Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Original article | Published 07 December 2021 | doi:10.4414/SMW.2021.w30103
Cite this as: Swiss Med Wkly. 2021;151:w30103

Mimics and chameleons of COVID-19: patient presentation and accuracy of triage during the first wave

Andrea S. Jauslin[a], Noemi R. Simon[a], Nina L. Giudici[a], Marco Rueegg[a], Tobias Zimmermann[b], Matthias Diebold[c], Sarah Tschudin-Sutter[de], Raphael Twerenbold[fg], Christian H. Nickel[a*], Roland Bingisser[a*]

[a] Emergency Department, University Hospital Basel, Switzerland
[b] Department of Intensive Care, University Hospital Basel, Switzerland
[c] Clinic for Transplantation Immunology and Nephrology, University Hospital Basel, Switzerland
[d] Division of Infectious Disease and Hospital Epidemiology, University Hospital Basel, Switzerland
[e] Department of Clinical Research, University of Base, Switzerland
[f] Department of Cardiology and University Centre of Cardiovascular Science, University Heart and Vascular Center Hamburg, Germany
[g] Department of Cardiology, University Hospital Basel, Switzerland
[*] Contributed equally to this work.

Summary

STUDY AIMS: To quantify mimics and chameleons of coronavirus disease 2019 (COVID-19), to analyse the diagnostic accuracy of the triage protocol, and to describe the resulting groups of mimics and chameleons – including their presenting symptoms and final diagnoses.

METHODS: Diagnostic accuracy study including all adult patients tested for severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) at the emergency department of the University Hospital Basel, Switzerland during the first wave of pandemic in spring 2020. Diagnostic accuracy of triage was determined by calculating sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratio. Triage to the group of suspected (+) and not suspected (–) COVID-19 was considered the index test, whereas a SARS-CoV-2 polymerase chain reaction test result was used as reference standard. Mimics were defined as false positives and chameleons as false negatives.

RESULTS: Of 2898 patients included in the analysis, 191 were true positives, 895 were false positives (mimics), 9 were false negatives (chameleons) and 1803 were true negatives. This resulted in a sensitivity of 0.95 (95% confidence interval [CI] 0.92–0.98) and a specificity of 0.67 (95% CI 0.65–0.69) for standardised triage. Among mimics, the main categories of final diagnoses were other infections (n = 513, 57.3%), cardiovascular diseases (excluding cerebrovascular) (n = 125, 14%), and non-infectious diseases of the respiratory system (n = 84, 9.4%). Fever (n = 357, 39.9% vs n = 104, 54.5%), cough (n = 466, 52.1% vs n = 126 66%), and smell or taste dysfunction (n = 60, 6.7% vs n = 24, 12.6%) were less frequently observed in mimics than in COVID-19 patients. Eight of nine COVID-19 chameleons presented with either nonspecific complaints (weakness and/or fatigue) or gastrointestinal symptoms.

CONCLUSION: The quantitative assessment of COVID-19 mimics and chameleons showed a high prevalence of mimics. Clinical differentiation between true positives and false positives is not feasible due to largely overlapping symptoms. Prevalence of chameleons was very low.

Correspondence:
Prof. Christian Nickel, MD
Deputy Head Emergency Department
University Hospital Basel
Petersgraben 2
CH-4031 Basel
christian.nickel[at]usb.ch

Introduction

Coronavirus disease 2019 (COVID-19) poses a challenge to emergency physicians, as most patients present with suspected but not confirmed COVID-19 to emergency departments (EDs). Although severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is a respiratory virus, different atypical complaints have been observed [1–4], including cardiovascular [5], neurological [6] and neuropsychiatric [7] symptoms and manifestations.

Therefore, the triage process is of utmost importance, and protocols focus on a high sensitivity regarding early isolation of COVID-19 patients – some including atypical complaints [8] and others focusing on the original clinical World Health Organization (WHO) definition of COVID-19 [9, 10]. Nonetheless, false positives (initially isolated, but ultimately tested negative) and false negatives (initially not isolated, but ultimately tested positive) are a hazard, even under the most conservative approaches. Such false positives and false negatives have been termed "mimics and chameleons of COVID-19" [11]. However, no attempts to quantify mimics and chameleons have been made.

Trade-offs, such as the high cost of isolation of too many patients (due to overtriage) versus safety concerns of "usu-

al care" in too many patients (due to undertriage) are evident.

We therefore aimed to quantify mimics and chameleons of COVID-19 under a triage protocol focusing on the typical presentation with respiratory symptoms [10], to analyse the results of this protocol and to describe the resulting groups of mimics and chameleons – including their presenting symptoms and final diagnoses.

Methods

Study design and setting

This was a diagnostic accuracy study performed as a secondary analysis of the prospective COronaVIrus surviVAl (COVIVA, ClinicalTrials.gov NCT04366765) trial. In the COVIVA cohort, we consecutively included adult patients presenting with suspected SARS-CoV-2 infection to the ED of the University Hospital of Basel, a tertiary care centre with approximately 54,000 annual ED visits, aiming to cover the first wave of COVID-19 pandemic. In addition, data on all patients tested for SARS-CoV-2 as a routine surveillance measure were analysed retrospectively using hospital electronic health records for the current analysis.

Population and inclusion criteria

All patients aged 18 years and older presenting with suspected SARS-CoV-2 infection to the ED of the University Hospital in Basel, Switzerland, during the first wave of COVID-19 pandemic between 22 March 2020 and 7 June 2020, were eligible for inclusion in the COVIVA study. At triage, SARS-CoV-2 infection was suspected in any patient with breathlessness, other respiratory symptoms or influenza-like symptoms, such as fever (i.e., feeling feverish), chills, sore throat, cough, myalgia, headache [10]. Patients were not yet systematically asked if they had any smell or taste dysfunction (hyposmia or anosmia or hypogeusia or ageusia), but all presenting symptoms were recorded prospectively. All olfactory and gustatory impairments were summarised as smell or taste dysfunction. Patients were either referred from the Triage and Test Centre [10] for further work-up, transported by paramedics, or directly presented to the ED (self-referrals). In some cases, patients might have been tested before presenting to the ED. However, these results were not available to study personnel.

