

Analysis of Symptoms of COVID-19 Positive Patients and Potential Effects on Initial Assessment

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Background: SARS-CoV-2 is a highly contagious virus, significantly impacting Germany among other countries since its emergence. Because of heterogeneous symptoms and a subset of patients even being asymptomatic at presentation, fast identification of infected patients remains challenging.

Objective: The goal of this study is the evaluation of different patient groups with a focus on symptoms and pre-existing illness at admission, as this is important for initial assessment and adequate emergency care.

Methods: COVID-19 positive patients at the University Hospital Heidelberg were retrospectively analyzed for disease history and symptoms at the initial presentation as well as mortality. The authors obtained institutional review board (IRB) approval by the Ethics Committee (Medical Faculty of Heidelberg University) prior to commencing the study.

Results: Dyspnea was more common in patients admitted to intermediate care/intensive care units (48 vs 13%, $P < 0.001$) and showed a significantly higher percentage in the deceased (91 vs 48%, $P = 0.004$). The symptoms of all presenting patients were highly variable, and many manifestations commonly associated with COVID-19 like cough, fever, and sore throat were only detected in a subset of patients, 60%, 43%, and 33%, respectively.

Conclusion: Dyspnea was present significantly more often in patients dying of COVID-19 compared to all patients admitted to the IMC/ICU, necessitating adequate observation and monitoring. In all presenting patients, initial symptoms showed large variation; therefore, COVID should be considered as a main differential diagnosis at every patient presentation, and patients with high pre-test probability should, if possible, be isolated until testing results are known.

Keywords: COVID-19, dyspnea, mortality, triage

Introduction

The novel coronavirus, severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China in December 2019.^{1–3} It has spread rapidly and globally ever since.^{4,5} In March 2020, it was recognized as a pandemic by the World Health Organization (WHO) and since then has had a considerable impact on the global economy and national health systems. Germany has been greatly affected by the virus. As of October 10, it ranked 22nd in numbers of infected patients worldwide (320.495), with 9.599 individuals having died of the disease (mortality rate of 3.0%).⁶

In the beginning, coronavirus disease 2019 (COVID-19) infection was suspected in symptomatic patients with either a travel history to a risk area or contact with an infected individual. With the increasing penetration of COVID-infection in

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the population, more emphasis was put on the triage of patients by clinical presentation.⁷ When comparing countries and regions, local differences in symptoms and death rates were found.^{8–11} These discrepancies, as well as varying symptoms at initial presentation, complicate and often delay the diagnosis. Therefore, a thorough investigation of every presenting patient is necessary.

In this report, data from more than 3,000 screenings and all thereof positive tested patients were analyzed. A particular focus was placed on the usefulness of a standardized emergency medical triage for COVID-19, as well as symptoms that may indicate increased mortality.

Investigation was centered on questions regarding 1) testing results, with admission rates (both hospitalization to a general ward and to an intermediate or intensive care unit (IMC/ICU)) as a primary outcome; 2) patients characteristics; 3) risk stratification evaluating potential stays in risk area(s) and chain of infection; 4) initial symptoms at presentation; 5) comorbidity; and 6) mortality analysis (secondary outcome).

Methods and Materials

Testing, Setting, and Selection

Included in the analysis were patients diagnosed and treated between February 25 and April 7, 2020. Different testing facilities for COVID-19 at the University Hospital Heidelberg were implemented: The Emergency Department began testing of patients on February 25. In an inaugural phase, both with expected organizational difficulties as well as many anticipated patients, an ambulatory COVID-19 testing center was launched for a span of 25 days, ranging from March 2 to March 27. With increasing patient numbers across the country, a dedicated Corona Emergency Department that provided case isolation was established and ambulatory testing was moved to drive-ins and primary care physicians. All patients presenting for SARS-CoV-2 testing were evaluated, and follow-up was performed until April 18.

All presenting patients were tested and included in the analysis. The patients' naso- and oropharyngeal swabs was processed in the virology laboratory and examined by means of reverse transcriptase polymerase chain reaction (RT-PCR) to SARS-CoV-2. Testing was processed with LightMix[®] Modular SARS-CoV (TIB MOLBIOL GmbH; Berlin, Germany), using base stratifications set by the Virology Department Charité, Berlin, which developed the test.¹² In addition, Allplex[™] 2019-nCoV Assay (Seegene, inc.) was used.

