has been documented in diabetes mellitus, arterial hypertension, and chronic lung disease, which are frequent comorbidities of severe COVID-19 patients. COVID-19 infection causes decreased ACE2 expression due internalization of the virus-receptor complex [61] decreasing its beneficial vasodilator, anti-inflammatory, antioxidant, and anti-apoptotic effects and increasing the dysregulation of RAS.

There was evidence of myocarditis in up to 11% of the cases. This may represent cytopathic viral effect as the virus has been demonstrated in the myocardium and vascular endothelium.

Renal failure has been observed in up to 15% of COVID-19 patients and correlates with severity and prognosis. While ACE2 is abundant in the brush border of proximal tubular epithelium direct infection resulting in tubulointerstitial nephritis is usually not observed. The most relevant finding in the kidney was acute tubular necrosis (ATN) present in 126 (45%) of cases. ATN is common in critically ill patients usually due to renal hypoperfusion due to hemodynamic compromise, however, a component of direct cytopathic effect cannot be entirely excluded [62]. Alternative causes for ATN include virus-induced cytokine storm

which can injure the kidney directly or indirectly via effects on other organs [63]. Some authors concluded that "the most significant finding in postmortem kidneys of patients with COVID-9 infection is the absence of significant findings". Microthrombi were observed only focally (<5% glomeruli) and only in a few cases (14%) and was not considered a significant cause of acute kidney injury [64].

Cutaneous lesions were observed mostly in younger patients with asymptomatic to mild disease and showed a broad spectrum of clinical manifestations including rashes, urticarial, vesicular, and livedoid eruptions like other viral diseases. Viral particles suggestive of SARS--CoV-2 were demonstrated in endothelial cells of the skin and all these manifestations may represent cytopathic effect. The reported skin abnormalities were not relevant for the overall outcome of the patients and should resolve after the infection subsides.

The placentas of women infected with SARS-CoV-2 show no significant increase in acute or chronic inflammatory pathology [65, 66]. Placenta changes were primarily vascular abnormalities, which are commonly found in complicated pregnancies of any cause; however increased antenatal surveillance for women with COVID-19 is prudent.

No significant findings were reported in the testes [33].

Significant advances have already been made in understanding the pathomechanisms of lethal COVID-19, and many studies have reported additional pathophysiology mechanisms of COVID-19, that need to be further explored [67, 68].

Limitations

This review has several limitations. Case reports and case series are from different countries and institutions with different levels of complexity, some of the articles were not peer reviewed, and some studies were performed by subspecialists, which may result in lack of accuracy or overstatement of some of the reported findings. Populations from different countries with different phenotypes and, mainly, genotypes may influence the clinical manifestations, laboratory results, evolution, and the histological findings.

Conclusion

The main pathologic/autopsy findings of severe COVID-19 infection causing fatality are DAD and changes related to coagulopathy and/or hemodynamic compromise. Knowing the pathogenesis and epidemiological, clinical, and pathological characteristics of patients with Covid-19 infection are key to identify potential targets for more effective therapies. The management guidelines developed for DAD of other etiologies translate well to COVID-19 associated DAD but need major breakthroughs given the still very high mortality of this pathology. Therapeutic interventions should be applied in the early phase of DAD, the step most amenable to intervention and should be tailored according to the timing and specific progress or development of complications. Because the coagulopathy of COVID-19 infection is different from SIC, this hypercoagulable state requires anticoagulation to improve patient outcomes.

Supporting information

S1 Checklist. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement.
(PDF)

S1 Text. Literature search performed using EMBASE, MEDLINE, PubMed, MedRxiv, Lilacs and Epistemonikos.
(PDF)

S1 Table. Murad tool—methodological quality assessment of case reports and case series.
(PDF)

S2 Table. First author, country, study type, peer review, sample size, gender, and age of cases of the included studies.
(PDF)

S3 Table. Classification of the histopathological findings in COVID-19 cases.
(PDF)

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Researchers characterize and predict post-acute sequelae of SARS-CoV-2 infection

By Bhavana Kunkalikar

Reviewed by Danielle Ellis, B.Sc.

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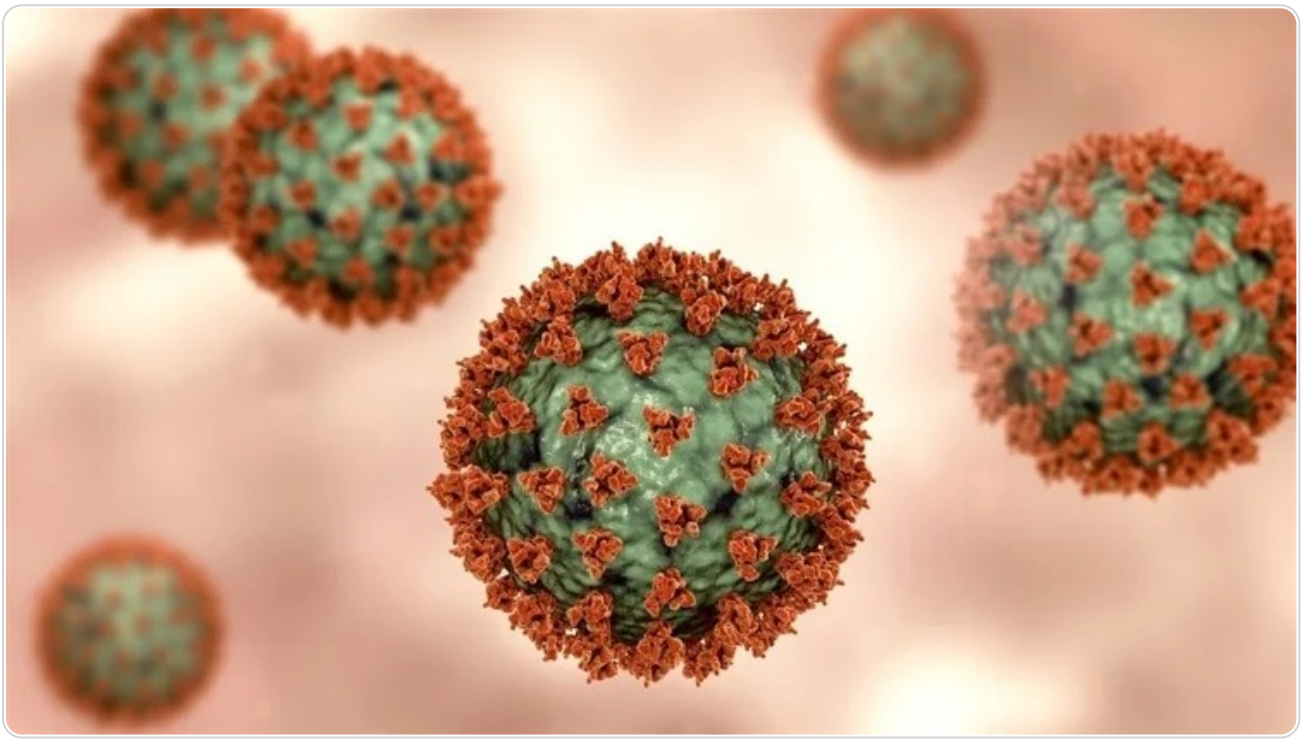
In a recent study posted to the *medRxiv** preprint server, researchers characterized and predicted post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (PASC) infection.



