Investigation of In-hospital COVID-19 Mortality and One-year Follow-up of Lung Function and Health Status with Respect to the Initial Disease Severity

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Abstract

Background: Globally, thousands of patients suffer from long-term COVID-19 symptoms, often referred to as post-acute COVID-19 syndrome, a condition that already affects our health systems. Although there is a growing literature upon the long-term effects of *SARS-CoV-2* infection, there are up to date only a few reports on long-term follow up of pulmonary function after severe COVID-19.

Methods: The study is an observational cohort of patients who were admitted to hospital care with confirmed COVID-19 during the first pandemic wave and those who required some form of supplementary oxygen delivery. Baseline characteristics, demographic data and information about hospital stay including mortality were obtained by medical charts. Patients were divided in to 3 groups: group 1 (intensive care unit (ICU)-invasive mechanical ventilation (IMV), group 2 (high-flow nasal-cannula (HFNC) and/or none-invasive ventilation (NIV) and group 3 (regular oxygen delivery treatment). All patients were required to answer questionnaires (mMRC scale, Post-COVID-19 Functional Status Scale (PCFS), Hospital anxiety and depression scale (HAD) and 36-Item Short Form Health Survey (SF-36)) at one year after acute infection, while patients in groups 1 and 2 performed also dynamic spirometry. The R-language of statistics was used for all calculations and visualisations.

Results: The study population consisted of 130 patients. Forty five (35%) patients died at the hospital. Risk factors for in-hospital mortality were age, hypertension, ischemic heart disease and renal disease. Patients who survived had, on average, a longer period from symptoms onset to hospital admission. No significant difference in all health scales between the 3 patient groups were found. Mean values of both FEV1% and FVC% in the groups 1 and 2 were detected within the lower normal limits while no difference was found between the two groups who were examined with spirometry.

Conclusions: The main result of the study is lung function values in the lower limit of normal evaluated with dynamic spirometry at one-year follow-up. There were no significant differences related to initial disease severity in lung function and long-term health status at 12 months, which suggests that more generous lung function testing even in less severe individuals with lingering symptoms could be indicated.

Background

Coronavirus disease 2019 (COVID-19) is caused by the novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has been an ongoing pandemic since spring 2020. Although the acute phase of the infection has been explored thoroughly, the long-term medical consequences and prognosis remain largely unclear (1).

Previous coronavirus epidemics (Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)) unfortunately had relatively few and short follow-up studies. They were characterized not only by a much more lethal acute phase than COVID-19, but also by significant long-term consequences, including chronic fatigue, psychiatric sequelae and reduced lung function (2-5).

Globally, thousands of patients report to be suffering from long-term COVID-19 sequela, often referred to as post-acute COVID-19 syndrome (6). However, exactly what encompasses this syndrome and how it is best treated is not well defined (1). There is a concern for permanent lung damage, which is not uncommon for advanced viral pneumonitis (7). Six-month data from China suggest that the majority of in-hospital treated patients still had not only residual symptoms at follow-up, mostly fatigue, muscle weakness, sleeping difficulties and anxiety or depression, but also residual lung parenchymal opacities and reduced lung function (8). These findings have caused increased concern for permanent pulmonary damage. Reports indicate reduced dyspnoea over time and a successive improvement of lung function measured with pulmonary function tests (PFTs) and radiological features (9). Others report chronic impairments with less or no improvement over time (10).

The goal of this study is to investigate patients with COVID-19 who were hospitalized during the first pandemic wave, by exploring risk factors for in-hospital mortality and by assessing their lung function and health status at one-year after hospital discharge.

Methods

Study design and participants

This is an observational cohort study in which we identified all patients in the Norrköping region (with a catchment area of approximately 180 000 people) that were admitted to in-hospital care with laboratory confirmed COVID-19 during the first pandemic wave (Mars 2020-June 2020) and required some form of supplementary oxygen delivery. Patients were identified by synoptic journal review of relevant wards focusing on positive COVID-19 test results, oxygen administration and diagnosis code used in the electronic health record. All patients were invited to answer questionnaires at one year after acute infection from COVID-19. Patients were stratified into three groups depending on the need of oxygen delivery as follows: Invasive mechanical ventilation (IMV)/Intensive care unit (ICU) (group 1), non-invasive ventilation (NIV)/high-flow nasal-cannula (HFNC) (group 2) or regular oxygen therapy (group 3). Those that had received IMV, NIV and/or HFNC also performed PFTs with dynamic spirometry in accordance with the American Thoracic Society (ATS) guidelines at one year after infection (11).

