

Providing care in isolation while awaiting SARS-CoV-2 test results

Considering differential diagnoses and avoiding anchoring bias

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Abstract

Isolation of confirmed or suspected coronavirus disease 2019 (COVID-19) cases is essential but, as symptoms of COVID-19 are non-specific and test results not immediately available, case identification at admission remains challenging. To inform optimization of triage algorithms, patient flow and patient care, we analyzed characteristics of patients admitted to an isolation ward, both severe acute respiratory syndrome coronavirus 2019 (SARS-CoV-2) positive patients and patients in which initial suspicion was not confirmed after appropriate testing.

Data from patients with confirmed or suspected COVID-19 treated in an isolation unit were analyzed retrospectively. Symptoms, comorbidities and clinical findings were analyzed descriptively and associations between patient characteristics and final SARS-CoV-2 status were assessed using univariate regression.

Eighty three patients (49 SARS-CoV-2 negative and 34 positive) were included in the final analysis. Of initially suspected COVID-19 cases, 59% proved to be SARS-CoV-2-negative. These patients had more comorbidities (Charlson Comorbidity Index median 5 (interquartile range [IQR] 2.5, 7) vs 2.7 (IQR 1, 4)), and higher proportion of active malignancy than patients with confirmed COVID-19 (47% vs 15%; $P = .004$), while immunosuppression was frequent in both patient groups (20% vs 21%; $P = .984$). Of SARS-CoV-2 negative patients, 31% were diagnosed with non-infectious diseases.

A high proportion of patients (59%) triaged to the isolation unit were tested negative for SARS-CoV-2. Of these, many suffered from active malignancy (47%) and were immunosuppressed (20%). Non-infectious diseases were diagnosed in 31%, highlighting the need for appropriate patient flow, timely expert medical care including evaluation for differential diagnostics while providing isolation and ruling out of COVID-19 in these patients with complex underlying diseases.

Abbreviations: CI = confidence interval, COVID-19 = coronavirus disease 2019, CT = computed tomography, IQR = interquartile range, OR = odds ratio, PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2019.

Keywords: anchoring bias, coronavirus disease 2019, differential diagnoses to coronavirus disease 2019, isolation ward, severe acute respiratory syndrome coronavirus 2019

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1. Introduction

In December 2019, medical officials first reported an unusual cluster of pneumonia cases in Wuhan, China. Later a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the underlying pathogen for the disease now called corona virus disease 2019 (COVID-19).^[1] Patients typically present with fever and respiratory symptoms such as cough and dyspnoea. Though, clinical presentation varies and can often not be easily distinguished from other diseases.^[2,3] Until now, gold standard for SARS-CoV-2 testing is polymerase chain reaction (PCR) of nasopharyngeal or pharyngeal swabs.^[4] Nevertheless, as test results are often not immediately available, clinical decisions and decisions on triage and hygiene measures have to be taken before COVID-19 can be confirmed or ruled out.^[5,6] Laboratory parameters usually show elevated inflammatory parameters (C-reactive protein, interleukin-6, ferritin), elevated D-Dimer and liver enzymes as well as lymphopenia, but are non-specific.^[7-9] Radiological imaging with computed tomography (CT) scans can be of help in the diagnostic process, as the infection can cause a distinct picture of viral pneumonia.^[10]

In order to detain the spread of the SARS-CoV-2 pandemic, isolation of infected patients, contact tracing, quarantine of contact persons and social distancing are recommended strategies.^[3,11,12] In in-patient settings, measures suggested by the World Health Organization as well as the German Public Health Authorities (Robert Koch Institute) to protect other patients and health care workers include strict isolation and treatment by separate health care personnel of patients with confirmed SARS-CoV-2 infection in settings where this is feasible. Suspected cases are supposed to be treated the same way until infection is ruled out.^[13,14] Accordingly, the University Hospital Cologne implemented a triage system in the adult emergency department, screening for suspected COVID-19 patients focusing on symptoms associated with SARS-CoV-2 infection.^[15] Subsequently, patients with suspected or confirmed SARS-CoV-2 infection and in need of in-patient treatment were transferred to a specialized COVID-19 isolation ward. Patients who had initially been triaged as suspected cases but were deemed negative after appropriate testing were then immediately transferred to regular wards.