Study: Characterizing and Predicting Post-Acute Sequelae of SARS CoV-2 infection (PASC) in a Large Academic Medical Center in the US. Image Credit: Kateryna Kon/Shutterstock

Background

The rising number of coronavirus disease 2019 (COVID-19)-recovered persons suffering from post-acute sequelae of SARS-CoV-2 infection (PACS) has become a global concern. However, the development of efficient treatments has been impeded by the novelty of this disease and the scant information available about the underlying pathomechanisms.

About the study

In the present study, researchers described PASC-associated diagnoses and developed models for risk assessment.

The study involved eligible individuals who were patients of Michigan Medicine (MM) and who were diagnosed with COVID-19 or tested positive for real-time reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 infection between 10 March 2020 and 31 August 2022. Data from RT-PCR tests were gathered for employee screening, standard screening at hospital admission, and routine screening before treatments. Symptomatic as well as asymptomatic subjects participated in the study. The index date for each participant was either their initial COVID-19 diagnosis or positive RT-PCR test, whichever was earlier.

The remaining COVID-19-positive patients were further divided into groups: (1) "no PASC" patients who had no recorded PASC diagnosis and (2) patients having a recorded diagnosis of PASC. Diagnoses for PASC were determined using either observation of the ICD10-CM codes B94.8, which indicated sequelae related to other specified infectious and parasitic disorders or U09.9, which indicated unspecified PASC or entries for PASC in the diagnosis component of the Problem Summary List (PSL) of the electronic health records (EHR) database.

Subsequently, the team conducted phenome-wide association studies (PheWASs) to identify enriched phenotypes associated with the post-COVID-19 era and putative PASC predisposing phenotypes related to the pre- and acute-COVID-19 periods.

Additionally, the team divided PASC patients into groups according to ICD10 diagnoses that corresponded to 29 phenotypic concepts that had previously been reported as typical PASC symptoms and that were simultaneously recorded with their initial PASC diagnoses. Furthermore, patient characteristics were assessed and adjusted for socioeconomic status and other factors, including age, gender, race/ethnicity, person-per-square-mile population density, and neighborhood disadvantage index (NDI) without Black community proportion.

Results

A PASC diagnosis was reported by 1,724 of the 63,675 COVID-19 positive patients a minimum of two months following their initial COVID-19 diagnosis or RT-PCR positive result. Within three months of COVID-19 diagnosis, the incidence of clinically confirmed PASC varied between 0.18% to 1.8%. The second peak of COVID-19 positive people at MM coincided with the largest quarterly number of PASC infections recorded in the fourth quarter of 2021.

The team also found that compared to controls, PASC cases had slightly longer periods covered in the pre-test EHRs than controls and had a higher chance of being older, female, and receiving primary care at MM in the previous two years.

Almost 34.3% of individuals reported shortness of breath, 30.6% experienced anxiety, 28.5% had fatigue and malaise, 27.2% had depression, 25.4% suffered from sleep disturbances, 23.6% reported asthma, 21.4% experienced headaches, 13.8% had migraine, 13.0% had a cough, and 12.6% had joint pain. All of the 29 PASC symptoms that were examined were enriched, with 27 of them reaching phenome-wide significance and two did not. PheWAS also suggested the enrichment of several illnesses, including musculoskeletal problems, infectious diseases, as well as digestive disorders.

PheWAS compared 1,212 cases to 11,919 matched controls, utilizing only the diagnoses reported at least two weeks before being COVID-19 positive. This allowed the identification of putative pre-COVID-19 symptoms that predispose COVID-19 diagnoses to PASC. Out of the 1,405 examined PheCodes, phenome-wide relevance was exhibited for irritable bowel syndrome (IBS), nausea and vomiting, concussion, respiratory abnormalities, food allergies, and general circulatory disease.

The frequencies and corresponding signals across the three PheWAS were employed to determine if PASC-associated phenotypes associated with the pre- and acute-COVID-19 periods resulted in novel PASC symptoms or whether they become long-term PASC symptoms by themselves.

Conclusion

Overall, the study demonstrated an agnostic screening of time-stamped EHR

data that revealed a wide range of diagnoses linked with PASC across several categories. The study also noted a complex arrangement of possible predisposing factors which may be used to develop risk stratification strategies. However, extensive research will be required to adequately characterize PASC and its variants, particularly with regard to long-term effects, and to take into account more thorough risk models.

*Important notice

medRxiv publishes preliminary scientific reports that are not peer-reviewed and, therefore, should not be regarded as conclusive, guide clinical practice/health-related behavior, or treated as established information.

Journal reference:

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Bhavana Kunkalikar is a medical writer based in Goa, India. Her academic background is in Pharmaceutical sciences and she holds a Bachelor's degree in Pharmacy. Her educational background allowed her to foster an interest in anatomical and physiological sciences. Her college project work based on 'The manifestations and causes of sickle cell anemia' formed the stepping stone to a life-long fascination with human pathophysiology.

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Skin Manifestations Associated with COVID-19: Current Knowledge and Future Perspectives

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Keywords
COVID-19 · Cutaneous manifestations · SARS-CoV-2

Abstract
Background: Coronavirus disease-19 (COVID-19) is an ongoing global pandemic caused by the "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), which was isolated for the first time in Wuhan (China) in December 2019. Common symptoms include fever, cough, fatigue, dyspnea and hypogeusia/hyposmia. Among extrapulmonary signs associated with COVID-19, dermatological manifestations have been increasingly reported in the last few months. ***Summary:*** The polymorphic nature of COVID-19-associated cutaneous manifestations led our group to propose a classification, which distinguishes the following six main clinical patterns: (i) urticarial rash, (ii) confluent erythematous/maculopapular/morbilliform rash, (iii) papulovesicular exanthem, (iv) chilblain-like acral pattern, (v) livedo reticularis/racemosa-like pattern, (vi) purpuric "vasculitic" pattern. This review summarizes the current knowledge on COVID-19-associated cutaneous manifestations, focusing on clinical features and therapeutic management of each category and attempting to give an overview of the hypothesized pathophysiological mechanisms of these conditions.