Symptoms and Prior Diseases

All patients testing positive were evaluated for symptoms at admission. By percentage of occurrence these were divided into main (>10% mean in all patients) and less common (<10%) symptoms.

Additionally, all patients were screened for comorbidities such as previous cardiovascular and/or lung diseases, previous or active cancer, diabetes mellitus or other metabolic diseases, hypertension, chronic kidney failure, and others.

Patient Information

Standard demographic characteristics such as age or gender were registered.

Additionally, this evaluation includes examination of baseline characteristics and symptoms of selected groups: patient admitted to IMC/ICU and those succumbing to COVID-19.

Data Collection, Study Design, and Public Involvement

According to the Declaration of Helsinki, written informed consent for all patients was obtained and data collection and analysis had been approved by the Ethics Committee (Medical Faculty of Heidelberg University, reference number: S-148/2020). A quality control program for standardized data collection (including using medical patients records by manual review) was implemented and the study was designed as a retrospective, non-randomized analysis. The abstractor was blinded to outcomes when assessing symptoms. The same applies for the study personnel, as they were blinded from symptoms when evaluating patient outcome. No funds or time were allocated for patients or public involvement. Therefore, patients were not involved in writing or editing of the research.

Data Analysis

Continuous variables were tested for normal distribution using Kolmogorov-Smirnov test for normality. A student's *T*-test was carried out if values were normally distributed, otherwise a Wilcoxon test was carried out. Qualitative variables were compared using Chi-square test or Fisher's exact test for small sample size. For all tests, 95%-confidence interval was calculated (denoted as CI; percentages displayed on a scale of 0–1) and a *P*-value<0.05 was considered to be statistically significant and indicated as follows:

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. For analysis, IBM SPSS 20 for Windows (IBM Corp. Armonk, NY, USA) was used.

Results

Testing Results

In total, 3,015 tests were administered from February 25 until April 7, 2020 in the departments of internal medicine, of which a total of 352 were positive. Of these patients, 13 (3%) were initially administered for a hospital stay, while 59 (17%) had to be treated in intermediate care (IMC) or intensive care units (ICU). Two hundred and eighty patients (80%) were not admitted for stationary treatment and released after testing.

Among the patients tested, age ranged from 1 month to 91 years, with a median of 38 years. More female (56%) than male presentations were registered. Of those tested for SARS-CoV-2, admission proportion for hospital stay (0.4%) or IMC/ICU (0.2%) was low.

Patients Characteristics

Overall, of the positive patients, 55% (CI=0.48–0.61) were male. A difference was detected comparing all these patients to those admitted to the IMC/ICU (n=59), where the number of male patients rose up to 63% (CI=0.57–0.68; $P=0.2$). Age and gender distribution of all patients and the respective subgroups is shown in Table 1A. The age of patients without a hospital admission (median=41, range=10–77 years, CI=0.39–0.43) was significantly lower than the median age of patients admitted to the IMC/ICU (64, range=21–88 years; CI=0.59–0.67; $P < 0.001$).

Seven patients (7%) were below age 18, none of these patients required hospitalization. Body mass index (BMI) of patients admitted to the general ward (26.1, range=18.1–31.0, CI=0.21–0.32) was comparable to those in need of IMC/ICU care (26.9, range=21.7–48.1, CI=0.24–0.31; $P=0.1$).

Risk Stratification

Stay in a Risk Area

The 289 patients testing positive at the COVID-19 testing center were examined for stays in risk areas, as defined by the Robert-Koch-Institute (RKI) and shown in Table 1B. While more than half of patients (52%) had no such travels, 28% had a travel history to Austria. Travel history to Italy (9%) could also be identified.