The aim of this study was to describe the patient population admitted to the isolation ward and compare patients in which COVID-19 had been initially suspected but was not confirmed by testing to patients with confirmed COVID-19 in order to inform future efforts to improve triage mechanisms, patient flow and hospital organization.

2. Materials and methods

2.1. Setting and study population

Foreseeing a surge in numbers of COVID-19 patients in March 2020, a new isolation ward was created for confirmed and suspected COVID-19 cases at University Hospital Cologne. After the ward opened on March 24, 2020, all confirmed and suspected COVID-19 patients requiring in-patient treatment were admitted to the ward, as long as no intensive care was required. In cases of suspected COVID-19, patients were immediately transferred to other wards if COVID-19 was ruled out. To prevent nosocomial infection, patients were isolated in single rooms with appropriate protection measures and suspected patients were treated as infectious until COVID-19 was ruled out. The isolation ward closed on May 13, 2020 due to lowering case numbers.

A triage system had been implemented in the emergency department, screening for cough, dyspnoea, headache, nausea or vomiting, diarrhoea and loss of olfactory or gustatory sense. Presence of any of these symptoms led to a standardized diagnostic algorithm, including a low dose chest CT and a specific panel of laboratory parameters. In all cases in which COVID-19 was suspected, a nasopharyngeal swab for SARS-CoV-2 PCR was taken and the patient was admitted to the isolation ward. Further testing, according to a defined algorithm was performed following admission. SARS-CoV-2 negative was defined as 2 nasal/pharyngeal swab PCRs negative for SARS-CoV-2 (with a time lab of 24 hours) followed by negative sputum testing. In this study, COVID-19 positive refers to patients with any positive test prior to admission or during hospitalization. Subsequently, positive patients were tested with a PCR on a nasopharyngeal swab twice per week for further evaluation of viral load and detection of the timepoint for de-isolation.

Patient records from all patients admitted to the isolation ward were analyzed retrospectively. Current symptoms possibly related to COVID-19 and their duration before admission were recorded (cough, fever, dyspnoea, myalgia, diarrhoea, loss of olfactory or gustatory sense, headache, nasal congestion, sore throat), as well as medical conditions previously suggested to be associated with severe COVID-19 (i.e., hypertension, cardiovascular disease, diabetes mellitus, active malignancy, immunosuppression, end-stage renal failure). In addition, the Charlson Comorbidity Index^[16] was calculated for every patient. Also, clinical, laboratory and chest CT findings at admission were included in the study. Chest CT scans evaluated by in-house radiologists were defined as either “not typical for COVID-19,” “possibly COVID-19” and “typical COVID-19” based on current data on typical findings in COVID-19 patients. Patients with asymptomatic SARS-CoV-2 infection (in need of in-patient treatment for another condition) and asymptomatic patients isolated because of a high risk exposure to individuals with COVID-19 were excluded from this study. In case of repeated admission, only data of the first admission were included in the analysis. Further epidemiological investigations were performed by German health authorities due to German administration specifications.

2.2. Statistics

Metric variables were expressed as median and interquartile range (IQR), categorical variables as number (n) and percentage (%). In addition to descriptive analysis, statistical associations were assessed using univariate logistic regression. Reported *P* values are 2-tailed, with *P* < .05 being considered statistically significant. SPSS (SPSS 25, SPSS Inc., Armonk NY, USA) was used for statistical analysis. Figures were designed using GraphPad Prism and Microsoft PowerPoint.

2.3. Ethics

This retrospective analysis was approved by the Institutional Review Board of the University of Cologne (vote 20–1356).

3. Results

Of 92 patients with prior confirmed or suspected diagnosis of COVID-19 admitted to the isolation ward, 83 were included in the final analysis (Fig. 1). COVID-19 was not confirmed in

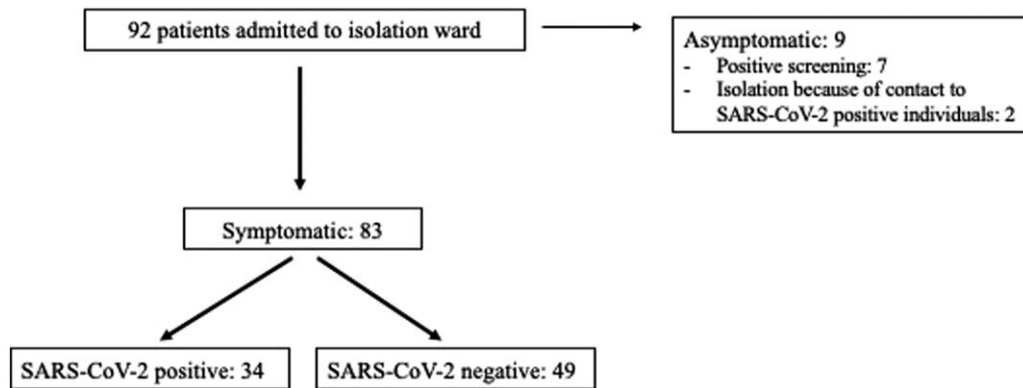


Figure 1. Selection of study participants.