Formal triage was performed with the Emergency Severity Index (ESI) and was conducted according to the local standard operating procedure as described in medStandards (www.medstandards.com) (see supplementary figure S1 in the appendix), based on the WHO definition [9], as modified by the Bundesamt für Gesundheit (BAG; Federal Office of Public Health). Disease severity was determined with the National Early Warning Score (NEWS). Patients with suspected COVID-19 were evaluated in a dedicated respiratory sector in the ED, where all patients underwent nasopharyngeal SARS-CoV-2 swab testing. Patients were considered COVID-19 positive cases if one or multiple SARS-CoV-2 polymerase chain reaction (PCR) swab tests performed on the day of ED presentation or within 14 days before or after ED presentation was positive, whereas patients with negative SARS-CoV-2 swab test results within that time frame were considered COVID-19 negative. Patients not suspected of COVID-19 received usual care in the ED, without isolation. However, patients not suspected of COVID-19 underwent nasopharyngeal swab SARS-CoV-2 PCR tests for screening purposes only if they were hospitalised or a clinician deemed a test necessary during work-up. If test results at ED presentation or during the subsequent hospitalisation were positive, the patients' data were included in order to quantitate chameleons of COVID-19.

Data collection

All patients suspected of COVID-19 included in the COVIVA cohort underwent a comprehensive clinical assessment by the treating ED physician according to local standard operating procedures. The patients' management was left to the discretion of the attending ED physicians. Study personnel were not involved in the care of patients.

Follow-up

Thirty days after discharge, patients suspected of having COVID-19 were contacted by telephone calls or in writing by research physicians or study nurses, and information about current health, hospitalisations and adverse events were obtained, guided by a predefined set of questions and item-checklists. Records of hospitals and primary care physicians, as well as national death registries, were screened for additional information, if applicable.

Adjudication of final diagnosis

To determine the final diagnosis that led to the index ED presentation, physicians reviewed all medical data available, including the 30-day post-discharge follow-up information, and selected a final diagnosis from a predefined list. Predefined categories included COVID-19, non-SARS-CoV-2 infections (e.g., other respiratory, gastrointestinal, urogenital), diseases of the circulatory system (acute coronary syndrome, atrial fibrillation, congestive heart failure, pulmonary embolism), non-infectious diseases of the respiratory system (e.g., lung cancer, asthma, chronic obstructive pulmonary disease), mental, behavioural and neurodevelopmental disorders (e.g., fear of COVID19, intoxication, depression), diseases of the nervous system, including cerebrovascular diseases (e.g., stroke, epilepsy), trauma or falls, post COVID-19, and electrolyte disorders. Initial final diagnoses "pain" and "weakness" underwent additional standardised chart reviews by two physicians, and in the case of disagreement by referees, and were attributed to the following categories: non-coronary chest pain, nonspecific abdominal pain and frailty syndrome.

Chart review

Information about the false positive patients (chameleons) were retrospectively obtained from the internal electronic health records hospital's database (ISMed® by Protec-Data, Boswil, Switzerland). Chart review was independently conducted by two trained study team members and was performed according to the 12 principles by Worster et al., [12] based on the 8 criteria of Gilbert et al. [13]. All criteria were fulfilled (12/12). The same predefined sets of di-

agnoses and symptoms as described above were applied. Additional symptoms were entered into an open text field. In the case of disagreement, a third study team member acted as referee. Patients with previously known symptomatic COVID-19, such as referrals by other caregivers, and direct hospitalisations were excluded from the analysis. Finally, two senior physicians independently reviewed all cases with PCR-positive SARS-CoV-2 nasopharyngeal swabs without initial suspicion of COVID-19 in order to review triage decisions.

Definitions

COVID-19 mimics

Patients presenting with symptoms suggestive of COVID-19 [11] with at least one negative SARS-CoV-2 PCR test result and no positive test results within 14 days before or after the ED visit.

COVID-19 chameleons

Patients presenting with symptoms that do not appear to represent COVID-19 initially [11] with at least one positive SARS-CoV-2 PCR test result during the ED visit or the subsequent hospitalisation.

Ethics

All participating patients or their legally authorised representatives consented by signing a local general consent form. This study was conducted according to the principles of the Declaration of Helsinki, approved by the local ethics committee (EKNZ identifier 2020-00566), including the amendment regarding the data analysis of patients tested for screening reasons. The authors designed the studies, gathered, analysed and present the data according to the STARD guidelines [14].

Outcome measures and statistical analysis

Descriptive statistics are presented as count and percentages, and mean and standard deviation, or median and interquartile range (IQR) in the case of visually non-normal distribution. Group comparisons were made using student's t-test, Mann-Whitney U-test or Fisher's exact test when expected frequencies were below 5.

Diagnostic accuracy is reported as sensitivity, specificity, negative predictive value, positive predictive value, positive likelihood ratio and negative likelihood ratio with their precision shown as a 95% confidence interval (CI). Triage to the group of suspected (+) and not suspected (–) COVID-19 was considered the index test, whereas SARS-CoV-2 PCR test result was used as reference standard for true positivity or negativity.

Chart review was evaluated by calculating the interrater reliability for the main diagnosis being COVID-19 or not in patients not suspected of COVID-19 but subsequently tested positive (chameleons). Interrater reliability is reported as Cohen's kappa coefficient κ. Patients re-presenting to the ED were not excluded from analysis. The entire analysis was performed using the statistical computing software R version 4.0.3. (https://www.r-project.org/).

Results

During the study period, 8691 patients presented to the ED, of whom 3073 were tested for SARS-CoV-2. Of these, 1261 were clinically suspected of COVID-19 with 174 exclusions due to refusal of consent or missing data. This resulted in 1086 patients suspected of COVID-19 being prospectively enrolled in the COVIVA trial, consisting of 895 COVID-19 negative (mimics) and 191 COVID-19 positive patients (true positives). Of these, 827 (76.1%) patients were referred by the Triage and Test Centre, 173 (15.9%) were transported by paramedics and 86 (7.9%) were direct self-referrals. An additional 1813 patients, not suspected of COVID-19, were tested for screening reasons. Of these, 1803 patients were COVID-19 negative (true negatives) and 9 were COVID-19 positive (chameleons) (fig. 1 and table 1).

