

# „What about the others – differential diagnosis of COVID-19 in a German emergency department“

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## Original Research

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# Abstract

**Background:** The ongoing COVID-19 pandemic is a major challenge for worldwide health care systems. Especially an early and safe triage in the emergency department (ED) is crucial for proper therapy. Clinical symptoms of COVID-19 comprise those of many common diseases thus differential diagnosis remains challenging.

**Method:** We performed a retrospective study of 314 ED patients presenting with possible symptoms of COVID-19. All were tested for COVID-19 with SARS-Cov2-nasopharyngeal swab. 47 patients were positive for COVID-19. We analyzed the 267 COVID-19 negative patients for their main diagnosis and compared COVID-19 patients with COVID-19 negative respiratory infections for differences in laboratory parameters, symptoms and vital signs.

**Results:** Among the 267 COVID-19 negative patients 42.7% had respiratory, 14.2% other infectious and 11.2% cardiovascular diseases, followed by 9.0% oncological and 6.7% gastroenterological diagnosis. Compared to COVID-19 negative airway infections, COVID-19 patients showed less dyspnea but more dysgeusia. Their hospital stay was significantly longer and their mortality significantly higher.

**Conclusion:** For many common ED diagnoses COVID-19 should be considered as a differential diagnosis. COVID-19 cannot be distinguished from COVID-19 negative respiratory infections by clinical signs, symptoms or laboratory results. When hospitalization is necessary, the clinical course of COVID-19 airway infections seems to be more severe compared to other respiratory infections.

## Introduction

With more than 36 million cases worldwide and more than 1.064.000 fatalities (date 10/11/20) COVID-19 is an unprecedented situation for society and health care (1). Although, most infections are not severe (2–5) or even asymptomatic (6), about 5 percent develop a critical disease with respiratory failure, shock or multiorgan dysfunction (5). The overall case fatality rate is estimated at around 0.7 to 2.3 percent (5, 7). Pneumonia appears to be the most frequent severe manifestation of infection (4, 7), but COVID-19 shows signs of a multi-system infectious disease involving central nervous system, coagulopathy and nephropathy. Additional COVID-19-induced coagulopathy might play an important role in COVID-19-related death (8).

Whereas the majority of patients presents with mild symptoms (2–5) and can be treated as outpatients, severely ill COVID-19 patients and patients with similar symptoms cross their way in the Emergency Department (ED). Due to the high infectiousness of SARS-Cov-2 it is crucial to separate patients with suspicion of COVID-19 and other patients as soon as possible to avoid further spread of the infection. Especially the variety of symptoms in COVID-19 patients are challenging for the primary triage in the ED: A report of over 370.000 documented symptomatic cases in the U.S. found cough (50%), fever (43%), myalgia (36%), headache (34%), dyspnea (29%) to be the most common symptoms, but also diarrhea (19%), nausea (12%) and taste/ smell disorders (< 10%) were present in a relevant number of cases (9).

Many of these can be found in other common ED diagnoses comprising heart failure, acute coronary syndrome, exacerbation of COPD and even gastroenterological and oncological diagnosis (Case report).

#### Case report:

A 91 year old male patient presented to the emergency department with progressive dyspnea, peripheral edema, dry cough and chest oppression. Medical history comprised a coronary heart disease with myocardial infarction and coronary bypass grafts.

Laboratory results showed an elevated nT-pro-BNP of 2858 pg/ml (< 450) and high sensitive Troponin I of 1641 ng/ml (< 45), so presumptive diagnosis was decompensated heart failure due to ischemic heart disease/ NSTEMI.

Surprisingly, D-dimers were massive elevated (> 35.2 mg/l), so an additional pulmonary CT angiogram was performed.

CT showed multiple bilateral ground glass opacities, suspicious of COVID-19. Pulmonary embolism was ruled out. COVID-19 was then confirmed by positive SARS-Cov2 nasopharyngeal swab testing.

Particular laboratory features like lymphopenia, elevated liver enzymes, elevated lactate dehydrogenase, C-reactive protein, elevated D-dimer, elevated prothrombin time, elevated troponin and acute kidney injury have been associated with worse outcomes (10, 11). However, data about possible parameters to distinguish between COVID-19 and other patients are sparse.

