

# Clinical Outcomes, Therapy Options and Risk Factor Impact Analysis on 1077 Patients Hospitalized for Covid-19

Štěpán Cimrman\*, Kateřina Hašková and Pavel Dlouhý

Department of Infectious Diseases, Masaryk Hospital in Ústí nad Labem, Czech Republic

## ABSTRACT

**Purpose:** In this retrospective study, a cohort of 1077 patients with covid-19 hospitalized in Masaryk hospital in Ústí nad Labem, Czech Republic, is examined. Several suggested risk factors for covid-19 are described and the impact of their presence on clinical outcome is explored. Treatment options for covid-19 are discussed.

**Methods:** Using statistical analysis (Fisher's exact test, logistic regression, induction of decision trees and random forests), the authors identify clinical and laboratory risk factors for mortality rate, development of severe disease and longer duration of hospitalization.

**Results:** Age was confirmed to be the most impactful risk factor on mortality and length of hospitalization (95% CI 4.62-11.67,  $p < 0.00001$ ). Obesity did not increase mortality but led to increased disease severity (95% CI 1.28-2.40,  $p < 0.00329$ ). Diabetes (95% CI 1.68-3.17,  $p < 0.00001$ ), heart disease (95% CI 2.85 -5.47,  $p < 0.00001$ ), chronic kidney disease (95% CI 3.27-7.04,  $p = 0.00001$ ) and cancer (95% CI 1.36-3.55,  $p = 0.00544$ ) had an impact on mortality. Lung disease and immune system suppression were not established as significant risk factors. CRP (95% CI 2.7-5.61,  $p < 0.00001$ ), D-dimer (95% CI 1.60-3.25,  $p = 0.00002$ ), procalcitonin (95% CI 4.24-11.95,  $p < 0.00001$ ) and lymphocyte count (95% CI 2.11-4.03,  $p < 0.00001$ ) are found to be significant early laboratory risk indicators in patients with covid-19.

**Conclusion:** We suggest the presence of confirmed risk factors and laboratory markers to be evaluated and considered in determining initial treatment options provided to patients with covid-19.

**KEYWORDS:** Covid-19; Czech Republic; Treatment; Risk factors; Risk factor impact; Mortality rate

## INTRODUCTION

Clinical course of covid-19 is mostly mild and uncomplicated [1]. Hospital treatment and oxygen therapy is required in about 3-14 % of people. About 1-3 % of those infected are placed in intensive care units, most commonly for hypoxemia despite low-flow oxygen therapy, acute respiratory distress syndrome (ARDS), septic shock and multi-organ failure [2]. The situation with covid-19 in the Czech Republic was at the time of data collection considered one of the worst in Europe, with the worst relative mortality rate and the second highest relative number of confirmed cases [3].

The mortality rate (death rate) of covid-19 reaches 1 to 10 % and varies from country to country [4]. In the Czech Republic, death rate was estimated to be around 1.7 % in patients with a recognized infection. Age was identified as the most important risk factor by other authors [5]. It is the subject of this paper to provide an overview of treatment options for patients with covid-19 and to determine the impact of several risk factor on mortality rate, severity of the disease and duration of hospitalization. We also describe the most common complications and their occurrence in our cohort.

### Quick Response Code:



**Address for correspondence:** Štěpán Cimrman, Department of Infectious Diseases, Masaryk Hospital in Ústí nad Labem, Czech Republic

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## METHODOLOGY

In our cohort we divided hospitalized patients into five groups based on the severity of their symptoms (Table 1). We attempted to establish and quantify the impact of previously identified risk factors [5-7] on the risk of death related to covid-19, progression to

a severe form of the disease, or extended hospitalization (defined as more than 10 days in hospital). The impact of identified risk factors on the severity of covid-19 was determined using Fisher's exact test, logistic regression, induction of decision trees and random forests. The risk factors were tested for their impact on mortality, severity of illness and duration of hospitalization separately.

**Table 1:** Clinical forms of Covid-19.

<b>Asymptomatic Form</b>
· Absence of clinical signs of Covid-19
<b>Mild Form</b>
· Presence of one or more clinical signs of Covid-19
· Fever, sore throat, cough, fatigue, muscle and joint pain, nausea, vomiting, diarrhea, loss of taste and smell, and more
· No shortness of breath or radiological signs of lower respiratory tract involvement (pneumonia)
<b>Moderate Form</b>
· See above plus radiological signs of lower respiratory impairment (pneumonia)
· SpO <sub>2</sub> ≥94 % with no oxygen support
<b>Severe Form</b>
· See above plus one or more of the following: significant shortness of breath, tachypnoea >30/ minute, radiological signs of more than 50% of pulmonary parenchyma infiltration.
· SpO <sub>2</sub> <94 % with no oxygen support
<b>Critical Form</b>
· See above plus one or more of the following: respiratory failure, septic shock, multi-organ failure

The diagnosis of covid-19 was made by direct SARS-CoV-2 testing using direct RNA detection via polymerase chain reaction (PCR) or an antigenic test of nasopharyngeal swab followed by PCR verification. Some patients were hospitalized for acute deterioration of their condition in home isolation for an already diagnosed covid-19 infection, some patients were diagnosed during admission to the hospital.