Triage accuracy

By comparing triage results (suspicion vs no suspicion) and PCR test results (COVID-19 positive or negative), 895 mimics (false positives) and 9 chameleons (false negatives) were identified (table 1). Calculating diagnostic accuracy, we obtained a triage sensitivity of 0.95 (95% CI 0.92–0.98) and a triage specificity of 0.67 (95% CI 0.65–0.69). The positive predictive value for triage was 0.18 (95% CI 0.15–0.20), whereas the negative predictive value was 1.00 (95% CI 0.99–1.00). This resulted in a positive likelihood ratio of 2.88 (95% CI 2.71–3.06), and a negative likelihood ratio of 0.07 (95% CI 0.04–0.13) (calculations based on table 1).

Baseline characteristics of patients suspected of COVID-19

In patients suspected of COVID-19, the median age was 59 years (IQR 42–73) and 472 (43.5%) patients were female, with no significant difference between groups (table 2). Patients tested negative (mimics) were more often triaged to higher acuity (ESI 2: COVID-19 negative n = 354 (40.5%) vs COVID-19 positive n = 47 (26.7%), p = 0.003) and less often to medium acuity (ESI 3: COVID-19 negative n = 431 (49.3%) vs COVID-19 positive *n* = 111 (63.1%), p = 0.003). They were hospitalised less often than COVID-19 positive patients (COVID-19 negative n = 444 (49.6%) vs COVID-19 positive n = 114 (59.7%), p = 0.014). Mimics presented less often with altered vital signs (NEWS ≥3: COVID-19 negative n = 349 (42.2%) vs COVID-19 positive n = 87 (52.1%), p = 0.024), the main differences being overall slightly lower body temperatures (COVID-19 negative mean 37.2 ± 0.9°C vs COVID-19 positive 37.4 ± 0.9°C), and higher peripheral oxygen saturations (SpO_2 (%): COVID-19 negative 96.5 ± 3.1 vs COVID-19 positive 95.7 ± 4.6). No significant differences were observed in the remaining vital signs (table 2).

Symptoms and diagnoses of patients suspected of COVID-19

The most common symptoms in all patients with suspected COVID-19 were cough (n = 592, 54.5%) and dyspnoea

(n = 520, 47.9%), followed by fever (n = 461, 42.4%). Mimics presented significantly less often with fever (COVID-19 negative n = 357 (39.9%) vs COVID-19 positive n = 104 (54.5%), p <0.001) and cough (COVID-19 negative n = 466 (52.1%) vs COVID-19 positive n = 126 (66.0%), p = 0.001) than SARS-CoV-2 positive patients; no significant difference for dyspnoea was detected (COVID-19 negative n = 439 (49.1%) vs COVID-19 positive n = 81 (42.4%), p = 0.112), with an overall high prevalence of the respective symptoms in both groups. Mimics additionally were significantly less often associated with smell or taste dysfunction (COVID-19 negative n = 60 (6.7%) vs COVID-19 positive n = 24 (12.6%), p = 0.009), whereas the following symptoms were reported more often

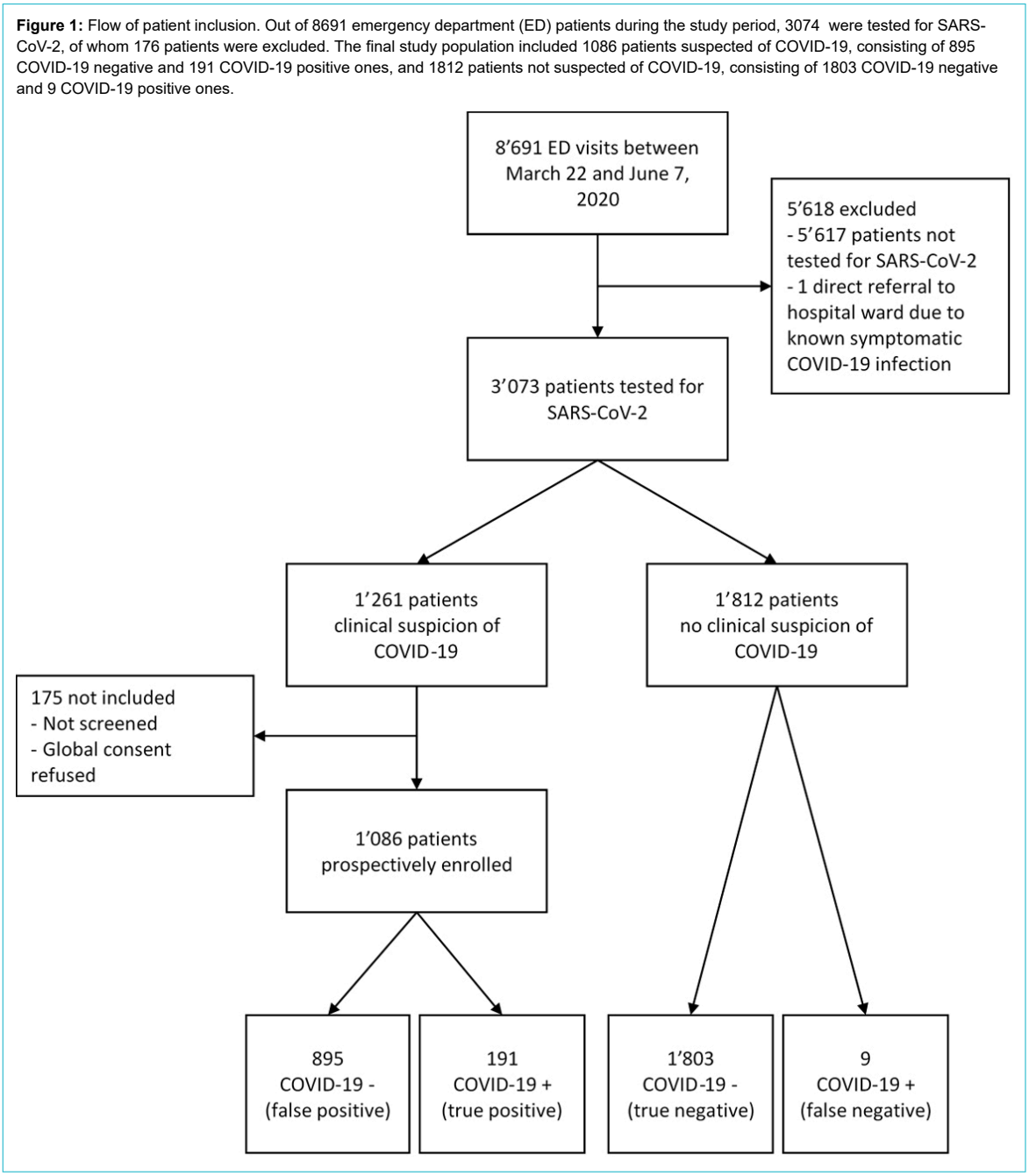

Figure 1: Flow of patient inclusion. Out of 8691 emergency department (ED) patients during the study period, 3074 were tested for SARS-CoV-2, of whom 176 patients were excluded. The final study population included 1086 patients suspected of COVID-19, consisting of 895 COVID-19 negative and 191 COVID-19 positive ones, and 1812 patients not suspected of COVID-19, consisting of 1803 COVID-19 negative and 9 COVID-19 positive ones.