No patients were actively excluded. Out of 204 eligible patients, 74 patients could not participate due to various issues (language issues, severe illness, lived in another geographical location, did not respond at all, withdrew consent). 130 patients were ultimately included for follow-up (figure 1). The Swedish Ethical Review Authority granted ethical approval for this study (registration number: 2020-03531). Patients were recruited by telephone or mail. Written informed consents were obtained for all those who were alive.

Baseline characteristics, including blood samples, were obtained by manual review of the medical records. Questionnaires were mailed to the patients at 1 year follow-up and if they were not completed and resubmitted, patients were contacted by telephone to give supplemental information. All PFTs were performed by the same physicians using the same level of enthusiasm. The Care Fusion MicroLab Mk8

Desktop Spirometer was used. At 1 year, a new review of the medical records was done to collect information concerning mortality, readmissions, unscheduled medical appointments and radiological examinations. Patients with available thoracic imaging by computed tomography at one year after infection were evaluated for signs of fibrotic pulmonary disease based on the radiological rapport. All except one patient in the IMV/ICU-group 1 provided complete information for analysis; however, this patient could not perform spirometry or answer questionnaires related to underlying co-morbidity.

Questionnaires

The modified Medical Research Council (mMRC) Dyspnea Scale is a well-validated scale for assessment of dyspnoea (12).

Post-COVID-19 Functional Status Scale (PCFS) is a new and validated scale that compare self-reported functional status before and after COVID-19 infection (13).

Hospital anxiety and depression scale (HAD) is a validated screening instrument for depression and anxiety (14).

36-Item Short Form Health Survey (SF-36) is a broad screening instrument that measures the general health in several domains (15).

Statistical method

The R-language was used for all calculations and visualisations (16). Continuous variables were summarized as mean± standard deviation (SD) if normally distributed and as median [interquartile range] (IQR) if non-normally distributed. Categorical variables were summarized as n (%).

Continuous variables were assessed for normality by use of the Anderson-Darling test for normality (17).

For continuous variables, differences between two groups were tested for statistical significance with the parametric t-test for normally distributed variables and with the non-parametric Wilcoxon test for non-normally distributed variables.

Differences in distributions of categorical variables across two or more groups were tested for statistical significance with the parametric Fisher Exact Test.

Analysis of variance (ANOVA) was used to detect differences in numerical variables between the three groups.

Associations between continuous variables were tested for statistical significance with regression analysis, though non-significant results are not shown.

Results

The study population consisted of 130 patients. Their demographic and clinical characteristics at the time of diagnosis of SARS-CoV-2 infection are given in Table 1. Forty-five (35%) patients died in the hospital (non-survivors) while 85 (65%) were discharged (hospital survivors). Out of 34 patients in

Table 1
Demographic and clinical characteristics of the study population, n=130

Age, year (median (IQR))	**71 (20.5)**
Sex (M/F)	(83/47)
Alive/Dead (hospital mortality)	85/45
Smoking history, n (%)	57(44%)
No smokers	64(49%)
Ex smokers	9 (7%)
Current smokers	
Hypertension	89(68%)
Diabetes	44(34%)
Heart disease	58(44%)
Ischemic heart disease	39(30%)
Chronic obstructive Pulmonary Disease (COPD)	22(17%)
Asthma	13(10%)
Immunsuppression treatment	19(14%)
Renal disease	14(11%)
Neurological disease (includes stroke)	30(23%)
Rheumatological disease	9 (7%)
Cancer (active and treated)	15 (11%)
BMI (n=123)	29±5
mean± SD	25(20%)
Normal weight (n %)	45(37%)
Overweight (n %)	53(43%)
Obesity (n %)	
Symptoms and laboratory data at presentation	n (%)
Fever	114(87%)
Cough	84 (64%)
Dyspnea	98 (75%)