### Cohort Description

This cohort ( $n=1077$ ) contains all patients hospitalized in the Infectious Diseases Department of Masaryk Hospital in Ústí nad Labem for covid-19 during 6 months from September 1, 2020, to February 10, 2021. Our hospital cared for patients mostly from Ústí nad Labem and Děčín regions, which have a combined population of approximately 250 000 people.

The entire course of hospitalization in our department from admission to discharge or transfer to another department was documented. Although the Masaryk hospital's Infectious Diseases Department has its own intensive care unit with a capacity for 15 patients, some patients requiring intensive care have been transferred to the Clinic of Anesthesiology, Perioperative and Intensive Care Medicine for capacity reasons. Due to the interdependence of our departments on the hospital information system, it was possible to map the further course of hospitalization in these patients and this data was also included.

The total number of patients in our cohort is 1077, 595 of which are men and 479 are women. The oldest patient in the group was 98 years old, the youngest was 2 weeks old. The median age of patients was 69 years. Patients were admitted from their own homes ( $n=778$ ; 72%), from sanitary facilities such as homes for the elderly ( $n=78$ ; 7%), long term care and rehabilitation facilities (LTC;  $n=63$ ; 6%), or other wards and hospitals ( $n=158$ ; 15%).

Of the 1077 hospitalized patients, 735 (68%) were diagnosed with pneumonia. 303 (28%) of patients developed mild covid-19

(Table 1). 322 (30%) patients were hospitalized for a moderate form of the disease and 413 (38%) patients suffered from a severe or critical form of covid-19. 39 people (4%) were asymptomatic but needed to be isolated in hospital for epidemiological reasons or other medical conditions. A total of 169 (18%) of patients were placed in intensive care units (ICU). 83% of the intensive care patients required high flow nasal oxygen therapy (HFNO), 17% non-invasive ventilation (NIV) and 31% artificial pulmonary ventilation (APV) at some point. 6 patients required extracorporeal membrane oxygenation (ECMO). The average time spent in intensive care was 12 days, the median was 8 days. The average time spent on APV was 17 days, the median was 14 days. The average time on all types of oxygen support in intensive care (excluding standard low flow nasal cannulae) was 11.6 days with a median of 7 days.

The average hospitalization time in the population was 9.5 days, the median was 8 days. The longest hospitalization time was 87 days. During hospitalization, 181 patients died, 72 of which died in intensive care. Another 34 patients died within 3 months after discharge. The overall three-month mortality rate in the cohort was 19 %. Mortality rate in intensive care was 39 %. The number of patients requiring follow-up care in long term care facilities was 107 (10 %). 49 of these patients originally came to the hospital from their homes. The number of patients whose condition required transfer to another department after isolation was 62.

### Risk Factors

Several laboratory markers have been identified in the past as risk factors for severe covid-19 [7]. In our cohort, we tried to test the reliability of 5 of these markers in the context of covid-19 patients. Specifically, we set the following parameters: CRP, procalcitonin, absolute leukocyte levels, absolute lymphocyte levels and D-dimers. We set the following cut-off values: CRP above 50mg/l, procalcitonin above 1µg/l, D-dimers above 1mg/l, leukocytes bellow  $4 \cdot 10^9/l$ , lymphocytes bellow  $0.8 \cdot 10^9/l$ . Other laboratory markers reported in the literature were not routinely

collected at our workplace during this period.

The importance of following clinical risk factors has been considered: age, obesity, diabetes mellitus, heart disease, lung disease (in our cohort specif. chronic obstructive pulmonary disease, bronchial asthma on therapy, pulmonary fibrosis), chronic kidney disease, active oncological disease, immunosuppression (corticoid therapy, biologic therapy, recent chemotherapy etc.).