Table 1:
Overview of clinical suspicion and plymerase chain reaction (PCR) test results.

Triage (clinical suspicion)	COVID-19 (PCR test result)		
	SARS-CoV-2 +	SARS-CoV-2 –	Total
Clinical suspicion of COVID-19 (+)	191	895	1086
No clinical suspicion of COVID-19 (–)	9	1803	1812
Total	200	2698	2898

Triage (see methods section and figure S1 in the appendix for the case definition) was considered the index test (suspicion: +, no suspicion: –) and the SARS-CoV-2 PCR test result was used as reference standard for COVID-19. A total of 2898 patients were included, of whom 191 were true positives, 895 false positives, 9 false negatives and 1803 true negatives.

than in patients with COVID-19: wheezing (p = 0.001), ear ache (p = 0.019), chest pain (p = 0.028), conjunctivitis (p = 0.039), rash (p = 0.048) and lymphadenopathy (p = 0.006).

Of all 1086 patients suspected of COVID-19, 191 (17.6%) were COVID-19 positive. As two diagnoses per patient were possible in cases of uncertainty of the main final diagnosis, a total of 956 diagnoses were recorded in the 895

Table 2:
Baseline characteristics of all patients clinically suspected of COVID-19 (n = 1086).

	All patients (n = 1086)	COVID-19 neg. (mimics) (n = 895)	COVID-19 pos. (n = 191)	p-value	Missings
Age, median IQR)	59 (42–73)	59 41–74)	57 (44–69)	0.388	0
Female gender, n (%)	472 (43.5%)	388 (43.4%)	84 (44.0%)	0.938	0
ESI, n (%)				0.003	36
– 1	31 (3.0%)	23 (2.6%)	8 (4.6%)		
– 2	401 (38.2%)	354 (40.5%)	47 (26.7%)		
– 3	542 (51.6%)	431 (49.3%)	111 (63.1%)		
– 4	74 (7.1%)	64 (7.3%)	10 (5.7%)		
– 5	2 (0.2%)	2 (0.2%)	0 (0%)		
Disposition, n (%)				0.014	0
– Outpatient	528 (48.6%)	451 (50.4%)	77 (40.3%)		
– Inpatient	558 (51.4%)	444 (49.6%)	114 (59.7%)		
NEWS, median (IQR)	2 (1–4)	2 (1–4)	3 (1–5)	0.057	92
NEWS ≥3, n (%)	436 (43.9%)	349 (42.2%)	87 (52.1%)	0.024	92
Body temperature (°C), mean ± SD	37.2 ± 0.9	37.2 ± 0.9	37.4 ± 0.9	0.005	72
Respiratory rate, mean ± SD	20.5 ± 31.3	20.6 ± 34.2	20.3 ± 5.4	0.908	73
SpO_2 (%), mean ± SD	96.4 ± 3.4	96.5 ± 3.1	95.7 ± 4.6	0.004	54
Heart rate (bpm), mean ± SD	89.9 ± 18.4	89.7 ± 18.8	90.9 ± 16.4	0.458	59
Systolic blood pressure (mm Hg), mean ± SD	137.9 ± 23.8	138.5 ± 24.2	135.0 ± 21.2	0.082	79
Diastolic blood pressure (mm Hg), mean ± SD	80.8 (15.5)	80.6 (15.4)	81.7 (16.3)	0.398	97

Comparison of baseline characteristics in all patients suspected of COVID-19, stratified by SARS-CoV-2 test result, those being negative classified as mimics.

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ESI: Emergency Severity Index;NEWS: National Early Warning Score; SD: standard deviation; IQR: Interquartile range; neg.: negative; pos.: positive

Table 3:
Symptoms in all patients clinically suspected of COVID-19.

Symptoms	All patients (n = 1086)	COVID-19 neg. (mimics) (n = 895)	COVID-19 pos. (n = 191)	p-value
Fever	461 (42.4%)	357 (39.9%)	104 (54.5%)	<0.001
Chills	198 (18.2%)	167 (18.7%)	31 (16.2%)	0.493
Cough	592 (54.5%)	466 (52.1%)	126 (66.0%)	0.001
Expectoration	226 (20.8%)	186 (20.8%)	40 (20.9%)	1.000
Haemoptysis	32 (3.0%)	29 (3.2%)	3 (1.6%)	0.316
Sore throat	272 (25.0%)	235 (26.3%)	37 (19.4%)	0.057
Rhinorrhoea	239 (22.0%)	199 (22.2%)	40 (20.9%)	0.768
Dyspnoea	520 (47.9%)	439 (49.1%)	81 (42.4%)	0.112
Wheezing	162 (14.9%)	149 (16.6%)	13 (6.8%)	0.001
Smell/taste dysfunction[a]	84 (7.7%)	60 (6.7%)	24 (12.6%)	0.009
Exhaustion	431 (39.7%)	359 (40.1%)	72 (37.7%)	0.591
Weakness	333 (30.7%)	286 (32.0%)	47 (24.6%)	0.056
Ear ache	103 (9.5%)	94 (10.5%)	9 (4.7%)	0.019
Bone ache	341 (31.4%)	282 (31.5%)	59 (30.9%)	0.935
Headache	359 (33.1%)	288 (32.2%)	71 (37.2%)	0.212
Chest pain	391 (36.0%)	336 (37.5%)	55 (28.8%)	0.028
Stomach ache	193 (17.8%)	163 (18.2%)	30 (15.7%)	0.473
Diarrhoea	173 (15.9%)	134 (15.0%)	39 (20.4%)	0.079
Nausea/vomiting	211 (19.4%)	179 (20.0%)	32 (16.8%)	0.353
Alguria	71 (6.5%)	65 (7.3%)	6 (3.1%)	0.054
Conjunctivitis	59 (5.4%)	55 (6.2%)	4 (2.1%)	0.039
Rash	57 (5.3%)	53 (5.9%)	4 (2.1%)	0.048
Lymphadenopathy	59 (5.4%)	57 (6.4%)	2 (1.1%)	0.006
Seizure	30 (2.8%)	26 (2.9%)	4 (2.1%)	0.706
Confusion	156 (14.4%)	134 (15.0%)	22 (11.5%)	0.262

Comparison of a set of predefined symptoms in all patients suspected of COVID-19, stratified by SARS-CoV-2 test result. Patients with a negative test result are considered mimics. Results are presented as count and percentages.