Therefore, we conducted a retrospective analysis of the differential diagnoses of the symptomatic, but COVID-19 negative patients in our cohort. Further, we tried to identify clinical parameters and laboratory features which could improve early triage between patients with proven COVID-19 and patients with acute respiratory infections from other origin.

## Methods

### Patients:

We performed a retrospective, single centre case control study. Patients with possible symptoms of COVID-19 presenting at the ED of the university hospital Essen between March and April 2020 that underwent SARS-CoV2 testing by nasopharyngeal swab and RT-PCR were included in this analysis. At least one of the following symptoms was mandatory for inclusion: dyspnea, sore throat, cough, fever, headache, fatigue, myalgia, chest pain, nausea, diarrhea and/ or dysgeusia. Our study was approved by the institutional ethics committee and informed consent was waived (Project number: 20-9310-BO). The study was registered at the German Clinical Trials registry (Trial number: DRKS00021675, Date 08.May.2020).

Patients and public were not involved in this study.

### Methods:

All patients were tested for COVID-19 by a SARS-Cov-2 nasopharyngeal swab (ViroCult®, Medical Wire & Equipment Co. Ltd., Corsham, Wiltshire, UK). To detect SARS-CoV-2 a RT-PCR (SARS-CoV-2 RT-PCR Kit 1.0, Altona Diagnostics GmbH, Hamburg, Germany) was performed (12). Additional laboratory testing and CT pulmonary angiography were performed when symptoms of lower respiratory tract involvement occurred. Retesting or additional bronchoscopy/ CT scan could be added in case of ongoing suspicion and negative swab testing. Strict isolation measures were kept until COVID-19 was definitely ruled out.

## Parameters

We analysed ICD-10 main diagnosis groups of all symptomatic, but COVID-19 negative patients. Of main diagnosis group “J” (respiratory diseases) all patients with acute infectious respiratory diseases were included, those with non-infectious diseases (i.e. pleural effusion, exacerbated COPD without acute infection, etc.) were excluded from further analysis (Fig. 2).

We compared and analysed clinical parameters, Manchester Triage System (MTS) categories and laboratory parameters between patients with positive swab results for SARS-CoV-2 and those with acute infectious respiratory disease of other origin as mentioned above.

Clinical parameters were symptoms upon arrival comprising dyspnea, sore throat, cough, fever, headache, fatigue, myalgia, chest pain, nausea, diarrhea and dysgeusia.

Laboratory results were white blood cell count, lymphocytes, C-reactive protein, procalcitonine, glomerular filtration rate, creatinine, troponine and D-dimers.

Patient data were obtained through the electronic medical record (ERPath, eHealth-Tec Innovations GmbH, Berlin, Germany; Medico, Cerner Health Services GmbH, Idstein, Germany).

Missing data that could not be extracted from patients' records were excluded from statistical analysis.

## Statistical analyses

We used a t-test to evaluate metric data. Data were tested by Levene's test to assess the equality of variances. In case of unequal variances, Welch's t-test was performed to analyse metric data. Results were reported as mean  $\pm$  standard deviations for continuous variables. The Pearson's  $\chi^2$  test or the Fisher's exact test were used to evaluate categorical data. Results for categorical variables were reported as percentages. All data were analysed using SPSS, version 26 (IBM, Armonk, NY, USA). Statistical significance was defined as two-tailed  $p < 0.05$ .

## Results

Of the initially 269 SARS-CoV-2 negative patients, 55 had been retested for ongoing clinical suspicion of COVID-19, 14 of these by PCR from bronchoalveolar fluid (BAL). Two of the retested ones revealed to be positive during retesting, so a total number of 267 SARS-CoV-2 negative patients were further analysed for their ICD main diagnosis group. Respiratory diseases (ICD 10 group J) were found in 42.7% (114/267)

of cases, followed by 14.2% (38/267) infections of other origin (ICD 10 groups A/B), 11.2% (30/267) cardiovascular (ICD 10 group I), 9.0% (24/267) oncological (ICD 10 groups C/D), 6.7% (18/267) gastrointestinal (ICD 10 group K), 4.9% (13/267) urogenital (ICD 10 group N), 1.9% (5/267) neurological (ICD 10 group G) and 9.4% (25/267) miscellaneous diseases (all remaining ICD 10 groups ) (Fig. 3).