Introduction

In December 2019, a novel zoonotic RNA virus named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) was isolated in patients with pneumonia in Wuhan, China. Since then, the disease caused by this virus, called "coronavirus disease-19" (COVID-19), has spread throughout the world at a staggering speed becoming a pandemic emergency [1]. Although COVID-19 is best known for causing fever and respiratory symptoms, it has been reported to be associated also with different extrapulmonary manifestations, including dermatological signs [2]. Whilst the COVID-19-associated cutaneous manifestations have been increasingly reported, their exact incidence has yet to be estimated, their pathophysiological mechanisms are largely unknown, and the role, direct or indirect, of SARS-CoV-2 in their pathogenesis is still debated. Furthermore, evidence is accumulating that skin manifestations associated with COVID-19 are extremely polymorphic [3]. In this regard, our group proposed the following six main clinical patterns of COVID-19-associated cutaneous manifestations in a recently published review article: (i) urticarial rash, (ii) confluent erythematous/maculopapular/morbilliform rash, (iii) papulovesicular exanthem, (iv) chilblain-like acral pattern, (v) livedo reticularis/racemosa-like pat-

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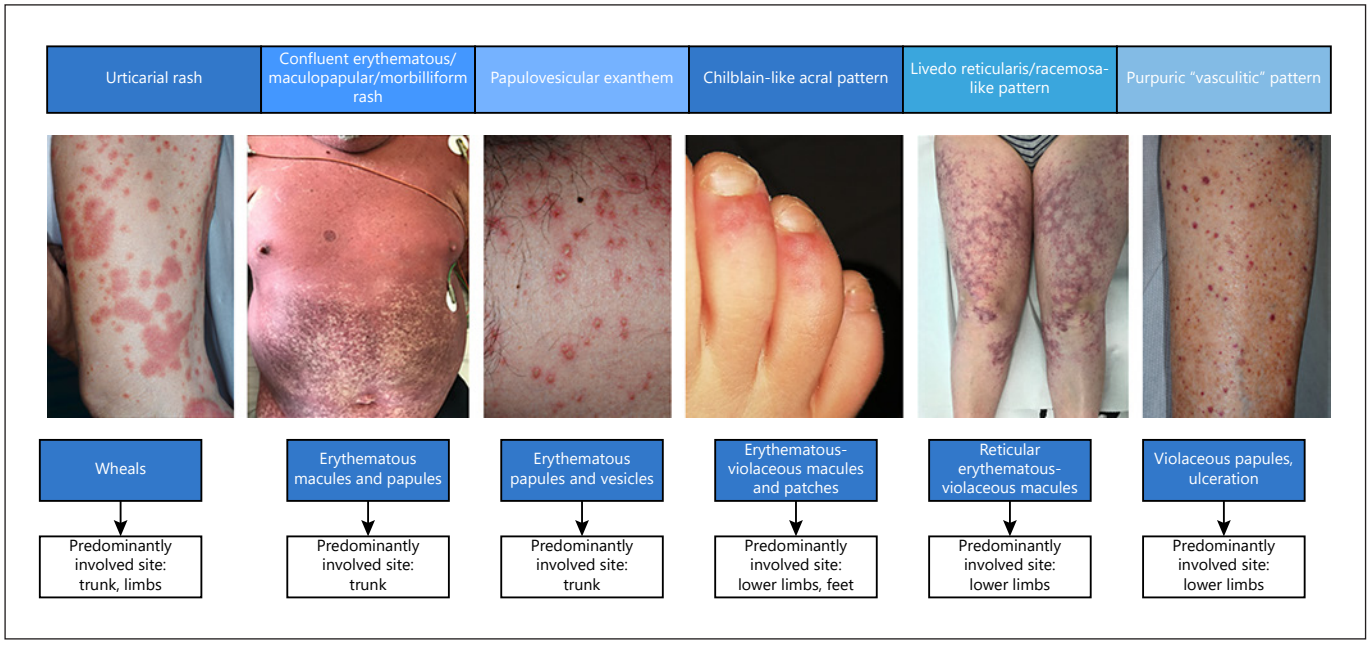

Fig. 1. Clinical features of COVID-19-associated cutaneous manifestations.

tern, (vi) purpuric "vasculitic" pattern (shown in Fig. 1) [2]. Other authors have attempted to bring clarity in this field, suggesting possible classifications of COVID-19-associated cutaneous manifestations [4–6]. Finally, distinguishing nosological entities "truly" associated with COVID-19 from cutaneous drug reactions or exanthems due to viruses other than SARS-CoV-2 remains a frequent open problem.

Herein, we have striven to provide a comprehensive overview of the cutaneous manifestations associated with COVID-19 subdivided according to the classification by Marzano et al. [2], focusing on clinical features, histopathological features, hypothesized pathophysiological mechanisms and therapeutic management.

Urticarial Rash

Clinical Features and Association with COVID-19 Severity

It is well known that urticaria and angioedema can be triggered by viral and bacterial agents, such as cytomegalovirus, herpesvirus, and Epstein-Barr virus and mycoplasma. However, establishing a cause-effect relationship may be difficult in single cases [7, 8]. Urticarial eruptions associated with COVID-19 have been first reported by Recalcati [9] in his cohort of hospitalized patients, accounting for 16.7% of total skin manifestations. Urticaria-like eruptions have been subsequently described in other cohort studies. Galván Casas et al. [4] stated that urticarial rash occurred in 19% of their cohort, tended to appear simultaneously with systemic symptoms, lasted approximately 1 week and was associated with medium-high severity of COVID-19. Moreover, itch was almost always present [4]. Freeman et al. [10] found a similar prevalence of urticaria (16%) in their series of 716 cases, in which urticarial lesions predominantly involved the trunk and limbs, relatively sparing the acral sites. As shown in Table 1, urticaria-like signs accounted for 11.9% of cutaneous manifestations seen in an Italian multicentric cohort study on 159 patients [unpubl. data]. Urticarial lesions associated with fever were reported to be early or even prodromal signs of COVID-19, in the absence of respiratory symptoms, in 3 patients [11–13]. Therefore, the authors of the reports suggested that isolation is needed for patients developing such skin symptoms if COVID-19 infection is suspected in order to prevent possible SARS-CoV-2 transmission [11–13]. COVID-19-related urticaria occurred also in a familial cluster, involving 2 patients belonging to a Mexican family of 5 people, all infected by SARS-CoV-2 and suffering also from anosmia, ageusia, chills and dizziness [14]. Angioedema may accompany COVID-19-related urticaria, as evidenced by the case published in June 2020 of an elderly man presenting with urticaria, angioedema, general malaise, fatigue,

Table 1. Prevalence of different clinical patterns in the main studies on COVID-19-associated cutaneous manifestations

First author (total size of study population)	Number of patients with urticarial rash (%)	Number of patients with confluent erythematous/ maculopapular/ morbilliform rash (%)	Number of patients with papulo-vesicular exanthem (%)	Number of patients with chilblain-like acral pattern (%)	Number of patients with livedo reticularis/ racemosa-like pattern (%)	Number of patients with purpuric "vasculitic" pattern (%)
Galván Casas [4] (375)	73 (19)	176 (47)	34 (9)	71 (19)	21 (6)	
Freeman [10] (716)	55 (8.1)	115 (16.1)	49 (7.2)	422 (62)	46 (6.4)	51 (7.1)
Askin [29] (52)	7 (13.5)	29 (55.8)	3 (5.8)	1 (1.9)	0	8 (15.4)
De Giorgi [20] (53)	14 (26)	37 (70)	2 (4)	0	0	0
Unpublished data from an Italian multicentric study (159)	19 (11.9)	48 (30.2)	29 (18.2)	46 (28.9)	4 (2.5)	13 (8.2)

fever and pharyngodynia [15]. Urticarial vasculitis has also been described in association with COVID-19 in 2 patients [16].