Age, year (median (IQR))	**71 (20.5)**
Gastrenterological symptoms	22 (17%)
Laboratory data	
Lymphocytopenia n (%)	61(47%)
CRP (mg/L) (median (IQR))	91 (134)
Haemoglobin (g/L) (median (IQR))	137 (25)
Troponin (ng/l) (n=127) (median (IQR))	20 (32.5)
Creatinine (µmol/L) (median (IQR))	93 (52)
eGFR (mL/min/1,73 kvm) (median (IQR))	66 (42)
Ferritin (µg/L) (n=64) (median (IQR))	903 (1410)
Albumin (g/L) (n=90) (mean ± SD)	27±5
ALAT (µ kat/L) (n=125) (median (IQR))	0.52 (0.59)

group 1 (ICU/IMV), 23 (67%) patients survived and were discharged. From group 2 (HNFC/NIV) and group 3 (oxygen treatment), 19 (51%) patients and 43 (73%) patients respectively were discharged (figure 1). Of those that were discharged, all patients from group 1 were alive one year after infection, while from group 2 and group 3, 1 patient and 10 patients had died, respectively. The median time between hospital discharge and death was 25 (56) days (median (IQR)). Only 2 patients from group 1 had unplanned revisits to the hospital regardless of the reason for admission while 4 patients from group 2 and 11 patients from group 3 had unscheduled hospital visits within one year after infection. The total hospitalization duration in days was significant longer for group 1 (34±30 days, mean±SD, p<0,001) than groups 2 (9.6±5.3 days) and group 3 (7.5±5 days).

Table 2
Significant demographical and clinical differences between hospital survivors and non-survivors

	Survivors, n=85, M/28 F	Non-survivors, n=45, 26M/19F	P-value
Age (median (IQR))	66 (19)	76 (16)	<0.001
Hypertension n(%)	53(62%)	36(80%)	0.047
Ischemic heart disease n(%)	19(22%)	20(44%)	0.015
Renal disease n(%)	4(5%)	10(22%)	0.005
Bronchial asthma n(%)	12(14%)	1(2%)	0.033
Haemoglobin (g/L) (median (IQR))	139 (25)	125 (26)	<0.001
Troponin (ng/L) (median (IQR))	14 (24)	35 (37.5)	<0.001
Creatinine (μmol/L) (median (IQR))	88 (40)	112 (89)	<0.001
eGFR (MDRD) (median (IQR))	72 (38)	51 (39)	<0.001
Albumin (g/L) (mean ± SD)	28±5	25±5	0.034
Cough at presentation n (%)	62(73%)	22(48%)	0.014
Gastroenterological symptoms at presentation n (%)	20(24%)	2(4%)	0.005
Days from first symptom to admission (median (IQR))	7 (5)	4 (5)	<0.001
M=male, F=female			

The statistically significant differences between hospital survivors and non-survivors are given in Table 2. Compared to the survivors, non-survivors were older (figure 2) and had higher incidence of hypertension, ischemic heart disease and renal disease (figure 3), while diabetes mellitus was not significantly associated with fatal outcome in our study (p=0.28). Body mass index (BMI) was available in 123 patients and despite being a very common co-morbidity with nearly 80% of patients being overweight or obese (Table 1) neither weight status nor BMI were associated with death at hospital (p=0.38, p=0.45 respectively). Bronchial asthma was a more common diagnosis within hospital survivors though this correlation was weak related to the small number of patients with asthma diagnosis (Table 2). Cough and gastroenterological symptoms at presentation were more commonly reported among hospital survivors (Table 2). Lower haemoglobin, estimated glomerular filtration rate (eGFR) and albumin and

higher troponin and creatinine levels were the laboratory markers which differed significantly between survivors and non-survivors (Table 2), while lymphocytopenia was not found to be significantly associated with in-hospital mortality (p=0.61). Patients who survived had, on average, a longer period from symptoms onset to hospital admission (Table 2, figure 4). Patients in group 3 (oxygen treatment) with a lower fraction of inspired oxygen (FiO2) (L/min) need had a higher hospital survival rate (p<0.001).