Further evaluation of the respiratory diseases group (n = 114) resulted in exclusion of 25 cases of non-infectious respiratory diseases (pulmonary edema, non-infectious exacerbation of COPD, pleural effusion, asthma, hypercapnic respiratory failure), so a total of 89 COVID-19 negative respiratory infections (50 pneumonia (J18.0-J18.9), 17 influenza/ viral pneumonia (J10.0, J10.1, J10.8, J12.1, J12.8), 6 upper respiratory tract infections (J06.8, J06.9), 16 acute bronchitis (J20.9, J22, J44.01, J44.09)) could be included.

A total of 136 patients (mean age 68 years  $\pm$  17.5 year.; 46 female (33.8%)) were included in the analysis. Baseline characteristics are summarized in Table 1. According to the MTS 14 patients were classified as "red" (10.3%), 12 patients as "orange" (8.8%), 50 patients as "yellow" (36.8%), 58 patients as "green" (42.6%) and 2 patients as "blue" (1.5%).

47 patients were tested positive for SARS-Cov-2.

Of all COVID-19 patients, 40% (19/47) reported dyspnea, while this clinical feature was present in 61% (54/89) of non COVID-19 patients ( $p = 0.024$ ). Among the COVID-19 patients, 15% reported taste disorders (7/47), whereas only 2% (2/89) of the COVID-19 negative patients did so ( $p = 0.005$ ). Significant differences between the two groups were not observed for other clinical features or vital parameters (table 2).

Patients with COVID-19 had significant less preexisting renal disorders (8.5% vs 24.7%;  $p = 0.025$ ). No significant differences were observed for the presence of a preexisting cardiac or pulmonary disorder, previous thrombosis or pulmonary embolism and oncological diseases between COVID-19 positive and COVID-19 negative patients.

There were significantly more active smokers in the COVID-19 negative group than in the group with COVID-19 positive patients (16.9% vs 2.1%;  $p = 0.011$ ). However, the number of patients with an unknown smoking status was, although not significantly, higher in the non-COVID-19 group than in the group tested positively (70.2% vs 58.4%;  $p = 0.177$ ).

The mortality of COVID-19 patients admitted to our hospital via the ED was 19.1%, which was significantly higher than of the group admitted with similar symptoms but negative COVID-19 result (5.6%) ( $p = 0.014$ ). The duration of hospital stay was longer among COVID-19 patients (9.0 vs. 5.6 days,  $p = 0.014$ ) than among COVID-19 negative patients.

In the group of COVID-19 patients, mean levels of lactate dehydrogenase (LDH) were significantly higher (439.5 vs. 335.8 U/l,  $p = 0.025$ ). The mean levels of procalcitonine tended to be higher in COVID-19 negative patients (6,74 versus 0.42  $\mu\text{g/l}$ ), but were not significantly different ( $p = 0.354$ ).

We could not find any significant differences regarding to other laboratory values, vital parameters and treatment modes between the two groups (table 2)

**Table 2: group comparison COVID-19 versus COVID-19 negative airway infections Discussion:**

Early triage and differential diagnosis of patients presenting with typical clinical symptoms of COVID-19 remains very challenging but relevant. Our study had the following main findings:

1. Differential diagnosis of typical COVID-19 symptoms is very broad and comprises many common respiratory, infectious and cardiovascular diseases whereas respiratory diseases are the most frequent. Diseases from nearly every field of clinical medicine can mimic a clinical picture similar to that of COVID-19 with respiratory diseases being the most prevalent.
2. Patients with COVID-19 present with similar symptoms as COVID-19 negative respiratory infections so clinical discrimination is not reliable.

Dyspnea is less frequent found in our COVID-19 patients, whereas dysgeusia is significantly more prevalent. The latter finding has been described by other studies before and can be found in up to 44% of cases following meta-analysis (13). Whenever present, dysgeusia should rise a high suspicion for COVID-19, especially during pandemic.

Dyspnea is a typical symptom of COVID-19, which could be found in about 29% of cases in a study of 270.000 patients in the U.S.(9). Controversially, several authors described a specific phenomenon called "happy hypoxemia" in COVID-19 with a disconnect between the severity of hypoxemia and a relatively mild respiratory discomfort (14, 15). Therefore, dyspnea might be less frequent in our COVID-19 positive patients than in other respiratory infections.