Histopathological Findings

Histopathological studies of urticarial rashes are scant. In a 60-year-old woman with persistent urticarial eruption and interstitial pneumonia who was not under any medication, Rodriguez-Jiménez et al. [17] found on histopathology slight vacuolar interface dermatitis with occasional necrotic keratinocytes curiously compatible with an erythema multiforme-like pattern. Amatore et al. [18] documented also the presence of lichenoid and vacuolar interface dermatitis, associated with mild spongiosis, dyskeratotic basal keratinocytes and superficial perivascular lymphocytic infiltrate, in a biopsy of urticarial eruption associated with COVID-19 (Fig. 2).

Therapeutic Options

Shanshal [19] suggested low-dose systemic corticosteroids as a therapeutic option for COVID-19-associated urticarial rash. Indeed, the author hypothesized that low-dose systemic corticosteroids, combined with nonsedating antihistamines, can help in managing the hyperactivity of the immune system in COVID-19, not only to control urticaria, but also to improve possibly the survival rate in COVID-19.

Confluent Erythematous/Maculopapular/ Morbilliform Rash

Clinical Features and Association with COVID-19 Severity

Maculopapular eruptions accounted for 47% of all cutaneous manifestations in the cohort of Galván Casas et al. [4], for 44% of the skin manifestations included in the study by Freeman et al. [10], who further subdivided this group of cutaneous lesions into macular erythema (13%), morbilliform exanthems (22%) and papulosquamous lesions (9%), and for 30.2% of the cutaneous manifestations included in the unpublished Italian multicentric study shown in Table 1. The prevalence of erythematous rash was higher in other studies, like that published by De Giorgi et al. [20] in May 2020, in which erythematous rashes accounted for 70% of total skin manifestations. In the series by Freeman et al. [10], macular erythema, morbilliform exanthems and papulosquamous lesions were predominantly localized on the trunk and limbs, being associated with pruritus in most cases. In the same series, these lesions occurred more frequently after COVID-19 systemic symptoms' onset [21]. The clinical picture of the eruptions belonging to this group may range from erythematous confluent rashes to maculopapular eruptions and morbilliform exanthems. Erythematous lesions may show a purpuric evolution [21] or coexist from the beginning with purpuric lesions [22]. Erythematous papules may also be arranged in a morbilliform pattern [23]. In a subanalysis of the COVID-Piel Study [4] on maculopapular eruptions including also purpuric, erythema multiforme-like, pityriasis rosea-like, erythema elevatum diutinum-like and perifollicular eruptions, morbilliform exanthems were the most frequent maculopapular pattern (n = 80/176, 45.5%) [24]. This study showed that in most cases lesions were generalized, symmetrical and started on the trunk with centrifugal progression. In the same subanalysis, hospital admission due to pneumonia was very frequent (80%) in patients with a morbilliform pattern [24]. In this group, the main differential diagnoses are represented by exanthems due to viruses other than SARS-CoV-2 and drug-induced cutaneous reactions.

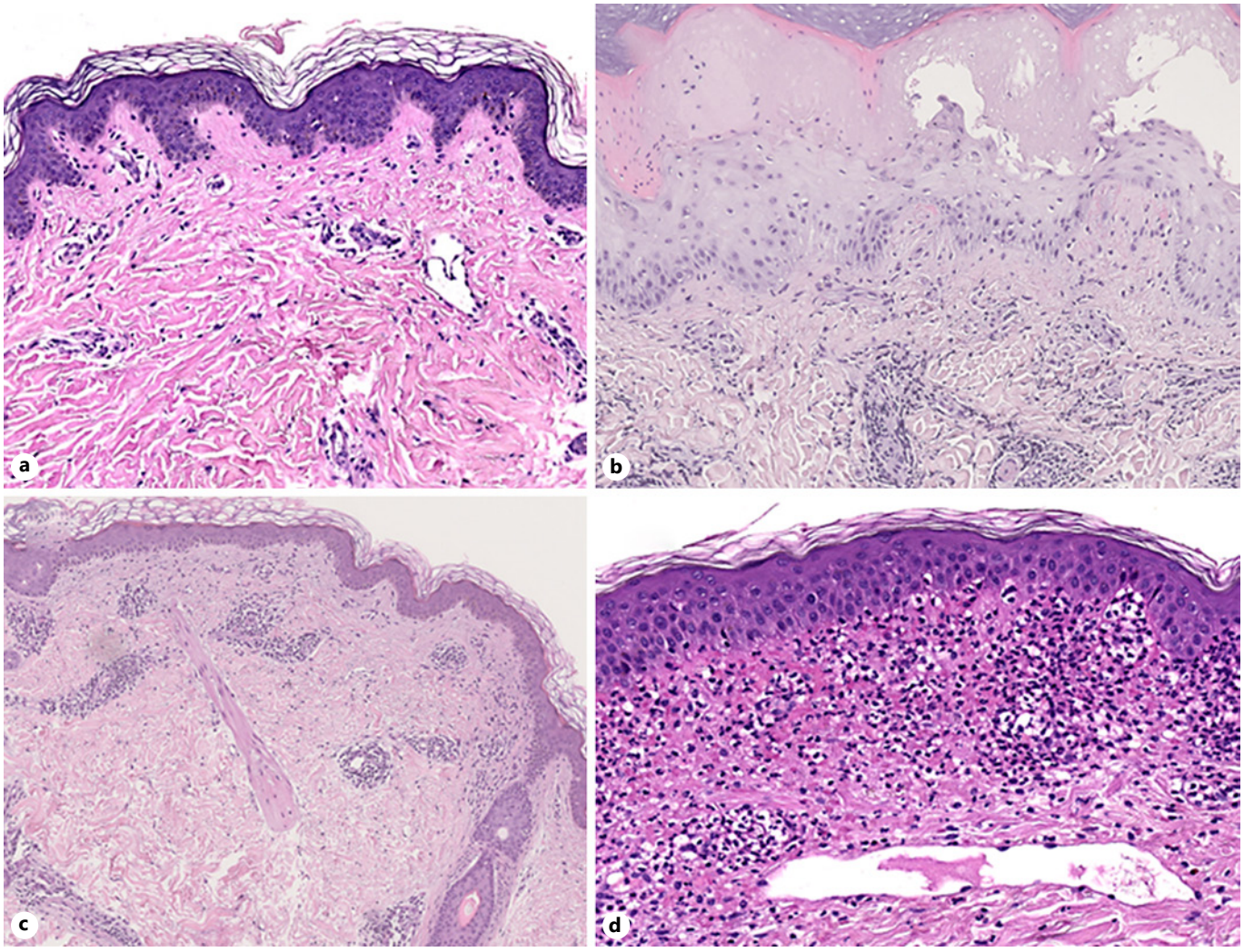

Fig. 2. Histopathological features of the main cutaneous patterns associated with COVID-19. **a** Urticarial rash. **b** Confluent erythematous maculopapular/morbilliform rash. **c** Chilblain-like acral lesions. **d** Purpuric "vasculitic" pattern.