The 3 groups of patients who were evaluated one year after COVID-19 infection were examined for differences. No differences were identified in age, BMI and smoking status, lung or renal disease as evaluated at baseline (data not shown). Hypertension and heart failure were a more common diagnosis in group 3 (Fisher test, p=0.018 and p=0.017 respectively).

The results of the spirometry in groups 1 (ICU/IMV) and 2 (HFNC/NIV) are shown in Table 3. No statistically significant differences were found between the 2 groups. Mean values of both Forced expiratory volume in 1 second (FEV1%) and Forced vital capacity (FVC%) indicate that average lung function tests performed on the patients one year after severe COVID-19 were within the lower normal limits. We did not find any correlation between the maximal oxygen need in FiO2 in group 2 (HFNC/NIV) and spirometry values (p=0.96 for FEV1%, p=0.35 for FVC%) .

Table 3
Spirometry results in groups 1 and 2

	ICU/IMV **Group 1, n=22**	**HNFC/NIV** **Group 2, n=17**	
FEV1% (mean ± SD)	86 ± 11	85± 16	p=0.74
FVC% (mean ± SD)	86 ±14	84±16	p=0.70
FEV1/FVC (mean ± SD)	76±9	77±8	P=0.89

Table 4 shows the results of the HAD, the PCFS scale and the SF-36 item. No significant differences were detected in the above scales inclusive of all the items of SF-36 among the 3 patient groups.

Table 4
Results of health scales, questionnaires and radiology

Scales	**ICU/IMV** **Group 1, n=22**	**HNFC/NIV** **Group 2, n=18**	**Oxygen treatment** **Group 3, n=33**	
HAD-anxiety (mean ± SD)	6 ±4	6 ±5	6 ±5	p=0.84
HAD-depression (mean ± SD)	5±3	6±3	5±4	p=0.44
PCFS difference (mean ± SD)	1±0.7	1±0.5	1±0.6	p=0.96
SF-general health (mean ± SD)	56±18	45±16	54±28	p=0.30
mMRC dyspnea scale	**ICU/IMV** **Group 1, n=22**	**HNFC/NIV** **Group 2, n=18**	**Oxygen treatment** **Group 3, n=33**	
0	5	5	7	*p=0.06
1	10	10	8	
2	7	1	13	
3	0	2	4	
4	0	0	1	
Pulmonary fibrosis after 1 year	**ICU/IMV** **Group 1, n=23**	**HNFC/NIV** **Group 2, n=18**	**Oxygen treatment** **Group 3, n=33**	
0=no	16 (70%)	13 (72%)	19 (58%)	*p=0.20
1=yes	6 (26%)	3 (17%)	2 (6%)	
2= has not been examined	1 (4%)	2 (11%)	12 (36%)	

*Statistical analysis for the comparison of the mMRC scale and pulmonary fibrosis across the 3 groups was performed with the parametric Fisher Exact Test.

The distribution of the mMRC dyspnea scale among the 3 groups is also depicted in Table 4. More patients in group 1 (ICU/IMV) and 2 (HFNC/NIV) suffered from mild dyspnea (mMRC 1) while there was a trend for more significant dyspnea mMRC grade 2 in the third group, though no statistically significant difference was noted between the 3 groups.

Finally, we found that 6 (26%) patients from group 1 (ICU/IMV) had radiological signs of pulmonary fibrosis one year after COVID-19 infection, 3 (17%) patients in group 2 and 2 (6%) patients in group 3

(Table 4). Only one patient was diagnosed with pulmonary fibrosis of idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP) type before COVID-19 and belongs to group 3. This patient was not included in the analysis (categorised as status 2=fibrosis has not been examined). The number of patients who were not radiologically examined in each group is also shown in Table 4. We could not identify any differences in the frequency of pulmonary fibrosis between the 3 groups.