Table 1 Baseline Characteristics and Risk Areas. Baseline Characteristics of the Investigated Patient Groups are Shown (1A). In Addition, The Table Displays Distribution of Patients Prior to Visiting Identified Risk Areas (1B)

	Gender (M/F), in %	Age Median (Range), in Years	Body Mass Index Median (Range), kg/m ²
A			
All tested patients (n=3,015)	43.7/56.3	38 (1 month–91)	NA
All positive tested patients (n=352)	55.4/44.6	45 (10–91)	NA
No admission (n=280)	54.2/45.8	41 (10–77)	NA
General ward (n=13)	38.5/61.5	54 (23–91)	26.1 (18.1–31.0)
IMC/ICU (n=59)	62.7/37.3	64 (21–88)	26.9 (21.7–48.1)
Deceased (n=11)	81.8/18.2	82 (42–91)	26.8 (24.8–37.2)
B			
Region	Patients n=289 (Percentage)		
No Risk area	149 (51.9)		
Austria	80 (27.7)		
Italy	27 (9.3)		
France	6 (2.1)		
Spain	3 (1.0)		
Iran	1 (0.4)		
Germany	1 (0.4)		
Unspecified Risk area	19 (6.6)		

Abbreviations: M, male; F, female; IMC/ICU, intermediate care/intensive care unit; NA, not available.

Chain of Infection

One hundred and fifty-seven of the 289 patients who tested positive were also identified to have had contact with a positive tested person (54%), according to the RKI and local authorities (Health department Rhein-Neckar). Of these patients, 110 (70%) had not been to an RKI-declared risk area.

Symptom Analysis

Figure 1 displays the main symptoms of COVID-19 positive patients. Coughing (60%) and fever (43%) were detected to be the two most prevalent symptoms in all patients. In between the analyzed subgroups however, significant differences regarding presenting symptoms were found across subgroups. While patients who were discharged after testing often experienced symptoms like sore throat (39%) and headache (30%), these symptoms were observed less frequently in patients admitted to the

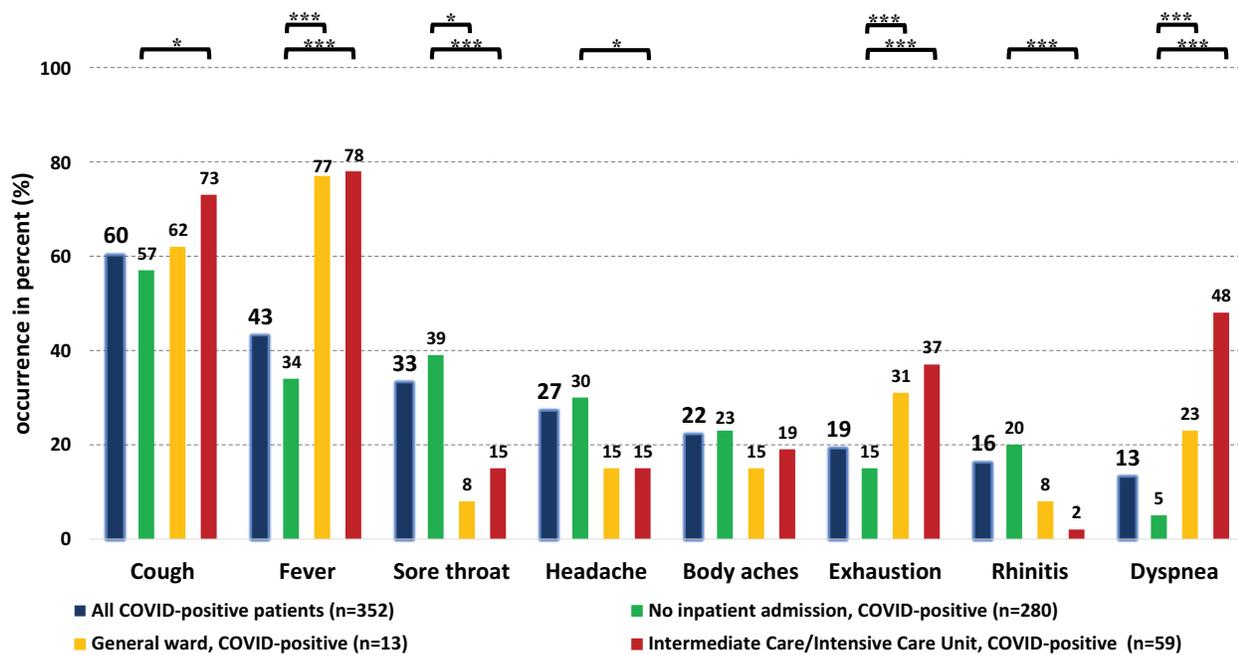


Figure 1 Main symptoms at presentation sorted by admission status. Main symptoms, with which patients presented at admission, are shown for distribution in the investigated subgroups. * $P < 0.05$, *** $P < 0.001$.