[a] Smell/taste dysfunction represents all quantitative and qualitative olfactory or gustatory impairments.

p-value is for comparison between groups. Abbreviations: neg.: negative; pos.: positive

COVID-19 negative patients. Of these, more than half (n = 513, 57.3%) were diagnosed with other infections, including respiratory infections (n = 327, 63.7%), urogenital infections (n = 59, 11.5%), fever of unknown aetiology (n = 38, 7.4%), gastrointestinal infections (n = 32, 6.2%), otorhinolaryngological infections (n = 29, 5.7%), soft tissue infections including skin and veins (n = 14, 2.7%) and others (n = 14, 2.7%). The second most common category was cardiovascular (excluding cerebrovascular) (n = 125, 14.0%), the majority being congestive heart failure (n = 65, 52.0%). Eighty-four patients (9.4%) had non-infectious diseases of the respiratory system. One of these three main categories was observed in 722 (80.7%) of all mimics. For a complete overview of all diagnoses see table 4.

Symptoms and diagnoses of COVID-19 chameleons

Of the 1812 patients tested for SARS-CoV-2 for epidemiological screening reasons only, 9 (0.5%) were positive. Median age was 78 years (IQR 62–88), 7 (77.8%) were male and all patients were hospitalised, the majority triaged to medium or high acuity (ESI 1: n = 1; ESI 2: n = 4; ESI 3: n = 3, ESI 4: n = 1) (table S1 in the appendix).

In three patients, COVID-19 was considered the most likely cause for the patient's symptoms by retrospective chart review. The interrater reliability for those cases was very good (Cohen's kappa coefficient κ = 1.0). The remaining six "chameleons" had congestive heart failure, atrial fibrillation, stroke, metastasised lung cancer, acute appendicitis, and anaphylactic shock as main diagnosis (table S1 in the appendix). Predominant symptoms were nonspecific complaints such as weakness (n = 4) and fatigue (n = 3), and gastrointestinal symptoms, namely nausea and/or vomiting (n = 4), stomach ache (n = 4), and diarrhoea (n = 3). Patients also complained of fever (n = 3), productive cough/haemoptysis (n = 2), dyspnoea (n = 3) and chest pain (n = 2). Additional, non-predefined symptoms were dizziness (n = 2), weakness in arm and leg (n = 1), bilateral leg swelling (n = 1) and pruritus (n = 1) (table S1 in the appendix).

Discussion

The main findings of this study were the high triage sensitivity for COVID-19, the striking similarities between COVID-19 and its mimics, and the low prevalence of chameleons. In detail, the triage accuracy was shown to be excellent in spite of the rather restrictive original definition [10] used for the suspicion of COVID-19. Most mimics had either fever or respiratory symptoms. In fact, the observed higher prevalence of fever and cough in COVID-19, as compared to mimics, is clinically irrelevant, as the difference is too small for any meaningful conclusion or even triage decision. Symptoms regarding smell or taste were not highly predictive in our cohort, as prevalence and absolute difference were both low, but comparable symptoms were present in mimics as well. However, there was no active interrogation regarding these symptoms, explaining the lower prevalence compared to other cohorts [15, 16]. The third surprising finding was the very low prevalence of chameleons, as several reports [1–4, 6, 7] have highlighted the meaning of atypical presentation of COVID-19. Analysis of the chameleons on an individual basis makes it evident that some are related to COVID-19, some unrelated to COVID-19, and others possibly related to COVID-19.

Table 4:
Main diagnoses of COVID-19 mimics.

	n	(%)
Infectious diseases (not COVID-19)	**513**	**(57.3)**
Respiratory infections	**327**	**(63.7)**
– Viral respiratory infection	230	(44.8)
– Bacterial pneumonia	97	(18.9)
Non-respiratory infections	**148**	**(28.8)**
– Urogenital	59	(11.5)
– Gastrointestinal	32	(6.2)
– Otorhinolaryngological	29	(5.7)
– Soft tissue, skin and vessels	14	(2.7)
– Unknown/others	14	(2.7)
Fever of unknown aetiology	**38**	**(7.4)**
Diseases of the circulatory system	**125***	**(14.0)**
Congestive heart failure	65	(52.0)
Pulmonary embolism	21	(16.8)
Acute coronary syndrome	17	(13.6)
Hypertensive urgency	15	(12.0)
Atrial fibrillation	5	(4.0)
Syncope	3	(2.4)
Takotsubo cardiomyopathy	1	(0.8)
Others	20	(16.0)
Non-infectious diseases of the respiratory system	**84**	**(9.4)**
Asthma / bronchitis / chronic cough	44	(52.4)
COPD	9	(10.7)
Lung cancer	9	(10.7)
Pulmonary fibrosis, interstitial pneumonia	7	(8.3)
Pneumothorax	3	(3.6)
Acute eosinophilic pneumonia	2	(2.4)
Others	10	(11.9)
Mental, behavioural and neurodevelopmental disorders	**57**	**(6.4)**
Fear of COVID-19	43	(75.4)
Intoxication	4	(7.0)
Delirium	2	(3.5)
Dementia	1	(1.8)
Depression	1	(1.8)
Others	6	(10.5)
Non-coronary chest pain	**35**	**(3.9)**
Diseases of the nervous system and cerebrovascular diseases	**32**	**(3.6)**
Epilepsy	9	(28.1)
Stroke/TIA	4	(12.5)
ICB	4	(12.5)
Others	15	(46.9)
Trauma/falls	**20**	**(2.2)**
Post COVID-19	**9**	**(1.0)**
Electrolyte disorders	**4**	**(0.5)**
Nonspecific abdominal pain	**4**	**(0.5)**
Frailty syndrome	**1**	**(0.1)**

Main diagnoses of all patients suspected of COVID-19 with a negative SARS-CoV-2 test result (mimics). Multiple diagnoses per patient were allowed with a total of 956 final diagnoses. Percentages are calculated in comparison to the total number of patients (n = 895) in main categories and subcategories are calculated relatively to the main categories.