Elevated levels of LDH have been described before (16) and were significantly higher among non-survivors in a case series from Wuhan (11) so this finding in our COVID-19 patients is in line with the more severe clinical course of this group. The tendency towards higher procalcitonine levels in COVID-19 negative patients may be explained by a higher rate of bacterial infections such as pneumonia, since elevated procalcitonine levels can usually only be found in advanced respectively complicated courses of COVID-19 (4). Case numbers might have been too small to reach significance here.

The significantly lower frequency of smokers in the COVID-19 group should be interpreted very cautiously since the rate of unknown smoking status is 70%, thwarting the attempt to draw any further conclusions.

Therefore, no clinical sign or symptom, nor any of the analysed laboratory values will be able to predict COVID-19 status in a reliable way. Only dysgeusia, when present, should raise a high suspicion of COVID-19 during pandemic. Strict isolation policy and frequent SARS-CoV-2 testing will remain the most important measures to keep control of the situation.

3. When inpatient treatment for respiratory infections is needed, COVID-19 patients seem to take a more severe clinical course.

The mortality of our COVID-19 positive inpatient patients is significantly higher than in the COVID-19 negative group. The mortality rate of 19.1% is comparable to those found by Petrilli et al (17), who reported a mortality of 24.1% among inpatients in New York City. The COVID negative group is a heterogeneous one, comprising different kinds of respiratory infections with pneumonia as the most frequent diagnosis (50/89). Inpatients with CAP showed a 30-day mortality of 11.9% in Europe in one study (18), so the lower mortality of the COVID negative group might be explainable hereby. A more severe course of disease can also explain the significantly higher time of admission (9.0 vs. 5.6 days,  $p = 0.014$ ) among the COVID-19 positive patients in our study.

4. The false-negative rate of nasopharyngeal swab testing was low

55 patients were retested due to ongoing clinical suspicion of COVID-19, some even more than one time including bronchoalveolar specimens in 14 cases. Only 2 more positive cases (3.6%) could be found, both by BAL. This suggests that the false-negative rate is low whenever experienced and well-trained staff carries out a nasopharyngeal SARS-Cov2 swab. Previous research has reported rates of 11% for false negative PCR results in COVID-19 (19). Of note, all patients were symptomatic so that very early stages of disease who might carry a higher likelihood of false negative testing were scarce in our study.

## Limitations

Our study has few limitations. Data collection was retrospective. Therefore, selection bias and errors in data entry could not be completely excluded. This study is a single centre study and for these reason data should not be generalised.

Further we included only patients admitted to our ED. As SARS-Cov-2 is often associated with minor symptoms or illness, the number of outpatient treatment could have been higher than in non-COVID-19 respiratory infections.

In our cohort, the number of patients with unknown smoking status is very high (62.5%). Therefore, in this study it seems to be difficult to evaluate the exact number of current smokers. We think that this might be the reason for the paradoxical finding that a history of smoking was more frequent in the non COVID-19 group.

## Conclusions

Differential diagnoses of COVID-19 are plentiful and comprise many common diseases, most notably ailments associated with respiratory impairment. Triage remains challenging in the emergency department, since there are no reliable clinical or laboratory parameters to distinguish safely between COVID-19 and airway infections of other origin. When inpatient, COVID-19 takes a more severe clinical course than comparable COVID negative airway infections. Therefore, strict isolation policy together with broad and rapid testing will remain the most important measures for the months to come.

# Declarations

## ***Ethics approval and consent to participate:***

Our study was approved by the institutional ethics committee and informed consent was waived (File number: 20-9310-BO, Date: 06.May.2020). The study was registered at the German Clinical Trials registry (Trial number: DRKS00021675, Date 08.May.2020).

Patients and public were not involved in this study.

## ***Consent for publication:***

Not applicable

## ***Availability of data and materials:***

The anonymised dataset supporting this conclusions is available upon reasonable request from the corresponding author.

## ***competing interests:***

The authors state that they have no competing interests.

## ***Funding:***

Funding did not take place for this study.