49 patients (59%). Most patients were admitted to the ward via the emergency department (n=66) followed by transfer from other wards (n=19) or intensive care units (n=7).

3.1. Patient characteristics

Median age was 60 years (IQR 50, 73) (Table 1), with no significant difference between groups. The 2 most common comorbidities of all patients were arterial hypertension (37%) and active malignancy (34%). Of all patients, 21% (n=17) were on immunosuppressive medication (n=5: solid organ transplantation, n=3: rheumatic disease, n=9 recent chemotherapy). SARS-CoV-2 negative patients suffered significantly more often from active malignancy compared to positive patients (47% vs 15%; $P=.004$; odds ratio (OR) 0.20 (95% confidence interval [CI] 0.07–0.59)). They also showed a higher proportion of underlying cardiovascular disease (28% vs 3%; $P=.015$; OR 0.76 (95% CI 0.01–0.61)) and a tendency towards a higher proportion of pulmonary diseases (including chronic obstructive pulmonary disease (n=5), asthma (n=3), pulmonary hyperten-

sion (n=1), interstitial lung disease related to Sjögren syndrome (n=1) and past lung transplantation (n=1)) (25% vs 12%; $P=.157$; OR 0.41 (95% CI 0.12–1.41)) (Fig. 2). The median number of registered comorbidities previously suggested to be associated with severe COVID-19 was significantly higher in SARS-CoV-2 negative patients (median 2 (IQR 1, 2.5) vs 1 (IQR 0, 2); $P=.004$; OR 0.50 (95% CI 0.31–0.80)) (Table 1). Among negative patients, 12% had none of these registered conditions, compared to over one third (35%) of SARS-CoV-2 positive patients. Accordingly, the Charlson Comorbidity Index was significantly higher in SARS-CoV-2 negative than in positive patients (median 5 (IQR 2.5, 7) vs 2 (IQR 1, 4); $P=.001$; OR 0.76 (95% CI 0.63–0.91)) (Table 1).

3.2. Reported symptoms and clinical presentation

The most frequently reported symptoms were cough (68%) and fever (69%), followed by dyspnoea (28%), headache (25%) and myalgia (21%). Reported symptoms significantly associated with COVID-19 were fever (59% vs 82%; $P=.029$; OR 3.22 (95% CI

Table 1

Age, gender and number of pre-existing conditions in SARS-CoV-2 positive and negative patients.

	SARS-CoV-2 negative N = 49 n (%)	SARS-CoV-2 positive N = 34 n (%)	Total N = 83 n (%)	P value	OR (95% CI)
Age				.605	0.61 (0.89–1.40)
<50	13 (27)	7 (21)	20 (24)		
50–64	13 (27)	15 (44)	28 (34)		
65–79	16 (33)	9 (27)	25 (30)		
≥80	7 (14)	3 (9)	10 (12)		
Female sex	22 (45)	18 (53)	40 (48)	.471	1.38 (0.57–3.32)
Number of registered pre-disposing conditions*		0.004	0.50 (0.31–0.80)		
none	6 (12)	12 (35)	18 (22)		
1	10 (20)	9 (27)	19 (23)		
2	21 (43)	10 (29)	31 (37)		
≥3	12 (25)	3 (9)	15 (18)		
Charlson Comorbidity Index			0.002	.497 (0.317–0.780)	
Negative (0)	4 (8)	6 (18)	10 (12)		
Mild (1–2)	8 (16)	13 (38)	21 (25)		
Moderate (3–4)	10 (20)	8 (23)	18 (22)		
Severe (>5)	27 (55)	7 (21)	34 (41)		

CI = confidence interval, OR = odds ratio.

* Hypertension, cardiovascular disease, diabetes mellitus, active malignancy, immunosuppression, end-stage renal failure.