632 patients (59%) in our cohort were over 65 years of age, 124 of whom were hospitalized in the ICU and 160 of whom died. 211 (20%) of patients in our cohort had GRADE II obesity or higher according to WHO classification, 52 of whom were hospitalized in ICU and 39 of whom died. There were 340 (32%) of patients in our cohort with diabetes mellitus, 76 of whom were hospitalized in ICU and 89 of whom died. Patients with a history of any form of ischemic heart disease or heart failure were of cardiovascular risk; we identified 294 of such patients (27% of the total) in this cohort, 63 of whom were hospitalized in the ICU, 93 of whom died. Diagnoses of chronic obstructive pulmonary disease (of any degree), bronchial asthma on therapy, and fibrosing lung disease were considered pulmonary risk factors for covid-19. There were 175 (16%) of such

patients in total, 40 of whom were hospitalized in the ICU and 37 of them died. We counted 144 (13%) patients with chronic kidney disease, 31 of whom were hospitalized in the ICU and 62 of them died. There were 95 (9%) patients with malignant tumors, 16 of them were hospitalized in the ICU and 26 of them died. 48 (4%) of our patients in this cohort had long term immunosuppression (most often recipients of solid organ grafts, bone marrow or long-term treatment with systemic glucocorticoids or biologic therapy), 19 of whom were hospitalized in the ICU and 12 of them died.

The results of statistical analysis to determine the impact of these risk factors on the course of covid-19 can be found in Table 2&3. Using decision tree learning, a model for disease outcome prediction was proposed in Figure 1-3. A decision tree for length of hospitalization could not be established. The order of importance of analyzed risk factors was determined by Gini coefficient decrease due to a related predictor in random forest model. The resulting hierarchy of importance of risk factors for all three outcomes (mortality, severity of disease and prolonged hospitalization) with out-of-bag error of 27,6 %, 35 % and 39 % respectively can be seen in Figure 4&5.

**Table 2:** Adjusted p values (using Holm method) on Fisher's exact test results.

	<b>Age &gt; 65</b>	<b>BMI &gt; 35</b>	<b>Diabetes</b>	<b>Heart Disease</b>	
Mortality Rate	<0.00001 (95% CI 4.62-11.67)	1.0000 (95% CI 0.75-1.62)	<0.00001 (95% CI 1.68-3.17)	<0.00001 (95% CI 2.85 -5.47)	
Severe Illness	1.00000 (95% CI 0.83-1.40)	0.00329 (95% CI 1.28-2.40)	0.18367 (95% CI 1.03-1.77)	1.00000 (95% CI 0.67-1.19)	
Prolonged Hospitalization	<0.00001 (95% CI 1.89-3.34)	0.33032 (95% CI 0.90-1.73)	0.00728 (95% CI 1.20-2.09)	0.01085 (95% CI 1.18-2.11)	
	<b>Lung disease</b>	<b>CKD</b>	<b>Cancer</b>	<b>Immuno-Deficiency</b>	
Mortality Rate	0.59605 (95% CI 0.88-1.97)	<0.00001 (95% CI 3.27-7.04)	0.00544 (95% CI 1.36-3.55)	1.00000 (95% CI 0.63-2.72)	
Severe Illness	1.00000 (95% CI 0.68-1.37)	1.00000 (95% CI 0.63-1.35)	1.00000 (95% CI 0.61-1.54)	0.11387 (95% CI 1.15-4.04)	
Prolonged Hospitalization	0.42923 (95% CI 0.80-1.63)	0.06770 (95% CI 1.10-2.33)	0.01926 (95% CI 1.25-3.06)	0.19492 (95% CI 0.94-3.31)	
	<b>↑CRP</b>	<b>↑PCT</b>	<b>↑DD</b>	<b>↓WBC</b>	<b>↓LY</b>
Mortality Rate	<0.00001 (95% CI 2.7-5.61)	<0.00001 (95% CI 4.24-11.95)	0.00002 (95% CI 1.60-3.25)	1.00000 (95% CI 0.62-1.78)	<0.00001 (95% CI 2.11-4.03)
Severe Illness	<0.00001 (95% CI 3.82-6.77)	0.00016 (95% CI 1.71-4.74)	<0.00001 (95% CI 1.88-3.53)	1.00000 (95% CI 0.69-1.65)	<0.00001 (95% CI 1.82-3.20)
Prolonged Hospitalization	0.00007 (95% CI 1.39-2.39)	0.06770 (95% CI 1.14-3.07)	<0.00001 (95% CI 1.75-3.29)	0.19492 (95% CI 0.99-2.35)	0.00064 (95% CI 1.33-2.36)