Histopathological Findings

Histopathology of erythematous eruptions was described by Gianotti et al. [25], who found vascular damage in all the 3 cases examined. A clinicopathological characterization of late-onset maculopapular eruptions related to COVID-19 was provided also by Reymundo et al. [26], who observed a mild superficial perivascular lymphocytic infiltrate on the histology of 4 patients. In contrast, Herrero-Moyano et al. [27] observed dense neutrophilic infiltrates in 8 patients with late maculopapular eruptions. The authors of the former study postulated that this discrepancy could be attributable to the history of new drug assumptions in the series of Herrero-Moyano et al. [26] (Fig. 2).

Therapeutic Options

The management of confluent erythematous/maculopapular/morbilliform rash varies according to the severity of the clinical picture. Topical corticosteroids can be sufficient in most cases [23], systemic corticosteroids deserving to be administered just in more severe and widespread presentations.

Papulovesicular Exanthem

Clinical Features and Association with COVID-19 Severity

COVID-19-associated papulovesicular exanthem was first extensively reported in a multicenter Italian

case series of 22 patients published in April 2020 [28]. In this article, it was originally described as "varicella-like" due to resemblance of its elementary lesions to those of varicella. However, the authors themselves underlined that the main clinical features of COVID-19-associated papulovesicular exanthem, namely trunk involvement, scattered distribution and mild/absent pruritus, differentiated it from "true" varicella. In this study, skin lesions appeared on average 3 days after systemic symptoms' onset and healed after 8 days, without scarring sequelae [28]. The exact prevalence of papulovesicular exanthems is variable. Indeed, in a cohort of 375 patients with COVID-19-associated cutaneous manifestations [4], patients with papulovesicular exanthem were 34 (9%), while they were 3 out of 52 (5.8%), 1 out of 18 (5.5%) and 2 out of 53 (4%) in the cohorts published by Askin et al. [29], Recalcati [9] and De Giorgi et al. [20], respectively. In the Italian multicentric study shown in Table 1, papulovesicular rash accounted for 18.2% of skin manifestations. Furthermore, even if papulovesicular exanthem tends to involve more frequently the adult population, with a median age of 60 years in the study by Marzano et al. [28], also children may be affected [30]. Galván Casas et al. [4] reported that vesicular lesions generally involved middle-aged patients, before systemic symptoms' onset in 15% of cases, and were associated with intermediate COVID-19 severity. Fernandez-Nieto et al. [31] conducted a prospective study on 24 patients diagnosed with COVID-19-associated vesicular rash. In this cohort, the median age (40.5 years) was lower than that reported by Marzano et al. [28], and COVID-19 severity was mostly mild or intermediate, with only 1 patient requiring intensive unit care support. In our cohort of 22 patients, a patient was hospitalized in the intensive care unit and 3 patients died [28]. Vesicular rash, which was generally pruritic, appeared after COVID-19 diagnosis in most patients (n = 19; 79.2%), with a median latency time of 14 days [31]. Two different morphological patterns were found: a widespread polymorphic pattern, more common and consisting of small papules, vesicles and pustules of different sizes, and a localized pattern, less frequent and consisting of monomorphic lesions, usually involving the mid chest/upper abdominal region or the back [31].

Histopathological Findings

Mahé et al. [32] reported on 3 patients with typical COVID-19-associated papulovesicular rash, in which the histological pattern of skin lesions showed prominent acantholysis and dyskeratosis associated with the presence of an unilocular intraepidermal vesicle in a suprabasal location. Based on these histopathological findings, the authors refused the term "varicella-like rash" and proposed a term which was more suitable in their view: "COVID-19-associated acantholytic rash." Histopathological findings of another case of papulovesicular eruption revealed extensive epidermal necrosis with acantholysis and swelling of keratinocytes, ballooning degeneration of keratinocytes and signs of endotheliitis in the dermal vessels [33]. Acantholysis and ballooned keratinocytes were found also by Fernandez-Nieto et al. [31] in 2 patients.

The differential diagnosis with infections caused by members of the *Herpesviridae* family has been much debated. Tammaro et al. [34] described the onset of numerous, isolated vesicles on the back 8 days after COVID-19 diagnosis in a Barcelonan woman and reported on 2 patients from Rome presenting with isolated, mildly pruritic erythematous-vesicular lesions on their trunk, speculating that these manifestations might be due to viruses belonging to the Herpesviridae family. On the other hand, classic herpes zoster has been reported to complicate the course of COVID-19 [35].

The controversy regarding the role of herpesvirus in the etiology of papulovesicular exanthems fuelled an intense scientific debate. Indeed, some authors raised the question whether papulovesicular exanthem associated with COVID-19 could be diagnosed without ruling out varicella zoster virus and herpes simplex virus with Tzanck smear or polymerase chain reaction (PCR) for the Herpesviridae family in the vesicle fluid or on the skin [36, 37]. In our opinion, even if seeking DNA of Herpesviridae family members is ideally advisable, clinical diagnosis may be reliable in most cases, and the role of herpes viruses as mere superinfection in patients with dysfunctional immune response associated with COVID-19 needs to be considered [38]. To our knowledge, SARS-CoV-2 has not been hitherto isolated by means of reverse transcriptase PCR in the vesicle fluid of papulovesicular rash [33, 31].

Therapeutic Options

No standardized treatments for COVID-19-related papulovesicular exanthem are available, also given that it is self-healing within a short time frame. Thus, a "wait-and-see" strategy may be recommended.