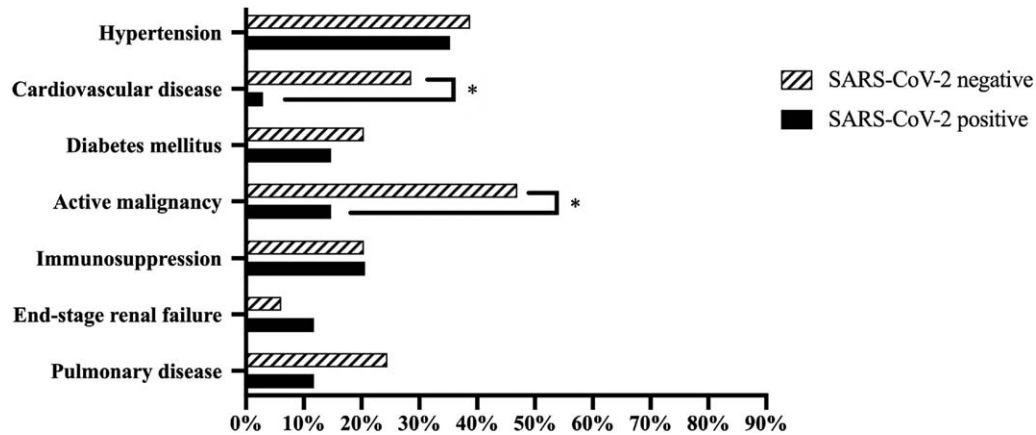


Figure 2. Pre-disposing conditions in SARS-CoV-2 positive and negative patients. Numbers are shown in percentage of total positive / negative patients. An asterisk indicates a *P* value below .05.

1.13–9.20)) and loss of olfactory and/or gustatory sense (4% vs 24%; $P=0.017$; OR 7.23 (95% CI 1.43–36.61)) (Fig. 3). SARS-CoV-2 negative patients reported a lower number of registered symptoms typical for COVID-19 than positive patients (median 2 (IQR 1, 3) vs 3 (IQR 1, 3); $P=.006$; OR 1.69 (95% CI 1.16–2.46)) (Table 2). Having 3 or more typical symptoms was reported by 35% of SARS-CoV-2 negative and 68% of SARS-CoV-2 positive patients ($P=.004$; OR 3.94 (95% CI 1.56–9.96)). Of patients who had only reported 1 typical symptom ($n=19$, 23%) all tested SARS-CoV-2 negative. Among these patients' singular symptoms were cough, dyspnoea and fever. Median duration of symptoms before admission was shorter among SARS-CoV-2 negative patients (median 3 days (IQR 1.25, 8.5)) than positive (median 7 days (IQR 4, 10)), the difference was not statistically significant (Table 2).

A lower proportion of SARS-CoV-2 negative than positive patients required low-flow supplemental oxygen at admission (22% vs 74%, $P<.001$; OR 10.00 (95% CI 3.55–28.2)). In contrast to reported symptoms, fever ($>38.0^{\circ}\text{C}$) at admission did not differ significantly in between the 2 groups, neither did hypotension (mean arterial pressure $<70\text{ mmHg}$) or tachycardia (heart rate $>90/\text{min}$).

3.3. Chest-CT and laboratory findings

A chest CT scan was performed in 74 patients (89%) at admission. The classification as “not typical for COVID-19,” “possible COVID-19” and “typical COVID-19” was significantly associated with the SARS-CoV-2 testing results ($P=<.001$; OR 17.35 (95% CI 5.19–58.04)) (Table 2). Among SARS-CoV-2 negative patients, 12% of chest CT scans had been described as “typical COVID-19,” as compared to 94% of positive patients. Only one COVID-19 patient's CT scan had been described as “not typical”.

Among the SARS-CoV-2 negative, a higher proportion of patients had an elevated leucocyte and neutrophil count (35% vs 12%; $P=.024$; OR 0.25 (95% CI 0.08–0.83) resp 38% vs 6%; $P=.005$; OR 0.11 (95% CI 0.02–0.50)). Of patients with an elevated leucocyte count, most (81%) tested negative for SARS-CoV-2. Of 15 patients with a low eosinophil count, all were SARS-CoV-2 positive (eosinophil count median 0.01 (IQR 0.00, 0.04) vs 0.08 (IQR 0.02, 0.22); $P=.013$; OR 0.00 (95% CI 0.00–0.17)).