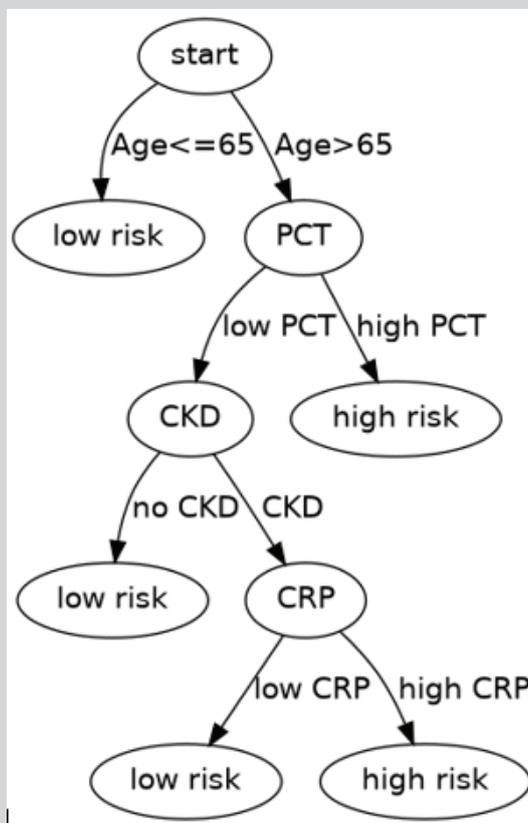
LY: lymphocyte; CKD: Chronic Kidney Disease; CRP: C-Reactive Protein; DD: D-Dimer; PCT: Procalcitonin; WBC: White Blood Cell Count; BMI: Body Mass Index

**Table 3:** Logistic regression. Model was created using stepwise selection procedure for selection of independent variables based on AIC.

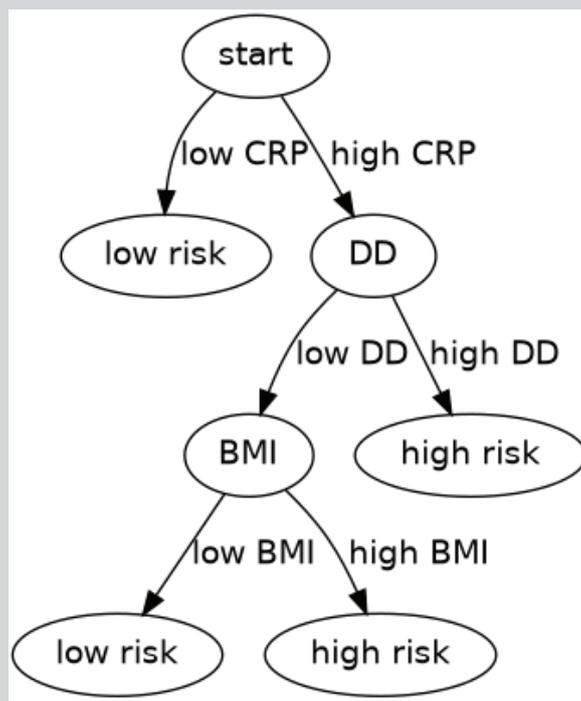
<b>Mortality Rate</b>	<b>Coefficient</b>	<b>Std. Error</b>	<b>z-value</b>	<b>Pr(&gt;  z )</b>
Intercept	-4.1361	0.2899	-14.268	< 2,00E-16
Age > 65	1.6343	0.2519	6.489	8.65E-11
BMI > 35	0.3405	0.2369	1.437	0.150736
Heart disease	0.8319	0.1984	4.193	2.75E-05
CKD	0.901	0.2258	3.989	6.63E-05
↑CRP	1.1423	0.21	5.439	5.35E-08
↑PCT	1.2084	0.3012	4.013	6.01E-05
↓LY	0.6928	0.1926	3.598	0.000321

Severe Illness				
Intercept	-1.6835	0.1347	-12.496	< 2,00E-16
BMI > 35	0.6742	0.1812	3.72	0.000199
CKD	-0.5212	0.2177	-2.394	0.016675
Cancer	-0.3788	0.2567	-1.476	0.14003
Immuno-Deficiency	0.6801	0.3407	1.996	0.045939
↑CRP	1.4475	0.1518	9.538	< 2,00E-16
↑DD	0.7119	0.1719	4.141	3.45E-05
↓LY	0.563	0.1611	3.494	0.000476
Prolonged Hospitalization				
Intercept	-1.8484	0.1563	-11.828	< 2,00E-16
Age > 65	0.9017	0.1516	5.948	2.72E-09
BMI > 35	0.3634	0.1791	2.029	0.042478
Cancer	0.4198	0.2392	1.755	0.07921
Immuno-Deficiency	0.6093	0.3282	1.856	0.063393
↑CRP	0.3955	0.1486	2.661	0.007781
↑DD	0.5749	0.167	3.443	0.000576
↓WBC	0.3972	0.2398	1.656	0.097728
↓LY	0.2835	0.162	1.75	0.080119