Discussion

In a rapidly expanding field of knowledge concerning long-term COVID-19 sequela and with heterogeneous patient groups, we contribute demographical data from a population of hospitalised patients. We hypothesized that the initial disease severity could have a lasting impact on the residual function, especially pulmonary. To this end, we divided patients into three groups depending upon the reliance of oxygen to keep them saturated as a surrogate marker of pulmonary disease activity. The main result of this study is that the lung function values were at the lower limit of normal when evaluated with dynamic spirometry at one-year follow-up. There were no significant differences related to initial disease severity in lung function and long-term health status at 12 months. Increased in-hospital mortality was associated with acute biochemical abnormalities, higher age, heart and renal disease.

Previous studies have shown reduced lung function, radiological abnormalities and increased rates of depression or anxiety because of COVID-19. Early follow-up at 4-8 weeks showed fatigue (60-72%), dyspnoea (42-65%) and psychological distress (23-46%), more commonly in patients that needed ICU-level care (18). Similarly, it has been shown that fatigue and dyspnoea were still common at 8-12 weeks, but significant radiological and lung function abnormalities were less frequent especially in patients without respiratory insufficiency in their acute infection (19). Huang et al provided large-scale follow-up data from Wuhan, the initial site of the pandemic, showing reduced diffusing capacity for carbon monoxide (DLCO) and radiological abnormalities (primarily ground glass opacities and irregular lines) at 6 months (8). There was a correlation between oxygen need and the residual pulmonary function and increased tendency of depression and anxiety (8). More recent one-year data from the same cohort showed slight improvement in pulmonary function over time although diffusion impairment, and radiographic abnormalities persisted up to one year especially in patients who were critically ill during their hospital stay (20). Another study showed persistent symptoms associated with post-acute COVID-19 syndrome in 67% of patients requiring hospital care compared to 50% of non-admitted patients (21). One-year radiological follow-up recently showed lingering fibrotic changes with traction bronchiectasis and reticular pattern (22). One of the most reported abnormality is a reduced DLCO (6), which by its nature, is difficult to measure in primary care where most patients with long-lasting symptoms seek medical attention. We focused therefore on pulmonary variables that are more easily obtainable, such as dynamic spirometry and questionnaires.

Collectively, we found a generally reduced, albeit within reference, pulmonary function with lower FEV1% and FVC%. These observations give credit to the possibility of long-lasting lung damage even after one year of the infectious event, even though the current evidence is still a bit speculative.

In the studied population, one can note a substantially more common occurrence of co-morbidities such as diabetes and obesity compared to the general prevalence (23, 24). This is an expected finding since these conditions are well-established risk factors for severe COVID-19. We did not see any increased mortality related to diabetes and obesity in this population. Otherwise, we have confirmed previously reported risk factors for mortality during the acute phase such as hypertension, ischemic heart disease, chronic renal disease, anaemia, rise of troponin and acute kidney injury (25–27). Acute kidney injury, in particular, has been identified as highly prognostic of a poor outcome (28). There is evidence that suggests correlation between acute kidney injury during COVID-19 and microtrombotic disease activity (29). Asthma had a small protective effect, which might seem paradoxical, but has also been reported previously (30). Perhaps this could be due to the use of inhaled corticosteroids (ICS) treatment, as there has been reported that ICS treatment alter the prognosis of COVID-19 in a beneficial fashion (31). Previous reports indicate that prior lung disease, especially advanced COPD, predicts higher mortality (32), which we could not replicate. This could potentially be due to a low prevalence of such patients in our study group, which could imply differences in medical priorities between countries concerning terminal lung disease. The high death toll in the regularly oxygen treated group (group 3) is also heavily skewed due to decisions to withhold advanced life-prolonging treatment in relation to co-morbidities.