* More than one disease of the circulatory system was allowed due to difficult differentiation in certain cases. Total of patients was 125, total of diseases of the circulatory system was 147.

COPD: chronic obstructive pulmonary disease; TIA: transient ischaemic attack; ICB: = intracranial bleeding.

Atypical presentations, such as weakness or other non-specific complaints, where no other underlying conditions were identified, are most likely related to COVID-19. Whereas some conditions associated with fever and other symptoms suggestive of COVID-19 might be, according to current knowledge, unrelated to COVID-19 (e.g., appendicitis), others such as stroke and acute myocardial infarction should very much be classified as possibly related to COVID-19, as numerous case reports have suggested an association [17–19], potentially due to observed hypercoagulability [20]. When analysing chameleons, it becomes evident that 2 patients felt feverish, and 1 had a fever (temperature 39.2 °C). According to the triage protocol, these should have been triaged as suspected COVID-19. As two patients complained of diarrhoea, and they presented at the beginning of the first wave, gastroenteritis was likely assumed at triage. One patient, however, reported nonspecific complaints and fever, which may be classified as an obvious mistriage due to non-adherence to the protocol.

Obviously, in a standardised environment with concise triage protocols [10], most cases could be identified at presentation. Of note, the trade-off of the high triage sensitivity and the consequently low prevalence of chameleons, is the low specificity. More patients were treated under isolation conditions than necessary. Apart from the high use of resources, patient-focused disadvantages such as less personalised care [21 ,22] and longer throughput times, as well as caregiver-focused disadvantages [23, 24] such as communication problems, adverse working conditions and fear of contagion may be mentioned [25]. Though anecdotal, arguments and disagreements between emergency staff and infection control staff should not be forgotten. Under normal, non-pandemic conditions, triage sensitivity of 95% at the cost of triage specificity of 67% would be reason for discussions and most likely be labelled as “overtriage”.

Chameleons can be reduced to few cases using such triage algorithms with a tendency towards overtriage, but mimics are numerous. Surprisingly, only three categories make up for the vast majority of mimics (other infection, and pulmonary and cardiovascular conditions). Particularly viral infection other than COVID-19 was still highly prevalent in the first wave of the pandemic [26], most likely due to the delayed federal obligation to wear face masks in public and confined places [27, 28].

Taken together, the quantitative assessment of COVID-19 mimics and chameleons has shown that, under the specific conditions and algorithms described, mimics were highly prevalent and clinical differentiation between true positives and false positives is hardly possible, which is in line with the literature [29]. On the other hand, chameleons were exceedingly rare.

Limitations

This is a single centre study, limiting its external validity. Admittedly, the adherence to the triage protocol was not studied. Therefore, a possible explanation for the high sensitivity could be the rather conservative interpretation and the inclusion of more atypical presentations than intended. Additionally, data about false negatives (chameleons), including their symptoms, were retrospectively collected and therefore not systematically assessed. An important limitation to consider is that systematic screening had not been implemented at the time of the study, which potentially resulted in a bias: Out of 8691 patients presenting to the ED during the study period, only 3073 were tested for SARS-CoV-2, which may have led to an underestimation of chameleons. This, in turn, might cause an overestimation of the diagnostic performance of our triage protocol. However, as we used a rather broad definition for suspicion of COVID-19 (see figure S1 in the appendix), we believe that the majority of those patients not tested were indeed COVID-19 negative. Asymptomatic cases may of course have been missed. All patients not tested for COVID-19 were instructed to return to the ED if they developed a fever or respiratory symptoms.

A small part of the patients had already been tested before their ED visit. It is therefore possible that triage clinicians were aware of COVID-19 status in these patients, leading to a potential bias in the allocation (suspected vs not suspected), but this was not quantified.

Furthermore, , smell or taste dysfunction was not systematically assessed, which is reflected by the low prevalence in our cohort (12.6%) compared with other studies reporting 33.9–68% [15, 16]. The higher prevalence in COVID-19 positive as compared to COVID-19 negative patients was nevertheless shown in our patient population. Similarly, gastrointestinal symptoms were not yet part of the COVID-19 case definition at the beginning of the study [9, 30]. Additionally, no distinction between a fever and feeling feverish was made in our cohort.

Data sharing statement

Data cannot be made open without written consent by the local ethics committee. Data sharing requests will be forwarded to the ethics committee. In the case of acceptance of the request, the data can be shared in fully anonymised form.

Acknowledgements

We thank the entire staff and all participating patients for their valuable contribution to this work. A special thanks to Klaus Baumgartl for his support in data collection.

Conflicts of interest

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. RB and CHN report being editors of medStandards.com. RT reports research support from the Swiss National Science Foundation (Grant No P300PB_167803), the Swiss Heart Foundation, the Swiss Society of Cardiology, the Cardiovascular Research Foundation Basel, the University of Basel, the University Hospital Basel and a research grant from Roche Diagnostics. Dr. TZ reports research support from the Freiwillige Akademische Gesellschaft Basel, outside of the submitted work. None of the other authors have any conflict of interest to declare.

Funding sources

The COVIVA study was financially supported by the Swiss Heart Foundation, the Scientific Funds of the Emergency Department, and the Cardiovascular Research Foundation Basel.