Chilblain-Like Acral Pattern

Clinical Features and Association with COVID-19 Severity

COVID-19-related chilblain-like acral lesions have been first described in a 13-year-old boy by Italian authors in early March [39]. Since then, several "outbreaks" of chilblain-like acral lesions chiefly involving young adults and children from different countries worldwide have been posted on social media and published in the scientific literature [40–46]. Caucasians seem to be significantly more affected than other ethnic groups [47, 48]. Chilblain-like acral lesions were the second most frequent cutaneous manifestation ($n = 46/159$; 28.9%) in the multicenter Italian study shown in Table 1. Different pathogenetic hypotheses, including increased interferon release induced by COVID-19 and consequent cytokine-mediated inflammatory response, have been suggested [49]. Furthermore, virus-induced endothelial damage as well as an obliterative microangiopathy and coagulation abnormalities could be mechanisms involved in the pathogenesis of these lesions [50]. Chilblain-like acral lesions associated with COVID-19 were depicted as erythematous-violaceous patches or plaques predominantly involving the feet and, to a lesser extent, hands [40, 51]. Rare cases of chilblain-like lesions involving other acral sites, such as the auricular region, were also reported [52]. The occurrence of blistering lesions varied according to the case series analyzed; Piccolo et al. [51], indeed, reported the presence of blistering lesions in 23 out of 54 patients, while other authors did not describe bullous lesions in their series [40, 47]. Dermoscopy of these lesions revealed the presence of an indicative pattern represented by a red background area with purpuric globules [53]. Pain/burning sensation as well as pruritus were commonly reported symptoms, even if a small proportion of patients presented with asymptomatic lesions [40, 44, 47]. Unlike other COVID-19-related cutaneous findings, chilblain-like acral lesions tended to mostly involve patients without systemic symptoms.

The frequent occurrence of chilblain-like lesions in the absence of cold exposure and the involvement of patients without evident COVID-19-related symptoms raised the question whether these manifestations were actually associated with SARS-CoV-2 infection.

Histopathological and Pathophysiological Findings

Chilblain-like lesions share many histopathological features with idiopathic and autoimmunity-related chilblains, including epidermal necrotic keratinocytes, dermal edema, perivascular and perieccrine sweat gland lymphocytic inflammation. Vascular changes such as endotheliitis and microthrombi may be found [40, 45, 54, 55] (Fig. 2).

Data on the real association between chilblain-like acral lesions and COVID-19 are controversial.

The first case series failed to perform SARS-CoV-2 testing in all patients, also due to logistic problems and economic restrictions, and diagnosed COVID-19 only in a minority of patients with chilblain-like acral lesions [40, 44, 47]. Subsequently, some authors systematically sought SARS-CoV-2 with serology and/or nasopharyngeal swab in patients with chilblain-like acral lesions. In their cohort of 38 children with pseudo-chilblain, Caselli et al. [56] showed no evidence of SARS-CoV-2 infection by PCR or serology. Chilblain-like acral lesions appeared not to be directly associated with COVID-19 also in the case series by Herman et al. [57]. These authors failed to detect SARS-CoV-2 in nasopharyngeal swabs and skin biopsies and demonstrated no specific anti-SARS-CoV-2 immunoglobulin IgM or IgG antibodies in blood samples. Therefore, they concluded that lifestyle changes associated with lockdown measures might be a possible explanation for these lesions [57]. Similar results were obtained also by other authors [58–63] weakening the hypothesis of a direct etiological link between SARS-CoV-2 and chilblain-like acral lesions.

Opposite conclusions have been drawn by Colmenero et al. [64], who demonstrated by immunohistochemistry and electron microscopy the presence of SARS-CoV-2 in endothelial cells of skin biopsies of 7 children with chilblain-like acral lesions, suggesting that virus-induced vascular damage and secondary ischemia could explain the pathophysiology of these lesions.

In the absence of definitive data on chilblain-like acral lesions' pathogenesis, the occurrence of such lesions should prompt self-isolation and confirmatory testing for SARS-CoV-2 infection [65].

Therapeutic Options

In the absence of significant therapeutic options for chilblain-like acral lesions associated with COVID-19 and given their tendency to spontaneously heal, a "wait-and-see" strategy may be suggested.

Livedo Reticularis/Racemosa-Like Pattern

Clinical Features and Association with COVID-19 Severity

Livedo describes a reticulate pattern of slow blood flow, with consequent desaturation of blood and bluish

cutaneous discoloration. It has been divided into: (i) livedo reticularis, which develops as tight, symmetrical, lace-like, dusky patches forming complete rings surrounding a pale center, generally associated with cold-induced cutaneous vasoconstriction or vascular flow disturbances such as seen in polycythemia and (ii) livedo racemosa, characterized by larger, irregular and asymmetrical rings than seen in livedo reticularis, more frequently associated with focal impairment of blood flow, as it can be seen in Sneddon's syndrome [66].

In our classification, the livedo reticularis/racemosa-like pattern has been distinguished by the purpuric "vasculitic" pattern because the former likely recognizes a occlusive/microthrombotic vasculopathic etiology, while the latter can be more likely considered the expression of a "true" vasculitic process [2]. Instead, the classification by Galván Casas et al. [4] merged these two patterns into the category "livedo/necrosis".

In a French study on vascular lesions associated with COVID-19, livedo was observed in 1 out of 7 patients [43]. In the large cases series of 716 patients by Freeman et al. [10], livedo reticularis-like lesions, retiform purpura and livedo racemosa-like lesions accounted for 3.5, 2.6 and 0.6% of all cutaneous manifestations, respectively. In the multicentric Italian study, livedo reticularis/racemosa-like lesions accounted for 2.5% of cutaneous manifestations (Table 1).

The pathogenic mechanisms at the basis of small blood vessel occlusion are yet unknown, even if neurogenic, microthrombotic or immune complex-mediated etiologies have been postulated [67].

Livedo reticularis-like lesions are frequently mild, transient and not associated with thromboembolic complications [68, 69]. On the contrary, livedo racemosa-like lesions and retiform purpura have often been described in patients with severe coagulopathy [60–72].

Histopathological and Pathophysiological Findings

The histopathology of livedoid lesions associated with COVID-19 has been described by Magro et al. [73], who observed in 3 patients pauci-inflammatory microthrombotic vasculopathy. The same group demonstrated that in the thrombotic retiform purpura of patients with severe COVID-19, the vascular thrombosis in the skin and internal organs is associated with a minimal interferon response permitting increased viral replication with release of viral proteins that localize to the endothelium inducing widespread complement activation [74], which is frequent in COVID-19 patients and probably involved in the pathophysiology of its clinical complications [75].

Therapeutic Options

In view of the absence of significant therapeutic options for livedo reticularis/racemosa-like lesions associated with COVID-19, a "wait-and-see" strategy may be suggested.

Purpuric "Vasculitic" Pattern

Clinical Features and Association with COVID-19 Severity

The first COVID-19-associated cutaneous manifestation with purpuric features was reported by Joob et al. [76], who described a petechial rash misdiagnosed as dengue in a COVID-19 patient. Purpuric lesions have been suggested to occur more frequently in elderly patients with severe COVID-19, likely representing the cutaneous manifestations associated with the highest rate of COVID-19-related mortality [4]. This hypothesis is corroborated by the unfavorable prognosis observed in several cases reported in the literature [77, 78].

The purpuric pattern reflects the presence of vasculitic changes probably due to the direct damage of endothelial cells by the virus or dysregulated host inflammatory responses induced by COVID-19.