In contrary to previous data indicating 26% depression and anxiety rates at 1 year in hospitalised patients (20), only 14 patients (11%) reported clinically relevant depression or anxiety based on the HAD scale, which is calibrated to rather include than exclude. These results could also be influenced by community restrictions, where Sweden as a nation never imposed a formal lock-down. Other studies analyzing the non-COVID mental health issues during the pandemic have not found clinically relevant depression and anxiety symptoms or severe psychological distress in general (33), but there are such findings concerning adolescents (34). And as such perhaps the higher age in our patient cohort has been a confounding factor. It is also a bit surprising that the prevalence of mental health symptoms is as low as it is when compared to reported numbers that reach close to 40% at 1-year follow-up of acute respiratory distress syndrome (ARDS) in the pre-COVID era (35). Probably, there is a protective element in COVID-19 being recognized as a global pandemic.

The rates of re-admissions and subsequent unscheduled medical visits in our group were not correlated to initial disease severity. We noted in addition that even though a large proportion of patients reported dyspnoea as lasting symptoms; many had not done any form of investigation with chest radiology or pulmonary function test outside of the study; suggesting strain on the health care apparatus to adequately follow-up patients and possibly lack of knowledge as well. This also led to relatively few radiological data points and as such, a robust analysis of prolonged radiological changes was not possible.

Obvious limitation of this study is the lack of pre-existing baseline pulmonary function data and the lack of a control group. Nonetheless, reduced lung function is not a recognized risk factor for hospital admission (36). To provide a baseline comparison in general functional level, we used the PCFS-scale where patients were asked to grade themselves retrospectively, though accuracy might have been

obscured by the passing of one year. The relatively small number of participants is also a limiting factor, but still, almost 64% of all hospitalised patients were ultimately included, providing excellent regional demographic data.

Conclusions

Our results indicate that the long-term prognosis of COVID-19 patients was not influenced to a great deal by how severe the initial infectious episode was. The lack of difference between the groups with differing acute disease severity suggests that more generous diagnostic manoeuvres, such as spirometry and radiology, could be indicated even in less severely affected individuals with lingering symptoms.

Abbreviations

ALAT - Alanine aminotransferase

ANOVA - Analysis of variance

ARDS - Acute respiratory distress syndrome

ATS - American thoracic society

BMI – Body mass index

COPD - Chronic obstructive pulmonary disease

COVID-19 – Coronavirus disease 2019

CRP – C-reactive protein

DLCO - Diffusing capacity for carbon monoxide

eGFR - estimated glomerular filtration rate

FEV1 - Forced expiratory volume in 1 second

FiO2 - Fraction of inspired oxygen

FVC - Forced vital capacity

HAD - Hospital anxiety and depression scale

HFNC - High-flow nasal-cannula

ICS - Inhaled corticosteroids

ICU - Intensive care unit

IMV - Invasive mechanical ventilation

IQR - Interquartile range

MERS - Middle east respiratory syndrome

mMRC - modified Medical Research Council

NIV - Non-invasive ventilation

PCFS - Post-COVID-19 Functional Status Scale

PFTs - Pulmonary function tests

SARS - Severe acute respiratory syndrome

SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2

SD - Standard deviation

SF-36 - 36-Item Short Form Health Survey

Declarations

- ### Ethics approval and consent to participate

The Swedish Ethical Review Authority granted ethical approval for the study (dnr: 2020-03531). Written informed consent was obtained for all living patients.

- ### Consent for publication

Not applicable

- ### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- ### Competing interests

The authors declare that they have no competing interests.

- ### Funding

The authors have no funding to declare.

- ## Authors' contributions

JA has recruited patients, gathered, analysed and interpreted the patient data, performed the pulmonary function tests and written the manuscript. KC, MS and PE have recruited patients and gathered the patient data. TE has recruited patients and performed the pulmonary function tests. KV has done the statistical analysis and interpreted data. CT has designed the study, gathered and interpreted the patient data and written the manuscript.