References

1. Lai CC, Ko WC, Lee PI, Jean SS, Hsueh PR. Extra-respiratory manifestations of COVID-19. Int J Antimicrob Agents. 2020 Aug;56(2):106024. http://dx.doi.org/10.1016/j.ijantimicag.2020.106024. PubMed. 1872-7913
2. Marzano AV, Cassano N, Genovese G, Moltrasio C, Vena GA. Cutaneous manifestations in patients with COVID-19: a preliminary review

of an emerging issue. Br J Dermatol. 2020 Sep;183(3):431–42. http://dx.doi.org/10.1111/bjd.19264. PubMed. 1365-2133
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb;395(10223):497–506. http://dx.doi.org/10.1016/S0140-6736(20)30183-5. PubMed. 1474-547X
4. Coleman JJ, Manavi K, Marson EJ, Botkai AH, Sapey E. COVID-19: to be or not to be; that is the diagnostic question. Postgrad Med J. 2020 Jul;96(1137):392–8. http://dx.doi.org/10.1136/postgradmedj-2020-137979. PubMed. 1469-0756
5. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. JAMA Cardiol. 2020 Jul;5(7):831–40. http://dx.doi.org/10.1001/jamacardio.2020.1286. PubMed. 2380-6591
6. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol. 2020 Sep;19(9):767–83. http://dx.doi.org/10.1016/S1474-4422(20)30221-0. PubMed. 1474-4465
7. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry. 2020 Jul;7(7):611–27. http://dx.doi.org/10.1016/S2215-0366(20)30203-0. PubMed. 2215-0374
8. Clifford CT, Pour TR, Freeman R, Reich DL, Glicksberg BS, Levin MA, et al. Association between COVID-19 diagnosis and presenting chief complaint from New York City triage data. Am J Emerg Med. 2021 Aug;46:520–4. http://dx.doi.org/10.1016/j.ajem.2020.11.006. PubMed. 1532-8171
9. WHO. COVID-19 Case definition. https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2. Updated 16.12.2020. Accessed 21 June 2021.
10. Mansella G, Rueegg M, Widmer AF, Tschudin-Sutter S, Battegay M, Hoff J, et al. COVID-19 Triage and Test Center: Safety, Feasibility, and Outcomes of Low-Threshold Testing. J Clin Med. 2020 Oct;9(10):3217. http://dx.doi.org/10.3390/jcm9103217. PubMed. 2077-0383
11. Nickel CH, Bingisser R. Mimics and chameleons of COVID-19. Swiss Med Wkly. 2020 Mar;150(13-14):w20231. PubMed. 1424-3997
12. Worster A, Bledsoe RD, Cleve P, Fernandes CM, Upadhye S, Eva K. Reassessing the methods of medical record review studies in emergency medicine research. Ann Emerg Med. 2005 Apr;45(4):448–51. http://dx.doi.org/10.1016/j.annemergmed.2004.11.021. PubMed. 1097-6760
13. Gilbert EH, Lowenstein SR, Koziol-McLain J, Barta DC, Steiner J. Chart reviews in emergency medicine research: where are the methods? Ann Emerg Med. 1996 Mar;27(3):305–8. http://dx.doi.org/10.1016/S0196-0644(96)70264-0. PubMed. 0196-0644
14. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open. 2016 Nov;6(11):e012799. http://dx.doi.org/10.1136/bmjopen-2016-012799. PubMed. 2044-6055
15. Meng X, Deng Y, Dai Z, Meng Z. COVID-19 and anosmia: A review based on up-to-date knowledge. Am J Otolaryngol. 2020 Sep - Oct;41(5):102581. http://dx.doi.org/10.1016/j.amjoto.2020.102581. PubMed. 1532-818X
16. Cherry G, Rocke J, Chu M, Liu J, Lechner M, Lund VJ, et al. Loss of smell and taste: a new marker of COVID-19? Tracking reduced sense of smell during the coronavirus pandemic using search trends. Expert Rev Anti Infect Ther. 2020 Nov;18(11):1165–70. http://dx.doi.org/10.1080/14787210.2020.1792289. PubMed. 1744-8336
17. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med. 2020 May;382(20):e60. http://dx.doi.org/10.1056/NEJMc2009787. PubMed. 1533-4406
18. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. Brain Behav Immun. 2020 Jul;87:115–9. http://dx.doi.org/10.1016/j.bbi.2020.04.077. PubMed. 1090-2139
19. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry. 2020 Aug;91(8):889–91. http://dx.doi.org/10.1136/jnnp-2020-323586. PubMed. 1468-330X
20. Spence JD, de Freitas GR, Pettigrew LC, Ay H, Liebeskind DS, Kase CS, et al. Mechanisms of Stroke in COVID-19. Cerebrovasc Dis. 2020;49(4):451–8. http://dx.doi.org/10.1159/000509581. PubMed. 1421-9786
21. Schittek GA, Bornemann-Cimenti H, Sandner-Kiesling A. Wellbeing of ICU patients with COVID-19. Intensive Crit Care Nurs. 2021 Aug;65:103050. http://dx.doi.org/10.1016/j.iccn.2021.103050. PubMed. 1532-4036
22. Roubille C, Ribstein J, Hurpin G, Fesler P, Fiat E, Roubille F. Confidence vanished or impaired until distrust in the doctor-patient relationship because of COVID-19: Confidence vanished or impaired until distrust: "COVID" in relationship. Rev Med Interne. 2021 Jan;42(1):58–60. http://dx.doi.org/10.1016/j.revmed.2020.10.007. PubMed. 1768-3122
23. Crowe S, Howard AF, Vanderspank-Wright B, Gillis P, McLeod F, Penner C, et al. The effect of COVID-19 pandemic on the mental health of Canadian critical care nurses providing patient care during the early phase pandemic: A mixed method study. Intensive Crit Care Nurs. 2021 Apr;63:102999. http://dx.doi.org/10.1016/j.iccn.2020.102999. PubMed. 1532-4036
24. Weilenmann S, Ernst J, Petry H, Pfaltz MC, Sazpinar O, Gehrke S, et al. Health Care Workers' Mental Health During the First Weeks of the SARS-CoV-2 Pandemic in Switzerland-A Cross-Sectional Study. Front Psychiatry. 2021 Mar;12:594340. http://dx.doi.org/10.3389/fpsyt.2021.594340. PubMed. 1664-0640
25. González-Gil MT, González-Blázquez C, Parro-Moreno AI, Pedraz-Marcos A, Palmar-Santos A, Otero-García L, et al. Nurses' perceptions and demands regarding COVID-19 care delivery in critical care units and hospital emergency services. Intensive Crit Care Nurs. 2021 Feb;62:102966. http://dx.doi.org/10.1016/j.iccn.2020.102966. PubMed. 1532-4036
26. Leuzinger K, Roloff T, Gosert R, Sogaard K, Naegele K, Rentsch K, et al. Epidemiology of Severe Acute Respiratory Syndrome Coronavirus 2 Emergence Amidst Community-Acquired Respiratory Viruses. J Infect Dis. 2020 Sep;222(8):1270–9. http://dx.doi.org/10.1093/infdis/jiaa464. PubMed. 1537-6613
27. Liang M, Gao L, Cheng C, Zhou Q, Uy JP, Heiner K, et al. Efficacy of face mask in preventing respiratory virus transmission: A systematic review and meta-analysis. Travel Med Infect Dis. 2020 Jul - Aug;36:101751. http://dx.doi.org/10.1016/j.tmaid.2020.101751. PubMed. 1873-0442
28. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ, et al.; COVID-19 Systematic Urgent Review Group Effort (SURGE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet. 2020 Jun;395(10242):1973–87. http://dx.doi.org/10.1016/S0140-6736(20)31142-9. PubMed. 1474-547X
29. Carpenter CR, Mudd PA, West CP, Wilber E, Wilber ST. Diagnosing COVID-19 in the Emergency Department: A Scoping Review of Clinical Examinations, Laboratory Tests, Imaging Accuracy, and Biases. Acad Emerg Med. 2020 Aug;27(8):653–70. http://dx.doi.org/10.1111/acem.14048. PubMed. 1553-2712
30. England PH. Investigation and initial clinical management of possible cases of Wuhan novel coronavirus (WN-CoV) infection https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases/investigation-and-initial-clinical-management-of-possible-cases-of-wuhan-novel-coronavirus-wn-cov-infection. Updated 14 December2020. Accessed 21 June 2021.