IMC/ICU. In contrast, dyspnea and exhaustion were far more common in patients admitted to the IMC/ICU than in discharged patients (48% (CI=0.34–0.60) vs 5% (CI=0.03–0.08), $P < 0.001$ and 37% (CI=0.25–0.50) vs. 15% (CI=0.11–0.19), $P < 0.001$; respectively). In addition, fever (78% (CI=0.67–0.89) vs 34% (CI=0.28–0.40), $P < 0.001$) was also seen more often in hospitalized patients.

No symptoms at presentation were registered in 8% of patients. Pediatric patients showed no significant differences in presenting symptoms compared to the adult cohort.

[Supplementary Table S1](#) shows the distribution of less common symptoms, while a more detailed overview and subgroup comparison of main and less common symptoms is displayed in [Supplementary Tables S2](#) and [S3](#).

Comorbidities

Patients were analyzed for pre-existing medical conditions and comorbidities. Regarding presumed main risk factors to a COVID-19 infection, 4% patients were identified to have a history of cardiovascular disease, and 2% had a history of lung disease, while 5% had cancer, or received immunosuppressive medication at the time of presentation. Regarding major cardiovascular risk factors, 7% had arterial hypertension, 2% diabetes mellitus, and 1% were obese. Another 6% showed metabolic diseases other than

diabetes (eg, hypothyroidism), 4% gastroenterological, 3% orthopedic, and 2% neurological diseases. Very rare were renal disease (2%), skin disorders (2%), and ear/throat (1%) diseases.

The seven pediatric patients had no known comorbidities, while no significant differences in comparison to the adult cohort were seen due to the small pediatric sample size.

[Supplementary Tables S4](#) and [S5](#) display a detailed overview with comparison of comorbidities and distribution of past medical conditions in all subgroups, respectively.

Mortality

A total of 11 patients (3%) died from COVID-19 infection, as of 18 April. These patients, all from the adult cohort, were treated for a median of 4 (range=1–11) days until their deaths, while the median age was 82 (range=42–91) years. Of the deceased, 82% (CI=0.70–0.93) were male (vs 63% in all patients receiving intensive care; CI=0.55–0.73; $P = 0.1$). Among the non-survivors, the age of two patients was younger than 70 years, whereas all other deceased were 75 or older. No significant differences were seen regarding the patients BMI (26.8, range=24.8–37.2, CI=0.23–0.32) compared to all other patients admitted to the general ward or IMC/ICU (26.9, range=18.1–48.1, CI=0.19–0.46, $P = 0.2$).