## ***Authors contribution:***

DF, DP, AH, BMS, LU, CH, JR contributed to data acquisition

DF, DP, AH, CK, contributed to data analysis

DF, DP, JR, BMS interpreted data

DF, DP, AH, BMS, LU, CH, SD, CK, JR, RM, CT drafted the article and substantially revised it

All authors read and approved the final manuscript

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## Tables

**Table 1** Characteristics of inpatients with airway infections

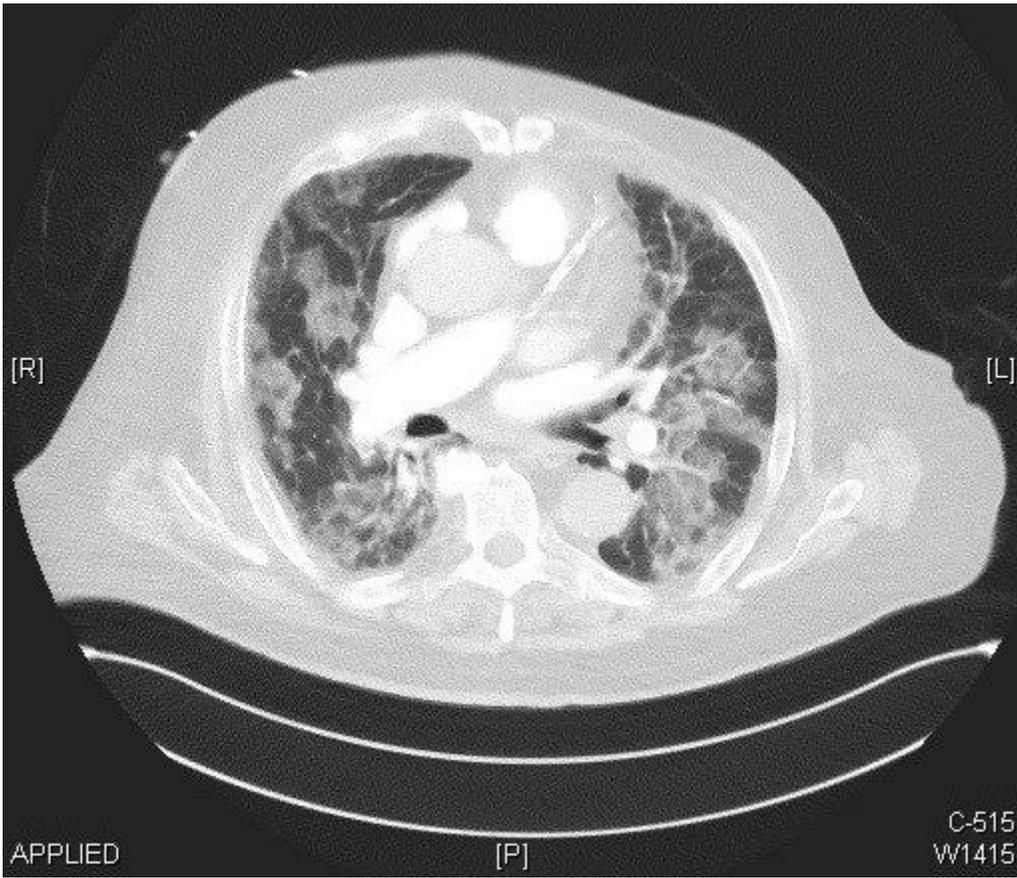
	All (n=136)	COVID19 + (n=47)	COVID19 – (n=89)	p-value
<i>Age, mean (±SD, range)</i>	68 (±17.54, 23-97)	70 (±17.65, 23-94)	67 (±17.51, 24-97)	0,420
Male gender, n (%)	90 (66.2)	31 (66.0)	59 (66.3)	0,969
<i>Manchester triage, n (%)</i>				
Red	14 (10.3)	4 (8,5)	10 (11.2)	0,619
Orange	12 (8.8)	3 (6,4)	9 (10.1)	0,466
Yellow	50 (36.8)	15 (31,9)	35 (39.3)	0,394
Green	58 (42.6)	25 (53,2)	33 (37.1)	0,071
Blue	2 (1.5)	0 (0)	2 (2.2)	0,301