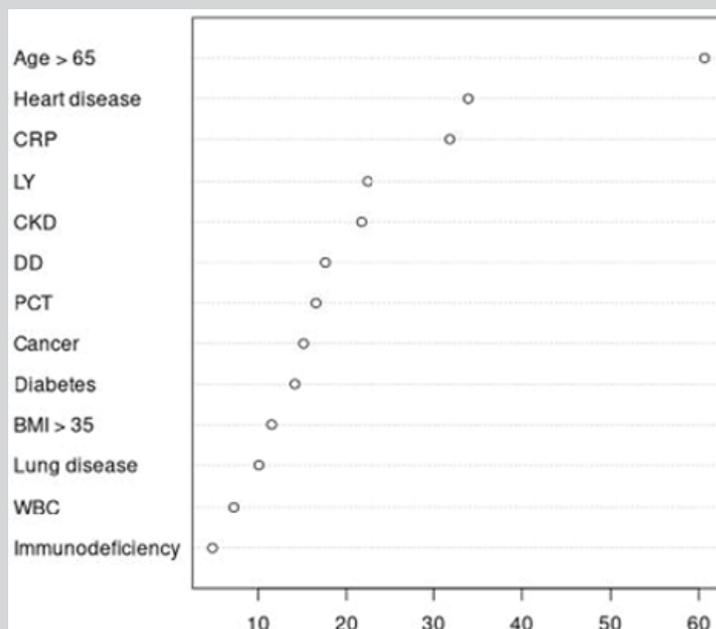
LY: lymphocyte; CKD: Chronic Kidney Disease; CRP: C-Reactive Protein; DD: D-Dimer; PCT: Procalcitonin; WBC: White Blood Cell Count; BMI: Body Mass Index



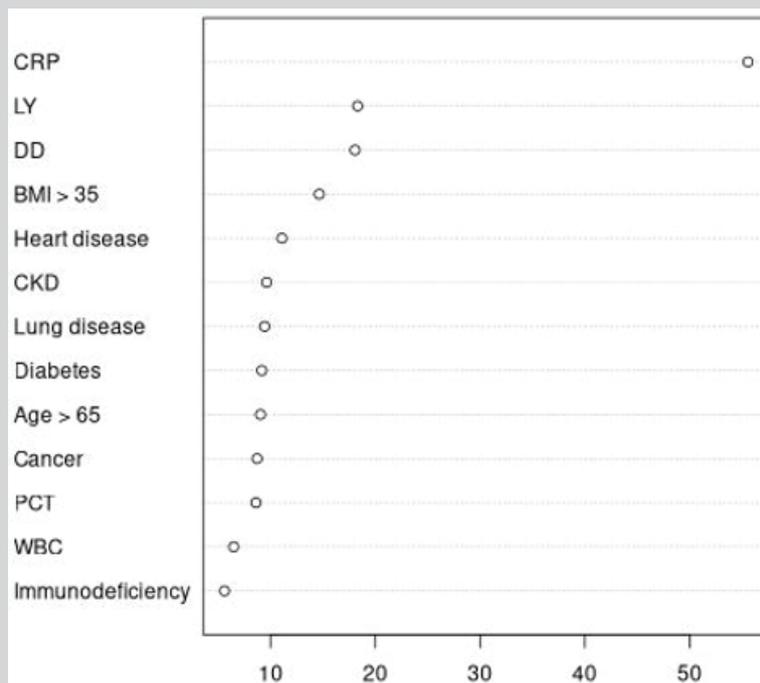
**Figure 1:** Decision tree for mortality risk prediction in patients with covid-19. CKD: Chronic Kidney Disease; PCT: Procalcitonin