Elevated ferritin levels were less frequent among SARS-CoV-2 negative patients (59% vs 88%; $P=.010$; OR 4.83 (95% CI 1.47–15.91)). No differences in frequency of lymphocyte abnormalities, C-reactive protein, procalcitonin, interleukin-6,

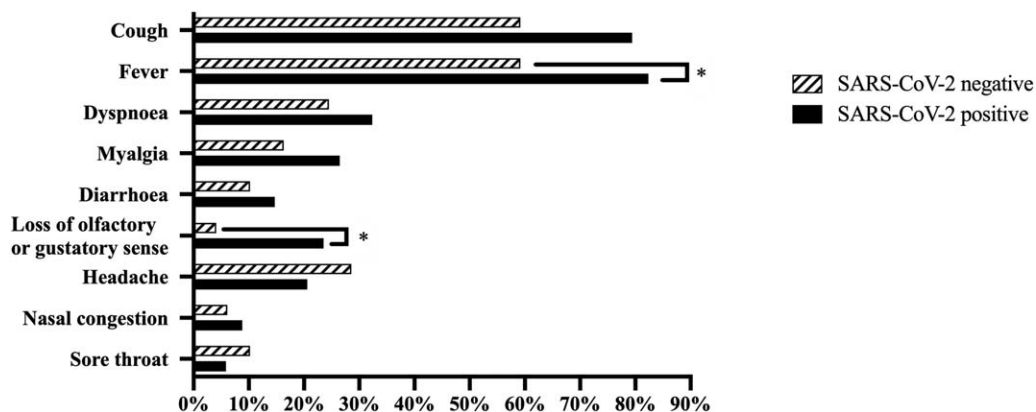


Figure 3. Reported symptoms typically associated with SARS-CoV-2. Numbers are shown in percentage of total positive / negative patients. An asterisk indicates a *P* value below .05.

Table 2
Number and duration of symptoms in SARS-CoV-2 positive and negative patients.

	SARS-CoV-2 negative N = 49 n (%)	SARS-CoV-2 positive N = 34 n (%)	Total N = 83 n (%)	P value	OR (95% CI)
Number of typical symptoms*					
1	19 (39)	0 (0)	19 (23)	.006	1.69 (1.16–2.46)
2	13 (27)	11 (32)	24 (29)		
3	6 (12)	11 (32)	17 (21)		
4	8 (16)	9 (27)	17 (21)		
5	1 (2)	3 (9)	4 (5)		
6	2 (4)	0 (0)	2 (2)		
Duration of symptoms					
0–3 d	27/48 (56)	7/29 (24)	34/77 (44)	.076	1.55 (0.96–2.50)
4–7 d	9/48 (19)	9/29 (31)	18/77 (23)		
8–14 d	7/48 (15)	13/29 (45)	20/77 (26)		
≥15 d	5/48 (10)	0/29 (0)	5/77 (7)		
Characterization of Chest CT Scan					
Not typical for COVID-19†	30/42 (71)	1/32 (3)	31/74 (42)	<.001	17.35 (5.19–58.04)
Possibly COVID-19	7/42 (17)	1/32 (3)	8/74 (11)		
Typical COVID-19	5/42 (12)	30/32 (94)	35/74 (47)		

CI = confidence interval, CT = computed tomography, OR = odds ratio.

*Cough, fever, dyspnoea, myalgia, diarrhoea, loss of olfactory or gustatory sense, headache, nasal congestion, sore throat.

†Including CTs without any changes and CTs with changes not known to be associated with COVID-19.

glomerular filtration rate, troponin T and D-Dimer were detected between groups.

3.4. Final diagnoses of severe acute respiratory syndrome coronavirus 2 negative patients initially triaged as suspected cases

Of SARS-CoV-2 negative patients initially triaged as suspected COVID-19, 34/49 (69%) were diagnosed with an infection other than COVID-19 (pneumonia (n=14), bloodstream infections (n=6), urinary tract infections (n=4), chronic obstructive pulmonary disease exacerbation due to infection (n=2), viral infections (n=4), tonsillitis (n=1), neutropenic fever (n=4) and infection of unknown origin (n=2); 3 patients suffered from multiple infections). The 15/49 patients (31%) with a non-infectious disease were diagnosed with pneumonitis after radio- or immunotherapy (n=4), symptomatic heart failure (n=3), pulmonary embolism (n=1), headache of unknown origin (n=3) acute leukaemia (n=1), bronchial asthma (n=1), uveitis anterior (n=1) and malignant pleural effusion (n=1).