**Table 2:** group comparison COVID-19 versus COVID-19 negative airway infections

	All (n=136)	COVID19 + (n=47)	COVID19 – (n=89)	p- value
<i>Medical history, positive for, n (%)</i>				
Cardiac	85 (62,5)	29 (61,7)	56 (62,9)	0,769
Pulmonary	44 (32,4)	10 (21,3)	34 (38,2)	0,108
PE/thrombosis	9 (6,6)	2 (4,3)	7 (7,9)	0,437
<b>Renal</b>	<b>26 (2,9)</b>	<b>4 (8,5)</b>	<b>22 (24,7)</b>	<b>0,025</b>
Cancer	31 (22,8)	10 (21,3)	21 (23,6)	0,808
<i>Smoker, n (%)</i>				
Never	26 (19,1)	9 (19,1)	17 (19,1)	0,995
<b>Yes</b>	<b>16 (11,8)</b>	<b>1 (2,1)</b>	<b>15 (16,9)</b>	<b>0,011</b>
Quitted	9 (6,6)	4 (8,5)	5 (5,6)	0,519
Unknown	85 (62,5)	33 (70,2)	52 (58,4)	0,177
<i>Symptoms, n (%)</i>				
<b>Dyspnoe</b>	<b>73 (53,7)</b>	<b>19 (40,4)</b>	<b>54 (60,7)</b>	<b>0,024</b>
Sore throat	10 (7,4)	4 (8,5)	6 (6,7)	0,707
Cough	79 (58,0)	25 (28,1)	54 (60,7)	0,400
Fever	85 (62,5)	31 (66,0)	54 (60,7)	0,545
Headache	14 (10,3)	5 (10,6)	9 (10,1)	0,924
Fatigue	68 (50,0)	22 (46,8)	46 (51,7)	0,589
Myalgia	24 (17,6)	6 (12,8)	18 (20,2)	0,278
Chest pain	11 (8,1)	2 (4,3)	9 (10,1)	0,234
Nausea	22 (16,2)	6 (12,8)	16 (18,0)	0,433
Diarrhea	35 (26,5)	13 (27,7)	22 (24,7)	0,709
<b>dysgeusia</b>	<b>9 (6,6)</b>	<b>7 (14,9)</b>	<b>2 (2,2)</b>	<b>0,005</b>
<i>Death, n (%)</i>				
	<b>14 (10,3)</b>	<b>9 (19,1)</b>	<b>5 (5,6)</b>	<b>0,014</b>

<i>Treatment, n (%)</i>				
O2-therapy	52	20 (42,6)	32 (36,0)	0,451
Ventilator	2	0 (0,0)	2 (2,2)	0,137
Intensive Care	24	6 (12,8)	18 (20,2)	0,278
Intermediate Care	12	4 (8,5)	8 (9,0)	0,926
<b>Time of admission (days)</b>	<b>6,8 (±6,4)</b>	<b>9,0 (±8,1)</b>	<b>5,6 (±5,0)</b>	<b>0,014</b>
<i>Vital parameters</i>				
Respiratory rate/min (±SD)	37,2 (±1,2)	23,7 (±7,4)	22,3 (±6,7)	0,283
Heart rate/ min (±SD)	96,7 (±21,6)	93,7 (±16,6)	98,4 (±23,8)	0,235
Saturation, O <sub>2</sub> in % (±SD)	94,3 (±7,1)	94,9 (±4,0)	94,0 (±8,4)	0,456
Temperature in °C, (±SD)	37,2 (±1,2)	37,3 (±1,0)	37,2 (±1,2)	0,552
BP systolic in mmHg (±SD)	132,5(±25,6)	136,2 (±24,1)	130,52 (±26,3)	0,219
BP diastolic in mmHg (±SD)	79,0 (±17,4)	82,9 (±18,1)	77,0 (±16,7)	0,057
<i>Laboratory values</i>				
C-reactive proteine, mg/L	9,57 (±7,86)	8,2 (±5,8)	10,3 (±8,7)	0,100
Procalcitonine, µg/L (±SD)	4,53 (±36,75)	0,42 (±1,49)	6,74 (±45,47)	0,354
Troponin I, µg/L (±SD)	73,27(±268,64)	76,59 (±278,7)	71,33 (±265,0)	0,928
<b>LDH, U/L (±SD)</b>	<b>370,67(±248,34)</b>	<b>439,5 (±264,9)</b>	<b>335,8 (±233,4)</b>	<b>0,025</b>
Creatinine, mg/dL (±SD)	1,21 (±0,87)	1,18 (±0,90)	1,23 (±0,86)	0,729
GFR, ml/min (±SD)	58,10 (±19,10)	58,7 (±19,18)	57,8 (±19,17)	0,805
D-dimer, mg/L (±SD)	3,10 (±6,13)	4,29 (±7,95)	2,44 (±0,61)	0,222
WBC/ mm <sup>3</sup> (±SD)	12,04 (±21,44)	8,00 (±4,11)	14,1 (±26,04)	0,115
Lymphocytes /mm <sup>3</sup> (±SD)	2,39 (±10,99)	1,20 (±1,40)	3,1 (±13,95)	0,322