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Figures

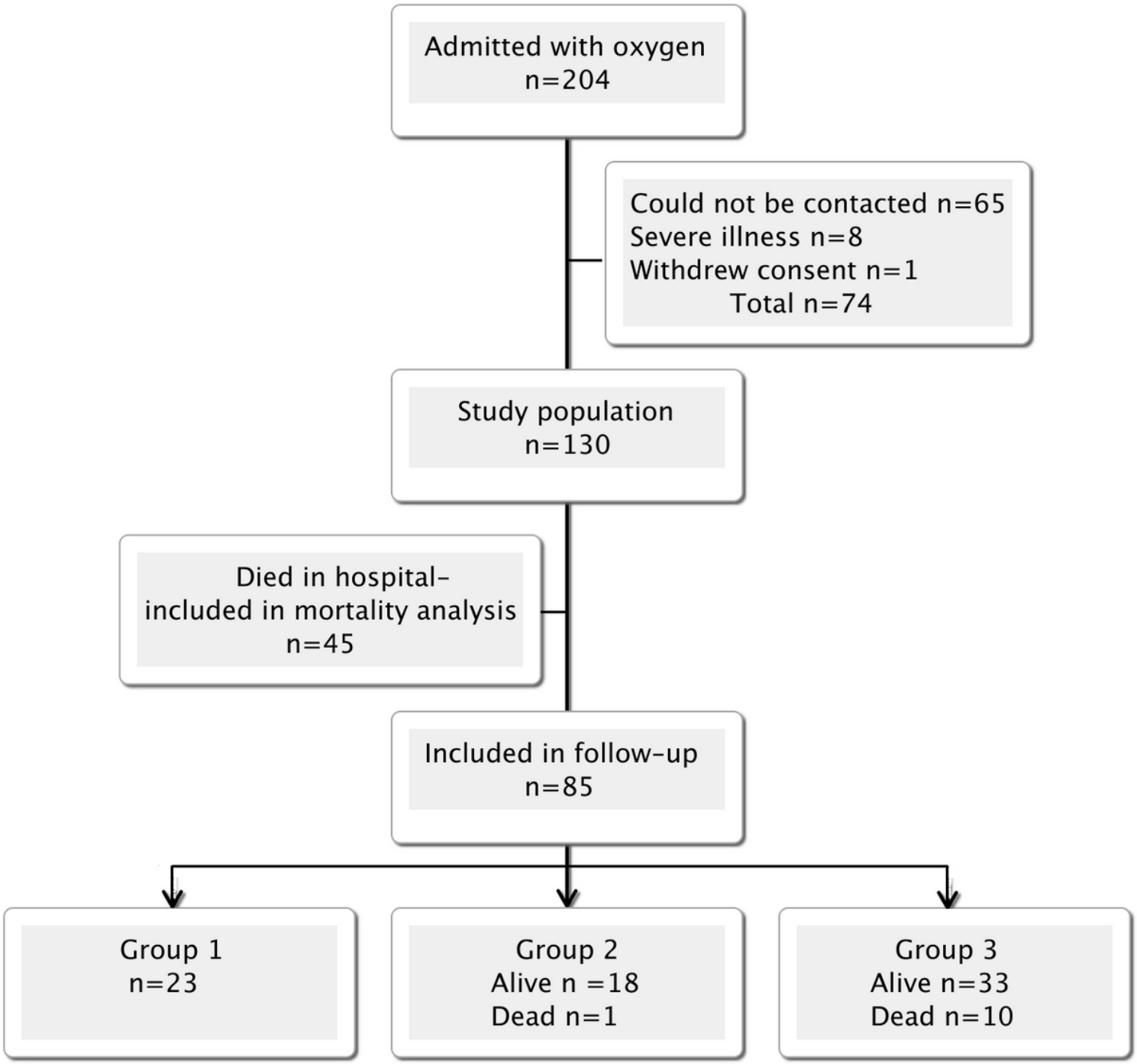

Figure 1

Flowchart of patient selection.