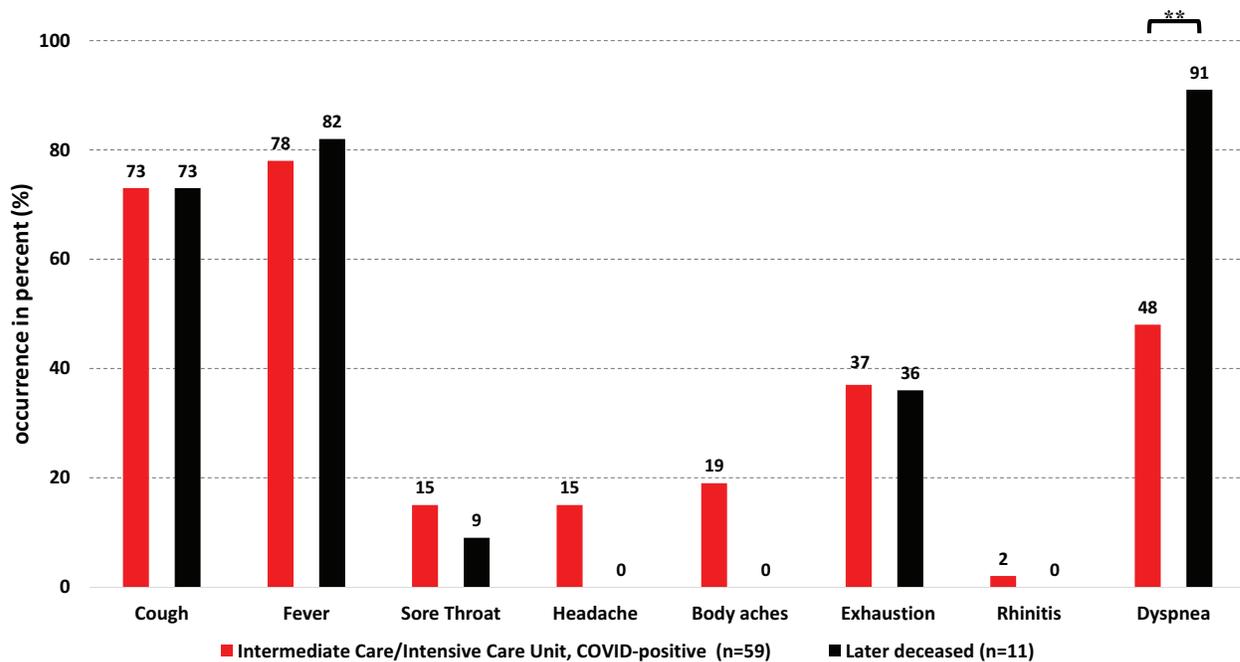


Figure 2 Main symptoms at presentation for all intensive care patients and those later deceased. ** $P<0.01$.

Dyspnea (91%), coughing (82%), and fever (73%) were the most prevalent symptoms at initial presentation, with an overview of symptoms of all patients in need of intensive care and those later deceased displayed in Figure 2. While the latter two showed no differences to the group of all IMC/ICU patients, percentages for dyspnea were significantly higher (91% (CI=0.73–1.0) vs 48% (CI=0.34–0.60), $P=0.004$). Analyzing pre-existing diseases and comorbidities, 55% showed cardiovascular and 36% lung disease, while hypertension was seen in 27%. The first-mentioned (CI=0.41–0.70) was seen significantly higher compared to all IMC/ICU patients (27%, CI=0.16–0.39; $P=0.04$).

Discussion

In all positive tested patients, age (median 45, range=10–91 years) and gender ratio were comparable with data shown from the RKI and other publications.^{13,14} Primary outcome (hospital admission) was reached in 20%, while 3% died from COVID-19 (secondary outcome).

Overall, cough and fever were the most prevalent symptoms in all evaluated patients and rates were consistent with data reported from the RKI on symptoms of positive tested individuals in the German population.^{11,15} In other evaluations, however, there were differences regarding the frequency of observed symptoms.^{8–12,16}

This could be due to the differences in number of cases, different population groups, or examination of groups with different stages of disease severity in these aforementioned publications.

On the contrary, dyspnea was seen more frequently in patients with severe or critical disease requiring intensive care treatment compared to patients who were not admitted (48% (CI=0.34–0.60) vs 5% (CI=0.03–0.08), $P<0.001$). Additionally, an even more drastic difference could be shown in deceased patients, as percentages of dyspnea at presentation were almost twice as high as in all IMC/ICU (91% (CI=0.73–1.0) vs 48% (CI=0.34–0.60), $P=0.004$). Supporting these findings, dyspnea had been described, in prior studies, as a potential marker for severe disease.^{10,17,18} As no other symptoms showed a significant difference between deceased and all other IMC/ICU patients, dyspnea needs to be closely monitored in all presenting patients because of its potential risk estimation for higher mortality.