These lesions are likely to be very rare, representing 8.2% of skin manifestations included in the Italian multicentric study shown in Table 1. In their case series of 7 patients with vascular skin lesions related to COVID-19, Bouaziz et al. [43] reported 2 patients with purpuric lesions with ($n = 1$) and without ($n = 1$) necrosis. In the series by Freeman et al. [10], 12/716 (1.8%) and 11/716 (1.6%) cases of patients with palpable purpura and dengue-like eruption, respectively, have been reported. Galván Casas et al. [4] reported 21 patients with "livedo/necrosis," most of whom presenting cutaneous signs in concomitance with systemic symptoms' onset.

Purpuric lesions may be generalized [79], localized in the intertriginous regions [80] or arranged in an acral distribution [81]. Vasculitic lesions may evolve into hemorrhagic blisters [77]. In most severe cases, extensive acute necrosis and association with severe coagulopathy may be seen [78]. Dermoscopy of purpuric lesions revealed the presence of papules with incomplete violaceous rim and a central yellow globule [82].

Histopathological Findings

When performed, histopathology of skin lesions showed leukocytoclastic vasculitis [77, 79], severe neutrophilic infiltrate within the small vessel walls and in their

Table 2. Summary of clinical features, histopathological findings, severity of COVID-19 systemic symptoms and therapeutic options of COVID-19-related skin manifestations

	Clinical features	COVID-19 severity	Histopathological findings	Therapeutic options
Urticarial rash	Itching urticarial rash predominantly involving the trunk and limbs; angioedema may also rarely occur	Intermediate severity	Vacuolar interface dermatitis associated with superficial perivascular lymphocytic infiltrate	Low-dose systemic corticosteroids combined with nonsedating antihistamines
Confluent erythematous/ maculopapular/morbilliform rash	Generalized, symmetrical lesions starting from the trunk with centrifugal progression; purpuric lesions may coexist from the onset or develop during the course of the skin eruption	Intermediate severity	Superficial perivascular lymphocytic and/or neutrophilic infiltrate	Topical corticosteroids for mild cases; systemic corticosteroids for severe cases
Papulovesicular exanthem	(i) Widespread polymorphic pattern consisting of small papules, vesicles and pustules of different sizes; (ii) localized pattern consisting of papulovesicular lesions, usually involving the mid chest/upper abdominal region or the back	Intermediate severity	Prominent acantholysis and dyskeratosis associated with unilocular intraepidermal vesicles in a suprabasal location	Wait and see
Chilblain-like acral pattern	Erythematous-violaceous patches or plaques predominantly involving the feet or, to a lesser extent, hands. Pain/burning sensation as well as pruritus were commonly reported symptoms	Asymptomatic status	Perivascular and periadnexal dermal lymphocytic infiltrates	Wait and see
Livedo reticularis/ racemosa-like pattern	Livedo reticularis-like lesions: mild, transient, symmetrical, lace-like, dusky patches forming complete rings surrounding a pale center. Livedo racemosa-like lesions: large, irregular and asymmetrical violaceous annular lesions frequently described in patients with severe coagulopathy	Livedo reticularis-like lesions: intermediate severity; livedo racemosa-like lesions: high severity	Pauci-inflammatory microthrombotic vasculopathy	Wait and see
Purpuric "vasculitic" pattern	Purpuric lesions may be generalized, arranged in an acral distribution or localized in the intertriginous regions. Purpuric elements may evolve into hemorrhagic blisters, possibly leading to necrotic-ulcerative lesions	High severity	Leukocytoclastic vasculitis, severe perivascular neutrophilic and lymphocytic infiltrate, presence of fibrin and endothelial swelling	Topical corticosteroids for mild cases; systemic corticosteroids for severe cases

The correlation between severity of COVID-19 systemic symptoms and skin manifestations has been inferred mainly from the study by Freeman et al. [10].

proximity [77], intense lymphocytic perivascular infiltrates [81], presence of fibrin [79, 81] and endothelial swelling [82] (Fig. 2).

Therapeutic Options

Topical corticosteroids have been successfully used for treating mild cases of purpuric lesions [80]. Cases with necrotic-ulcerative lesions and widespread presentation may be treated with systemic corticosteroids.

Other COVID-19-Associated Cutaneous Manifestations

Other peculiar rare COVID-19-related cutaneous manifestations that cannot be pigeonholed in the classification proposed by our group [2] include, among others, the erythema multiforme-like eruption [83], pityriasis rosea-like rash [84], multi-system inflammatory syndrome in children [85], anagen effluvium [86] and a pseudoherpetic variant of Grover disease [87]. However, the spectrum of possible COVID-19-associated skin manifesta-

tions is likely to be still incomplete, and it is expected that new entities associated with this infection will be described.

Conclusion

COVID-19-associated cutaneous manifestations have been increasingly reported in the last few months, garnering attention both from the international scientific community and from the media. A few months after the outbreak of the pandemic, many narrative and systematic reviews concerning the dermatological manifestations of COVID-19 have been published [2, 3, 6, 88–91]. A summary of clinical features, histopathological findings, severity of COVID-19 systemic symptoms and therapeutic options of COVID-19-related skin manifestations has been provided in Table 2.

Albeit several hypotheses on pathophysiological mechanisms at the basis of these skin findings are present in the literature [50, 92, 93], none of them is substantiated by strong evidence, and this field needs to be largely elucidated. Moreover, cutaneous eruptions due to viruses other than SARS-CoV-2 [35, 37] or drugs prescribed for the management of this infection [94, 95] always need to be ruled out.

Experimental pathophysiological studies and clinical data derived from large case series are still needed for shedding light onto this novel, underexplored and fascinating topic.

Key Message

Although COVID-19-associated cutaneous manifestations have been increasingly reported, their pathophysiological mechanisms need to be extensively explored. The conditions may be distinguished in six clinical phenotypes, each showing different histopathological patterns.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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Letter to the editor

Symptoms persist in patients two years after COVID-19 infection: a prospective follow-up study

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To the editor:

Studies have shown patients can experience post-acute COVID-19 syndrome, characterized by the persistence of symptoms ≥4 weeks after initial infection with COVID-19, for ≤1 year [1–5]. We sought to gain further perspective by conducting a 2-year follow-up study of patients diagnosed with COVID-19 to evaluate long-term sequelae.

This is a prospective, longitudinal, Institutional Review Board–approved cohort study consisting of patients diagnosed with COVID-19 infection in March and April of 2020 in the St. Joseph's Health Network. The individuals with confirmed SARS-CoV-2, who were either hospitalized or tested positive in the outpatient setting, were included. The patients <18 years of age or those with cognitive impairment were excluded. Informed consent was obtained over telephone and participants were contacted during March and April of 2021 to complete a comprehensive questionnaire to evaluate for persistent symptoms after their initial diagnosis with COVID-19. The patients who reported persistence of symptoms at a 1-year follow-up were contacted again at a 2-year follow-up in March of 2022 to assess for persistence of COVID-19–related symptoms. Logistic regression analysis was performed to identify predictors of symptom persistence and the McNemar test was used to compare the duration of symptoms among those surveyed both years.