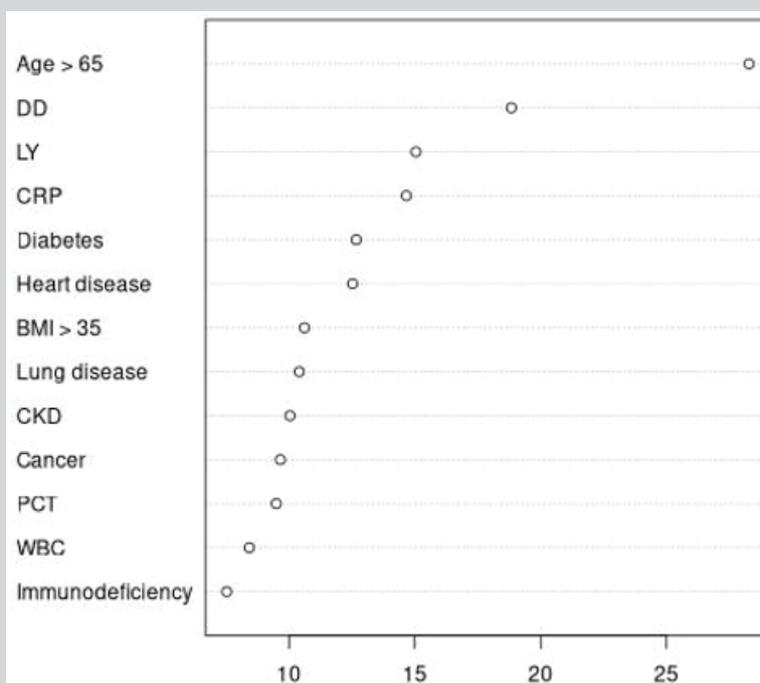
**Figure 2:** Decision tree for severe disease prediction in patients with covid-19. DD: D-Dimer Elevation; BMI: Body Mass Index



**Figure 3:** Importance of risk factors for random forest mortality prediction measured by mean decrease in Gini coefficient. The horizontal axis shows mean decrease in Gini coefficient. LY = lymphocyte decrease; CKD = chronic kidney disease; DD = D-dimer elevation; PCT = procalcitonin; WBC = white blood cell count elevation



**Figure 4:** Importance of risk factors for random forest severe disease prediction measured by mean decrease in Gini coefficient. The horizontal axis shows mean decrease in Gini coefficient. LY: Lymphocyte Decrease; CKD: Chronic Kidney Disease; DD: D-Dimer Elevation; PCT: Procalcitonin; WBC: White Blood Cell Count Elevation



**Figure 5:** Importance of risk factors for random forest long-term hospitalization (more than 10 days) measured by mean decrease in Gini coefficient. The horizontal axis shows mean decrease in Gini coefficient. LY: lymphocyte Decrease; CKD: Chronic Kidney Disease; DD: D-Dimer Elevation; PCT: Procalcitonin; WBC: White Blood Cell Count Elevation

### THERAPY

Patients with covid-19 were given symptomatic therapy in the form of antipyretics, analgesics (paracetamol, ibuprofen, metamizole), antitussives (codeine, butamirate), mucolytics (acetylcysteine, erdosteine, ambroxole). When signs of bronchial

obstruction were found, bronchodilators (salbutamol, ipratropium-bromide) and inhalation corticoids were given [8].

In an effort to achieve a positive fluid balance in order to prevent renal injury due to dehydration, almost all symptomatic patients were given infusion therapy with balanced crystalline solutions

(Ringerfundin, Hartmann, Plasmalyte) at least on the first day of hospitalization [9]. In patients with hypoxia, oxygen therapy was initiated with a nasal cannula or oxygen mask, which was titrated according to peripheral saturation with a target of 94 %, with the exception of patients with chronic obstructive pulmonary disease, who are usually adapted to lower values [10]. Oxygen therapy in standard care beds was technically limited by a maximum flow of 15 l/min. Patients who required higher oxygen flow were transferred to intensive care.

Patients with pneumonia were encouraged to actively position themselves on their sides and abdomen (awake prone positioning) [11]. This procedure is derived from the positioning of critically ill patients with ARDS [12,13] and contributes to the so-called "recruitment" of hypoventilated pulmonary alveoli. Patients with pneumonia were indicated for respiratory physiotherapy, patients with reduced mobility or the presence of risk factors also for lower limb physiotherapy to prevent thromboembolic complications.

Prophylactic anticoagulant therapy was given to all patients with covid-19, except those with contraindications (e.g. ongoing bleeding or significantly increased risk of bleeding) [14]. Enoxaparin was most often administered at a dose of 4000 U subcutaneously once daily, in these patients the dose was increased to 6000 U per day. In some patients with both thromboembolic complications and bleeding, the dose of enoxaparin was altered depending on the value of anti-Xa. Ongoing effective anticoagulation therapy prior to hospitalization was not changed or discontinued.

Systemic glucocorticoid therapy was given to patients with diagnosed pneumonia and to patients with acute exacerbation of chronic obstructive pulmonary disease or bronchial asthma. Dexametasone was the drug of choice, most commonly administered at a dose of 8 mg daily [15,16]. There was no clear consensus on the duration of corticosteroid therapy at the time and it varied from patient to patient, mainly guided by the general development of the patient's condition. The median time of administration of glucocorticoids was 6 days.