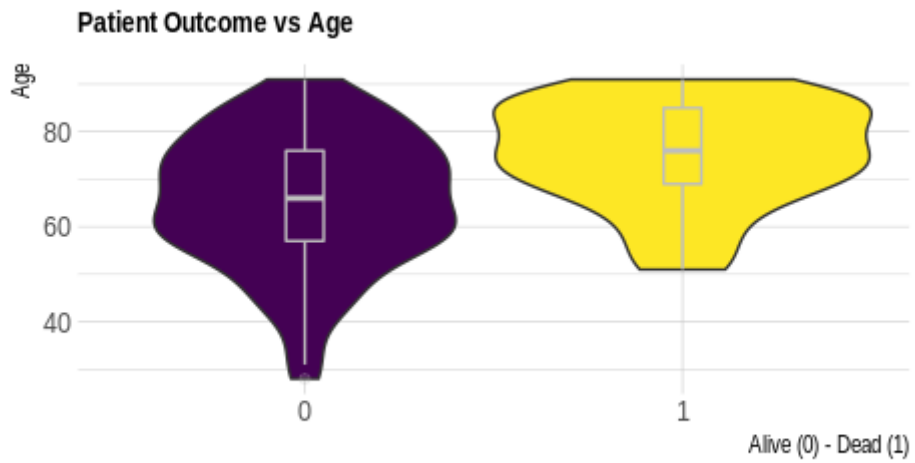

Figure 2

Violin plot showing that the in-hospital mortality among patients with COVID-19 was related to higher age when examining the entire study population (p<0,001).

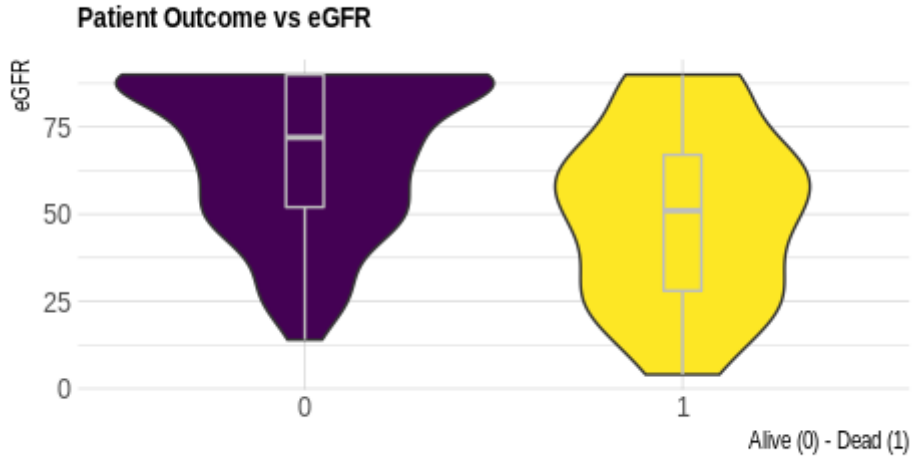

Figure 3

Violin plot. Renal failure expressed as low eGFR (estimated glomerular filtration rate) was shown to be a significant predictor of mortality (p<0,001).

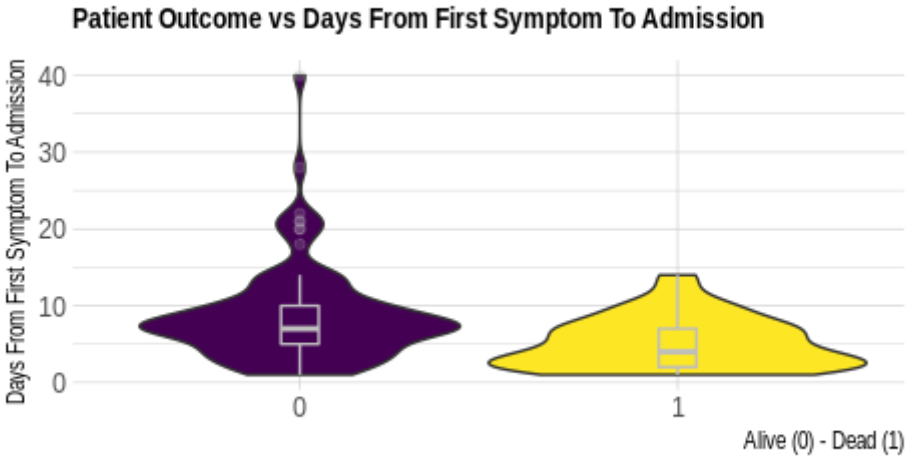

Figure 4

Patients who survived had a longer period from symptoms onset to hospital admission (violin plot, p<0,001).