Additional to testing of COVID-19 suspicious patients with symptoms, detection of risk areas and contact persons are indispensable components of infection control. Of the positive tested patients, 54% had contact with a positive tested person, but 70% had not been to an RKI-declared risk area. Therefore, if these patients had not developed any symptoms, they would potentially not have been

tested and subsequently might have contributed to a further spread of the virus. In addition, a recent study suggests the number of people distributing the virus while still asymptomatic/pre-symptomatic to be higher than previously expected.¹⁹

Nine months since COVID-19 has been declared as a pandemic disease, detection and treatment of infection with SARS-CoV-2 remains challenging, as is management of positive tested patients. A sequential model was implemented at our institution for adequate testing while at the same time adjusting capacities for possibly rapidly increasing numbers of cases. In the Corona testing Center, many patients with mild or absent symptoms, presenting after having traveled to a risk area or had contact with a positive tested person, could be tested simultaneously. After the initial wave of infected patients, mostly returning from risk areas in Italy or Tyrolia (Austria), the newly established Corona Emergency Department took over for a more individualized check-up on potential COVID-19 positive patients. Additionally, a “corona taxi” was initiated for regular assessment of positive tested patients not admitted to hospital.²⁰

In summary, when analyzing all patients presenting, symptoms showed to be inconsistent, with symptoms varying heavily from patients with COVID-19 suspicious symptoms – like cough, fever, and sore throat – to patients with little (like rhinitis), unspecific (like epigastric pain or fainting), or no symptoms. Respiratory symptoms were the most common findings in this analysis as well as in other studies.^{21,22} With this and more knowledge about the distribution of SARS-CoV-2 through asymptomatic/pre-symptomatic patients, a change in selection and triage might be needful. Additionally, fever was found in less than half of all patients and only in a third of the patients not admitted. In this context, a fever measurement alone or facilities such as special fever clinics appear to be of little use to adequately quantify a risk for infection. Therefore, most or at least those patients with high pre-test probability should be treated like a suspected COVID-19 issue.²¹ Because of this, sufficient protective measures as well as thorough laboratory, radiological, and other symptom-specific diagnostic investigations can be provided, leading to a reduction of infection or missed cases.²² These measures should be maintained until a negative test result on COVID-19 is obtained. This can potentially contribute to containment with return to the situation at the beginning of the pandemic – individual cases, where a detailed analysis for suspects and whereabouts as well as sufficient medical

care at all times is possible again. Infection control by stringent quarantine of symptomatic patients and rigorous contact tracing have so far been the most effective measures.²²

Limitations of this analysis include small sample size in some evaluated patient groups like patients admitted to a general ward as well as the relatively small number of deceased patients with regards to all patients. In addition, not all findings may be applicable to the general public due to the character of a single center report and relative short time frame. Therefore, while some findings may be concerning regarding the differences in symptoms at presentation, there is caution needed in the interpretation of these findings due to the small number of cases (59 patients in intensive care and 11 deceased) and its data being collected retrospectively. There is likely confounding between the symptoms at presentation and the disposition of the patient, as patients with fever and dyspnea are more likely to be admitted to the hospital/ICU, which may limit the interpretation. Furthermore, not enough data on sensitivity and specificity of the SARS-CoV-2 PCR testing is available yet, leaving questions to whether there is a clear and complete picture on COVID-19 and its effects.

Conclusion

The unspecific nature of symptoms of patients with COVID-19 infection prohibits a proper preselection of patients that require isolation in order to reduce contamination. Dyspnea indicates a more severe disease stage and may predict a fatal outcome with a more than 2-fold higher risk in comparison to all IMC/ICU patients. However, while this warrants close monitoring during stationary treatment, dyspnea itself remains unspecific. Additionally, at times when COVID-19 infection cannot be suspected by a travel history to a risk area, triage of patients to a regular emergency department or chest-pain unit versus a dedicated isolation ward is increasingly challenging as COVID-19 spreads within the population. Therefore, every patient presentation should feature COVID as a main differential diagnosis, and patients with high pre-test probability should be, if possible, isolated until testing results are known.

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Author Contributions

FK and LPK designed the research project. FK acquired and analyzed the data. FK, LPK, EG, and UM discussed the data and the organization of the manuscript. FK wrote the manuscript. All authors critically reviewed the manuscript, FK, LPK, and EG edited the manuscript. LPK supervised the work. FK and LPK undertook recruitment of participating patients and managed the data, including quality control. FK, EG, and LPK provided statistical advice on the study design and analyzed the data. LPK chaired the data oversight committee. All authors contributed (as listed above) to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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