Remdesivir therapy was indicated in patients with pneumonia, respiratory insufficiency and the need for oxygen therapy [17,18]. It was initiated only in the first 7 days after the onset of symptoms of infection at the standard dose of 200 mg on the 1st day and 100 mg the following 4 days intravenously in a 30-minute infusion. In patients with advanced renal disease, remdesivir was not administered. Patients with respiratory failure who received invasive ventilation or non-invasive ventilation (HFNO/NIV) from the beginning of the hospitalization were not given remdesivir. If the patient's condition worsened during remdesivir therapy, the treatment was not discontinued. Due to the absence of a randomized control group of patients, it is not possible to comment conclusively on the effect of remdesivir on reducing the hospitalization time or mortality rate of covid-19 patients in our cohort.

Antibiotic therapy or antifungal therapy was indicated in 398 people (37% of the total number of patients). Average duration of administration of antibiotic therapy 6.8 days, median 5.5 days. Antibiotics and antimycotics were indicated when bacterial or mycotic respiratory superinfection was suspected or proven. In general, these were states of rapid clinical deterioration of the patient's condition with local or general symptoms of inflammation and simultaneous progression of inflammatory parameters (among others leukocytes, CRP, procalcitonin and adequate clinical findings such as fever, productive cough, etc.) [19,20]. Antibiotic therapy

administered for another infection with no relation to covid-19 (e.g., community urinary tract infection, erysipelas, enterocolitis caused by *C. difficile*, etc.) was not included in this cohort.

In intensive care, the main treatment option was artificial breathing support [9,21]. In case of insufficiency of conservative oxygen therapy, HFNO was initiated. Despite the standing recommendation to avoid the use of non-invasive ventilation to prevent infectious aerosol from forming, it was preferred over HFNO in patients with acute exacerbation of chronic obstructive pulmonary disease, acute cardiogenic pulmonary edema or alveolar hypoventilation syndrome in obesity. In 44 % of HFNO and NIV patients, these ventilation support methods were sufficient to stabilize the patient's condition and lead to recovery.

In cases of further progression of respiratory insufficiency, intubation and artificial pulmonary ventilation had to be administered. Intubations were carried out in accordance with the standing recommendations [9] by an experienced intensive care physician, using procedures to reduce the number and duration of intubation attempts, due to the higher risk of staff infection. Artificial pulmonary ventilation was conducted in accordance with the general rules applicable to ARDS patients in order to reduce ventilator-induced pulmonary impairment [9,21,22]. The APRV ventilation regimen [23,24] was often used, patients were positioned in pronation positions (abdomen, sides). 46 % of the patients on artificial pulmonary ventilation died. ECMO was indicated in 6 cases of patients on artificial pulmonary ventilation for refractory hypoxemia despite of all other attempted measures [25]. Three of these patients died.

## COMPLICATIONS

During the treatment of covid-19, several complications were identified. In our cohort, we focused on: bacterial superinfection, bleeding complications, thromboembolic complications (pulmonary embolism, ischemic stroke), pneumothorax, empyema and cardiopulmonary resuscitation following cardiac arrest.

Bacterial respiratory superinfection was the most common complication in covid-19 patients. A total of 132 people (12%) were diagnosed with bacterial superinfection based on laboratory findings and corresponding clinical findings, most often these included determination of the general state of the patient, and the finding of a causative microorganism by cultivation of endotracheal aspirate or hemoculture. It most often occurred in patients in intensive care (103 patients, i.e., 52 % of patients in intensive care in our cohort) and was more common in longer hospitalized patients.

The second most common group of complications were bleeding conditions (30 patients). Epistaxis, gastrointestinal bleeding, and hemorrhagic stroke were the most common. Patients in intensive care were affected the most frequently (20 patients, 10% of patients in intensive care).

In the category of thromboembolic complications, we recorded 15 pulmonary embolisms and ischemic strokes. This number is very low in comparison to early reports [26], mainly due to anticoagulation therapy [27]. Pneumothorax developed in 5 cases, all in patients in intensive care at HFNO or artificial pulmonary ventilation. This complication occurred more frequently in case of patients on APRV mode of artificial pulmonary ventilation. Thoracic empyema was diagnosed and subsequently treated in 4 people. 5 people had sudden cardiac arrest with cardiopulmonary resuscitation during hospitalization, 4 of whom died.