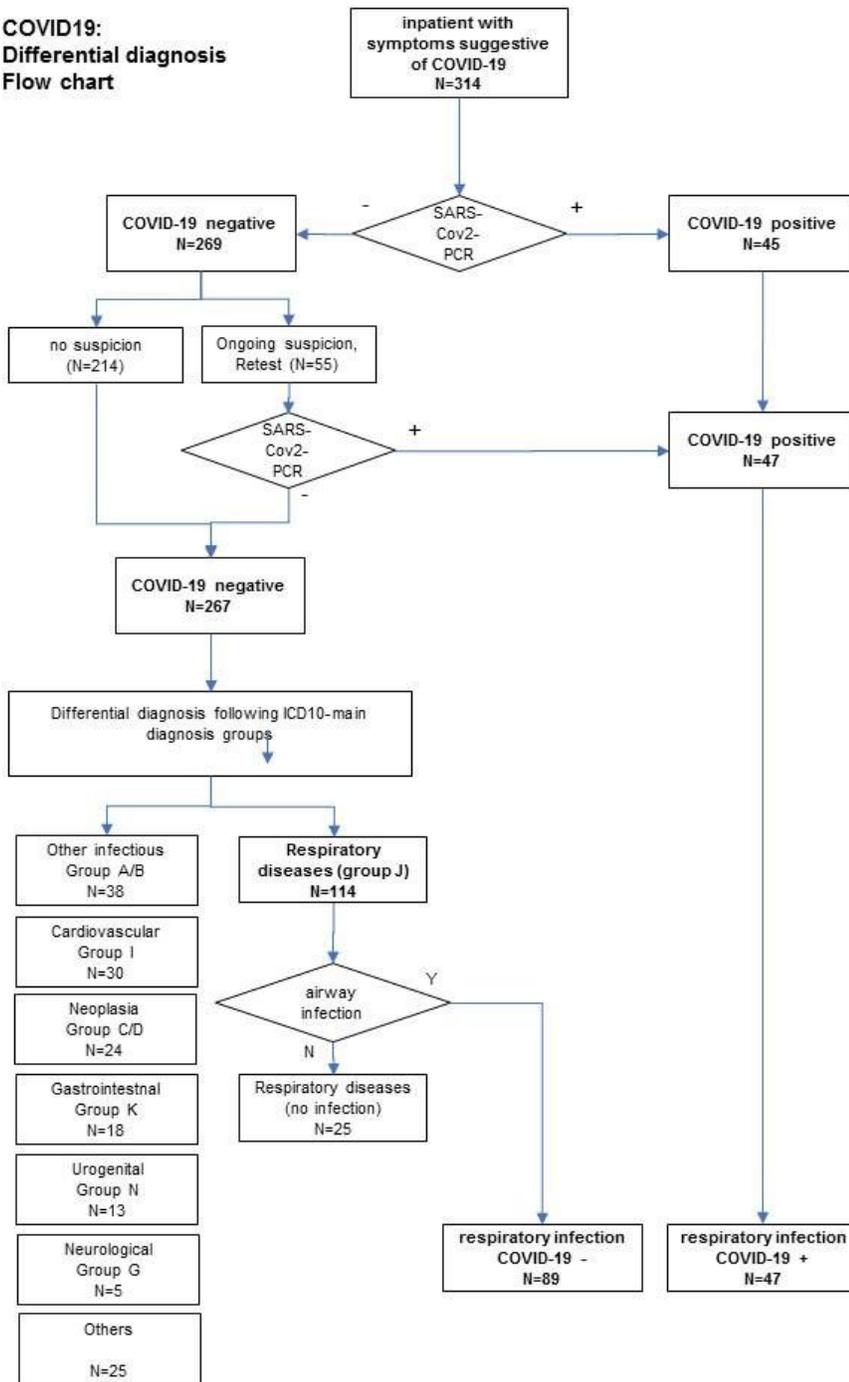
## Figures



**Figure 1**

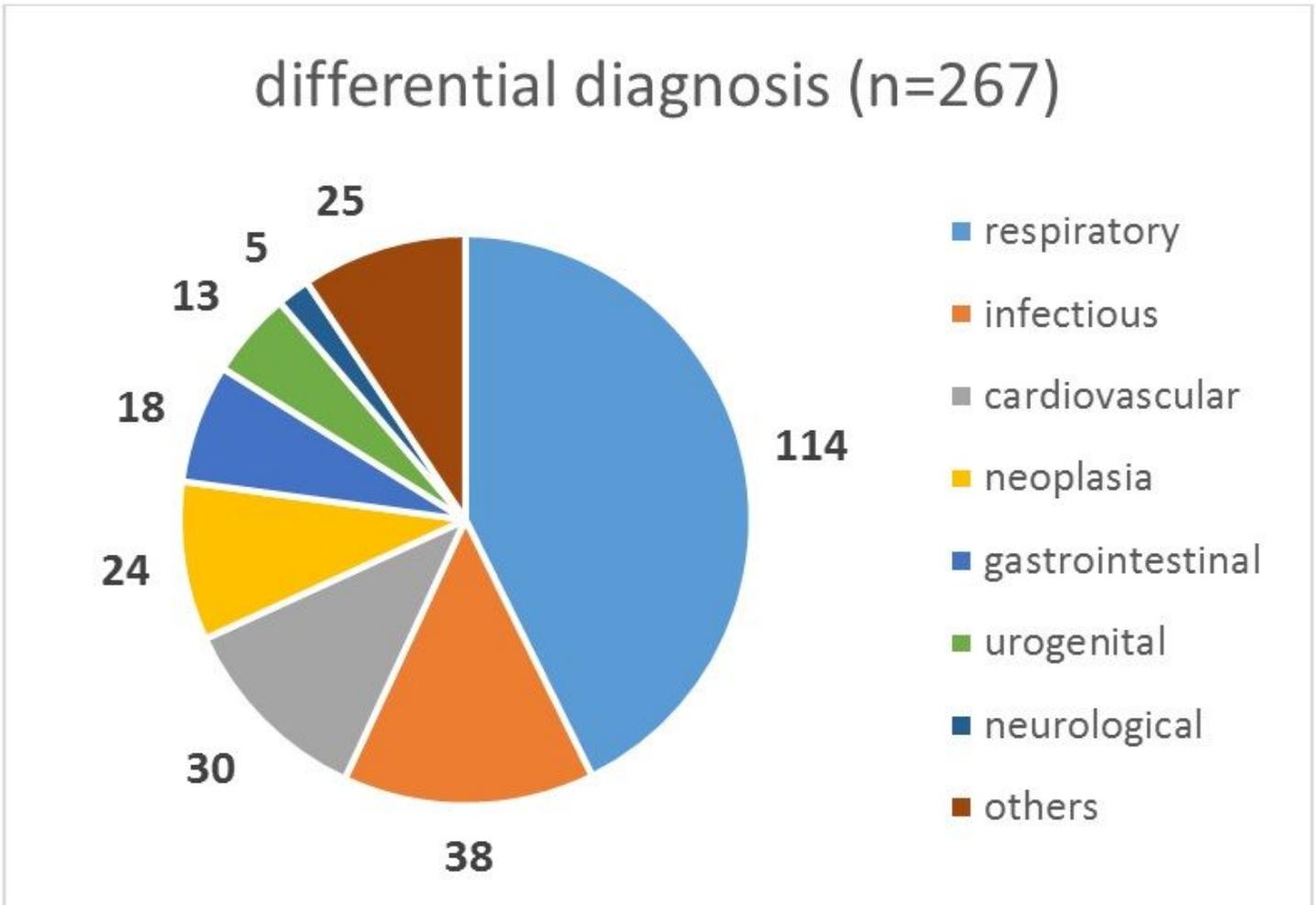
bilateral ground glass in CT

**COVID19:  
Differential diagnosis  
Flow chart**



**Figure 2**

flow chart differential diagnosis



**Figure 3**

Differential diagnoses of COVID-19 negative patients