Appendix: Supplementary material

Figure S1: Triage algorithm during the first wave of COVID-19.

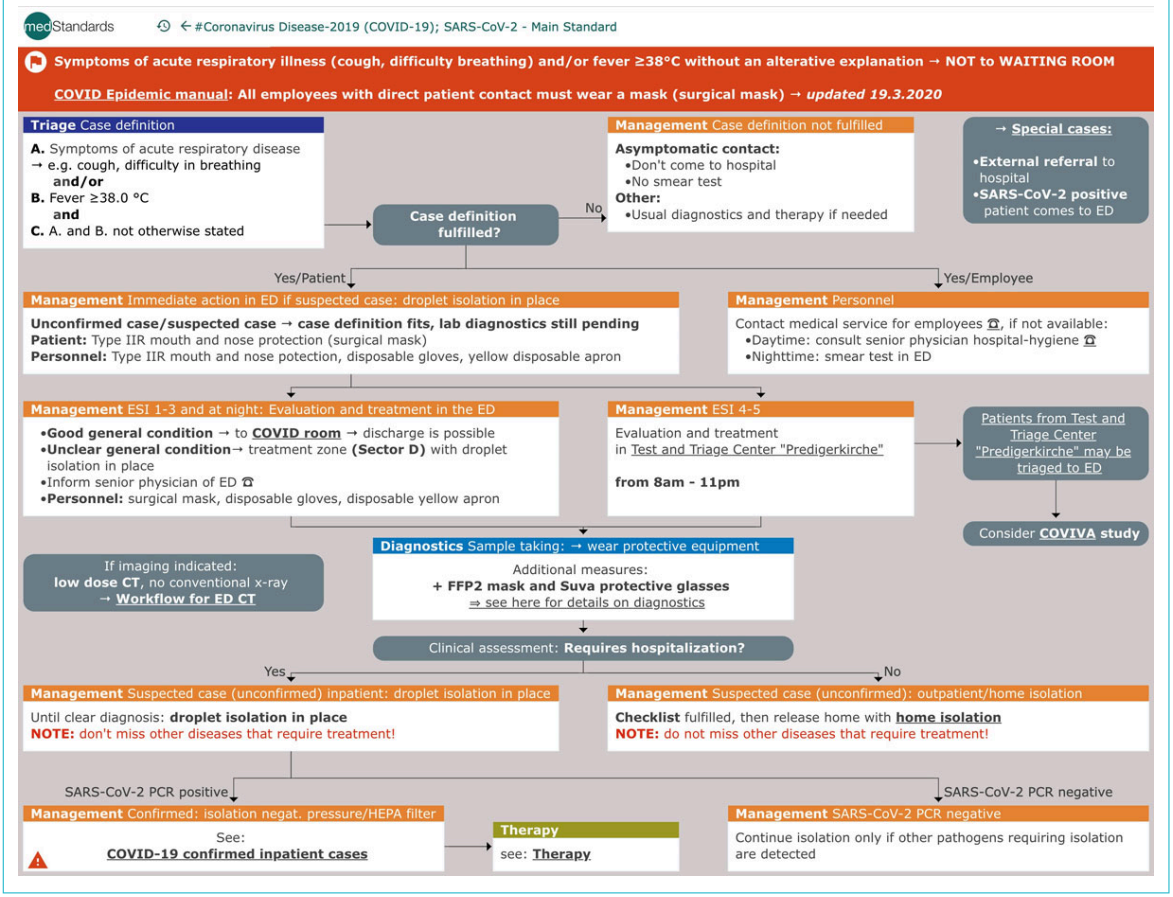

Table S1:
Chameleons.

Age	Gender	ESI	SARS-CoV-2	Disposition	Symptoms at presentation	Main diagnosis
82	Male	4	Positive	Inpatient	Fever, weakness and fatigue	COVID-19
79	Male	3	Positive	Inpatient	Diarrhoea, vomiting, fever, weakness	COVID-19 with bilateral pneumonia and enteritis
75	Female	3	Positive	Inpatient	Diarrhoea, stomach ache, fever	Sepsis due to COVID-19 with enteritis
90	Female	2	Positive	Inpatient	Dyspnoea, weakness, dizziness, bilateral leg swelling, stomach ache	Congestive heart failure
82	Male	2	Positive	Inpatient	Weakness in right arm and leg	Stroke
58	Male	1	Positive	Inpatient	Dyspnoea, vomiting, dizziness, pruritus	Anaphylactic shock
78	Male	2	Positive	Inpatient	Weakness, fatigue, chest pain, dyspnoea, known productive cough, diarrhoea	Atrial fibrillation
62	Male	2	Positive	Inpatient	Haemoptysis, chest pain, stomach ache (constipation), nausea, fatigue	Metastasised lung cancer (treated: chemotherapy)
37	Male	3	Positive	Inpatient	Stomach ache, nausea	Acute appendicitis

ESI: Emergency Severity Index

M nine patients not suspected of COVID-19 tested positive for SARS-CoV-2 (chameleons). Main diagnosis was defined as the main cause for emergency department presentation.