## DISCUSSION

We suggest the following interventions to be the cornerstones of therapy for patients with covid-19: oxygen support, glucocorticoids and prophylactic anticoagulation. We urge caution when considering antimicrobial therapy in patients with covid-19.

The topic of antibacterial and antimycotic therapy in covid patients has been discussed at length. While certain situations remain open to different approaches, it is mostly agreed upon, that starting antimicrobial therapy should be carefully considered and is not to be initiated in all patients with pneumonia. Our results show, that in our hospital, antibiotic therapy was used sparingly and, on average, in appropriate duration, in order not to promote bacterial antibiotic resistance, which remains a major issue in healthcare worldwide.

Our data suggest that age over 65 years is by far the most reliable predictor of mortality (95% CI 4.62-11.67,  $p < 0.00001$ ) and longer duration of hospitalization (10 days or more; 95% CI 1.89-3.34,  $p < 0.00001$ ) in patients with covid-19. Age alone, however, does not seem to invite more severe forms of covid-19, but rather suggests a much slower and more difficult recovery from these forms of covid-19.

Our data sample, rather surprisingly, does not show higher death rates or longer hospitalizations in obese patients. Obesity is rather suggested to be a strong risk factor for development of severe and critical forms of covid-19 (95% CI 1.28-2.40,  $p = 0.00329$ ). This may be in line with the long established "obesity paradox" in ICU patients [28].

We can confirm diabetes mellitus (95% CI 1.68-3.17,  $p < 0.00001$ ), heart disease (ischemic heart disease and heart failure; 95% CI 2.85 -5.47,  $p < 0.00001$ ) and cancer (95% CI 1.36-3.55,  $p = 0.00544$ ) to be risk factors for covid-19 related mortality and longer stay in hospital. Chronic kidney disease is, in our sample, confirmed as a risk factor for mortality in patients with covid-19 (95% CI 3.27-7.04,  $p < 0.00001$ ). Our data does not suggest that lung disease (COPD, asthma and lung fibroses) or immune system deficiencies significantly increase the likelihood of death, severe illness or longer hospitalization in patients with covid-19. Out of all five laboratory markers measured in our sample of patients, we found CRP elevation above 50mg/l (95% CI 2.7-5.61,  $p < 0.00001$ ), D-dimer elevation above 1mg/l (95% CI 1.60-3.25,  $p = 0.00002$ ) and absolute lymphocyte count of less than  $0.4 \cdot 10^9/l$  (95% CI 2.11-4.03,  $p < 0.00001$ ) to each be individually significant risk factors for covid-19 related mortality, disease severity and longer hospitalization.

Procalcitonin elevation above 1µg/l was also found to be indicative of higher risk of death and severe disease (95% CI 4.24-11.95,  $p < 0.00001$ ). Additionally, we found CRP to be the most reliable and significant predictor of patients developing severe or critical form of illness (95% CI 3.82-6.77,  $p < 0.00001$ ). We suggest using these laboratory markers in initial evaluation of patients with covid-19. White blood count decrease was not found to be significantly related to either mortality, disease severity or duration of stay in hospital.

The high price and relatively limited supply of novel and promising therapeutical interventions [29,30] for covid-19 will, in many healthcare settings, demand sophisticated risk stratification to guide their distribution. We propose the identified risk factors to be used in risk stratification of patients with covid-19.

## LIMITATIONS

Our analysis has several limitations. Firstly, the data was collected retrospectively. Many patients in the sample were not initially evaluated for all five discussed laboratory markers. Furthermore, the analyzed sample does not contain patients who were not hospitalized. It is theoretically possible, that this skews the analysis (in case that, for example, patients with BMI less than 35 were significantly less often admitted to the hospital).

Selected patients (geriatric patients with a high degree of fragility according to clinical frailty scale, patients suffering from incurable terminal disease, etc.) were denied certain treatment methods due to rational and ethical concerns. In these cases, therapy was limited HFNO/NIV or standard oxygen therapy so as not to prolong or intensify the suffering of the patient. Invasive treatment or diagnostic procedures would most likely be of no benefit to these patients and would likely not improve their overall fitness and quality of life. It is therefore likely that some complications have not been identified in these patients, such as thromboembolic events, the diagnosis of which requires costly and difficult to access procedures (e.g. CT angiography). This may in turn cause some distortion in the number of complications observed. Cardiopulmonary resuscitation was also not initiated in these patients for the same reason.

Despite that, indication criteria of APV remained very broad and many patients that received APV were of severe pre-hospitalization morbidity and in conditions severely limiting their potential clinical outcome. This may be one of the causes contributing to a very high mortality in patients receiving APV in our cohort.

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