Five hundred patients were invited, of which 173 participated, including 91 patients who were previously hospitalized. The mean age was 51.5 years old, with an age range of 18 to 95, of whom 49.42% were male. The most common ethnicity was Hispanic (46.24%) and the most common comorbidity was hypertension (39.5%) (Table 1). At 12 months follow-up 50.8% of the patients experienced at least one persistent symptom (Fig. 1A); the most common symptoms were shortness of breath (25%), fatigue (24%), anxiety (21%), difficulty focusing/brain fog (18%), body aches (18%), and headaches (16%) (Fig. 1B). At 24 months follow-up, 23.1% of the patients experienced at least one persistent symptom (Fig. 1A); the most common symptoms being shortness of breath (13.2%), fatigue (12.1%), difficulty focusing/brain fog (10.4%), memory loss (9.2%), and anxiety (8.1%) (Fig. 1B). Thirteen patients were lost to follow-up from year 1 to year 2.

Anxiety (p: 0.001), headaches (p: 0.002), shortness of breath (p: 0.012), and fatigue (p: 0.049) were most likely to improve between the 1- to 2-year follow-ups. Logistic regression analysis adjusted for age, gender, obesity, and comorbidities (at least 1) was used for the comparison of men to women and inpatients to outpatients. Wilcoxon rank sum test or Fisher's exact test were used for the continuous and categorical comparisons of the two groups. At 1-year follow-up, women were more likely than men to have persistent symptoms (62.9% vs 38.1%, respectively, p: 0.001). At 2-year follow-up, women again were more likely than men to have at least one persistent symptom (53.6% vs 31.3%, respectively, p: 0.048). The proportion of those with persistent symptoms was similar between inpatients and outpatients (52.9% vs 48.0%, respectively, p: 0.052), although there appeared to be a trend toward higher rates among inpatients.

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Table 1
Baseline characteristics and demographics of patient sample

Baseline characteristics & demographics	Total population $n = 173$ (%)	Inpatient $n = 91$ (%)	Outpatient $n = 82$ (%)
Mean age in years	51.8 (SD:15$_2$)	55.7 (SD:155)	47.5 (SD:13.5)
Sex			
Male	85 (49.42)	50 (55.56)	35 (42.68)
Female	87 (50.58)	40 (44.44)	47 (57.32)
Medical comorbidities			
Hypertension	68 (39.5)	43 (47.78)	25 (30.49)
Obesity	45 (26.9)	27 (30.34)	17 (21.52)
Diabetes	33 (19.1)	27 (29.67)	6 (7.32)
Asthma	25 (14.5)	12 (13.19)	13 (15.85)
Coronary artery disease	9 (5.2)	7 (7.69)	2 (2.44)
Chronic obstructive pulmonary disease	3 (1.7)	3 (3.30)	0 (0)
Race/ethnicity			
Hispanic	80 (46.24)	41 (45.05)	39 (47.56)
African American	48 (27.74)	30 (32.96)	18 (21.95)
Caucasian/white	32 (18.49)	13 (14.28)	19 (23.17)
Asian	13 (7.51)	7 (7.69)	6 (7.31)
Required invasive mechanical ventilation	3 (1.8)	3 (3.37)	N/A

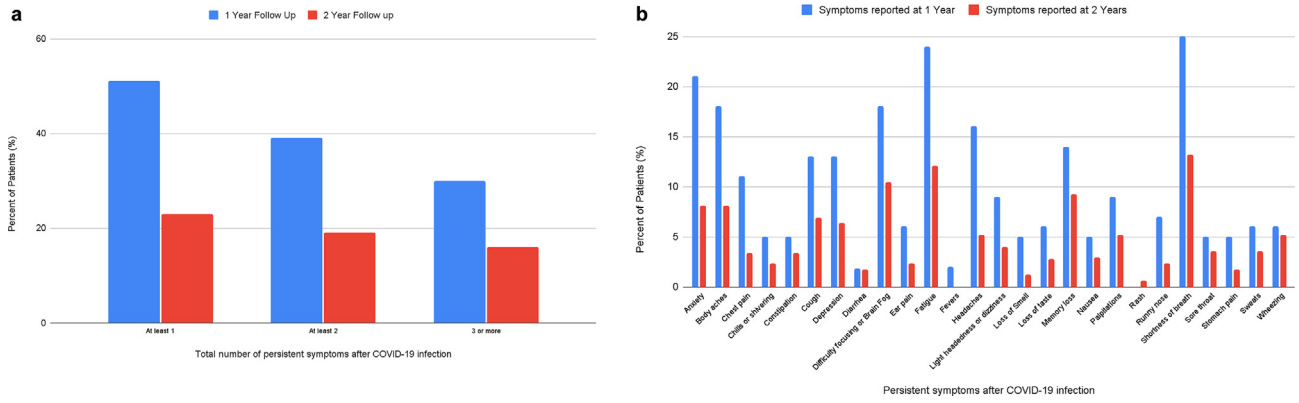

Fig. 1. Number of Persistent symptoms following infection with COVID-19 at one and two year follow up

Two years after infection, 23.1% of patients still experienced at least one persistent symptom. At 1- and 2-years follow-up, shortness of breath and fatigue were the most common symptoms. In other studies, fatigue and shortness of breath were similarly found to be amongst the most commonly reported symptoms after 1 year [1–5]. The symptoms most likely to improve between years 1 and 2 were anxiety, headaches, shortness of breath, and fatigue. Women were more likely to have persistent symptoms at 2 years compared with men. Women have been found to experience more persistent symptoms in other studies as well [4,5].

To our knowledge this was the first U.S. study to describe the duration and symptomatology of COVID-19 in patients over a 2-year follow-up period. Most of the patients had reduction and resolution in their symptoms over the 2-year period; however, nearly a quarter of patients still experience persistent symptoms. The study limitations included a small patient sample, self-recall bias, loss of patients to follow-up, and being a single centre study. The study would have benefited from more frequent follow-up intervals to provide a more accurate timeline of symptom recovery. The aetiology and treatment of post-acute COVID-19 syndrome remains poorly defined. With over half a billion people infected worldwide, thousands of new infections daily, and waning protection from immunization or prior infection, a global public health crisis could be looming. For millions of patients, post-acute COVID-19 syndrome can significantly impair cognitive function, quality of life, and the ability to work at full capacity for years to come [1–4]. These points highlighted the urgent need for larger scale studies to better understand and effectively treat this post viral phenomenon.

Transparency declaration

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Author contributions

CM was responsible for concept and design. CM, SN, SC, SR, GH, and HJ were responsible for acquisition, analysis, and interpretation of data. CM, SN, and HJ drafted the manuscript. HJ was responsible for statistical analysis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.06.008.

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