4. Discussion

We present a comprehensive analysis of patients with confirmed or suspected COVID-19 admitted to an isolation ward after structured triage. Our main findings were as follows:

1. 59% of admitted patients proved to be SARS-CoV-2-negative,
2. negative patients showed more comorbidities and suffered to a higher extend from an active malignancy than patients with confirmed COVID-19,
3. immunosuppression was frequent in both patient groups and
4. 31% of the negative patients were diagnosed with other non-infectious diseases.

As described above, in the majority of patients initially admitted to the isolation ward with suspected COVID-19, SARS-CoV-2 was later ruled out. This is due to the locally implemented triage system

focusing on unspecific symptoms such as fever and cough, and the proportion surely also depends on the current local COVID-19 incidence, which is a limitation of the presented study. However, while complex pre-existing conditions and immunosuppression were frequently present in all patients admitted to the ward, interestingly, in these pre-selected hospitalized patients it was shown that SARS-CoV-2 negative patients had both more comorbidities in general (assessed by the Charlson Comorbidity index) and more pre-existing conditions that have been suggested to be associated with a severe course of COVID-19 (e.g., cardiovascular disease).^[17] Almost half of these SARS-CoV-2 negative patients suffered from active malignancy (47% vs 15% of SARS-CoV-2 positive). This, as well as the high proportion of immunosuppressed patients in both groups, can be explained by the tertiary care setting, but also by these patients' general vulnerability to infections causing symptoms included in the screening algorithm.^[18] However, seeing every patient with fever and or cough as a potential COVID-19 patient in the time of a pandemic can lead to an anchoring bias, which is known to be associated with diagnostic errors.^[19] Thus, as SARS-CoV-2 negative patients suffered from different infectious as well as non-infectious diseases, other differential diagnoses need to be considered while awaiting SARS-CoV-2 test results. At the same time, as these patients were admitted to the isolation ward until infection with SARS-CoV-2 was ruled out, they were exposed to the downside of care in isolation rooms. It is known that patients do not only suffer psychologically from isolation but are also seen less frequently by medical personnel and have a higher probability of experiencing adverse events.^[20,21] This can impact quality of medical care, which is a great concern in these patients in need of specialized quality care.^[22,23] Looking at the diverse final diagnoses of SARS-CoV-2 negative patients, they suffered from a broad range of diseases requiring timely and highly specialized management, which has implications on considerations regarding patient flow, patient care and allocation of resources in hospitals.

Apart from the need for optimizing triage algorithms, rapid testing is an important factor in order to identify or rule out COVID-19, which can facilitate diagnostic decisions regarding differential

diagnoses. As long as the patient's status is unknown, diagnosis and care of conditions other than COVID-19 in the isolated patient can be challenging. To evaluate whether a patient likely suffers from COVID-19 several predictive scores are under investigation. Sun et al stated that, among others, elevated body temperature at admission in combination with radiological evidence of pneumonia as well as low neutrophil and eosinophil counts have a high predictive value of COVID-19.^[24] Further studies have emphasized the importance of CT scans in the diagnostic pathway of COVID-19 in emergency rooms.^[5,20,21] Even though our data does not allow for formal evaluation of the triage algorithm due to low patient numbers, the above named findings are reflected in our results as the vast majority of SARS-CoV-2 positive patients in our study showed typical chest CT findings. Further, we observed that the mean eosinophil count was lower in confirmed COVID-19 cases, and 15 patients with confirmed COVID-19 had low eosinophil counts as compared to none among negative patients.

5. Conclusion

Looking at our results, it becomes evident that a high proportion of patients (59%) triaged to the isolation unit with suspected COVID-19 were later tested negative for SARS-CoV-2. Of these, many suffered from active malignancy (47%) were immunosuppressed (20%) and diagnosed with a non-infectious disease. This highlights that, when planning COVID-19 isolation wards in tertiary care settings, it needs to be considered that many of these patients have complex comorbidities and require specialized care. Differential diagnoses have to be considered already during the time needed to confirm or rule out COVID-19, so that appropriate diagnostic steps can be taken. Potential anchoring bias present in clinical care during a pandemic should be acknowledged and avoided.

Author contributions

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