

# OVERVIEW AND OUTCOMES OF PATIENTS HOSPITALISED WITH COVID-19 PNEUMONIA IN RĪGA EAST UNIVERSITY HOSPITAL

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*The COVID-19 pandemic is still a burden to the global health care system, affecting its capacity to maintain essential health services. Even though specific treatment and prevention options are available, the SARS-CoV-2 virus keeps accumulating mutations over time and challenging the efficiency of vaccines, causing new outbreaks and increasing hospitalisation. Early studies suggest that mortality from COVID-19 is increased by age and certain comorbidities. Thus, the goal of this study was to analyse patients hospitalised with COVID-19 pneumonia in terms of age, sex, and comorbidities. Additionally, the influence of treatment with Remdesivir and vaccination on hospitalisation duration and disease outcome was also analysed. The results showed that lethal disease outcome is mainly increased by age and gender, where older and male patients are at a higher risk. There were less deaths in patients with primary arterial hypertension. Other comorbidities did not have a statistically significant influence on disease outcome. Among those who survived, a higher number of patients had been treated with Remdesivir. Vaccination did not have an impact on disease outcome. It could be concluded that older and male patients are the risk group with a worse disease outcome. Treatment with Remdesivir shows a positive effect on disease outcome, although further detailed analysis is necessary.*

**Keywords:** comorbidities, age, gender, remdesivir, vaccination, disease outcome.

## INTRODUCTION

The novel coronavirus SARS-CoV-2, which emerged from Wuhan, China, in December 2019, has spread worldwide causing a pandemic (Zoumpourlis *et al.*, 2020). Shortly after its first outbreak, when new cases were being rapidly reported every day, the World Health Organisation (WHO) announced the disease COVID-19 (coronavirus disease – 19) in February 2020 (World Health Organisation, 2020). According to WHO data, there were more than half of billion confirmed cases of COVID-19 infection worldwide and more than 6 million disease related deaths (World Health Organisation, 2022) till 15 June 2022.

The clinical appearance of COVID-19 is very diverse — in some individuals the disease is asymptomatic while others exhibit symptoms such as cough, fever, shortness of breath, extreme fatigue, myalgia and arthralgia, loss of smell and taste. In some cases it can lead to severe respiratory or multi-organ failure resulting in death (Esakandari *et al.*, 2020).

The main transmission of COVID-19 is airborne by inhaling contaminated respiratory droplets with the average incubation period 5.2 days (Mohapatra *et al.*, 2020). A person can be infectious two to three days before the onset of symptoms and can remain infectious for at least eight days.

Of all transmissions, it is estimated that more than a half arise from asymptomatic individuals (Johansson *et al.*, 2021; Centers for Disease Control and Prevention, 2022).

The first antiviral drug to be approved by the Food and Drug Administration was Remdesivir — an adenosine analogue that inhibits the RNA-dependant-RNA polymerase and showed an effect on virus replication *in vitro* and *in vivo* trials (Wang *et al.*, 2020). However, the results from clinical trials in treating hospitalised patients with moderate to severe COVID-19 remain controversial, ranging from having minimal to no effect in disease outcome (Beigel *et al.*, 2020; Tanni *et al.*, 2022). The effect of Remdesivir seems to increase with early treatment in non-hospitalised patients (Gottlieb *et al.*, 2022).

The first approved vaccines against SARS-CoV-2 virus were available in 2020 with efficacy reaching up to 95% (Polack *et al.*, 2020; Rogers, 2022).

Over time the mutations in viral genome have created new variants, challenging the effectiveness of vaccines and increasing the risk of recurrent infections in patients that have already recovered from previous COVID-19. Mutations affect the spike protein of the virus, which is responsible for binding with the cell and is the main immunogen used in vaccines. The new variants are named by Greek letters in alphabetic order, with Alfa being the first one discovered with eight mutations in Spike protein and Omicron being the last with more than 30 mutations (Almehdi *et al.*, 2021; Aleem *et al.*, 2022). From the clinical perspective the Delta variant is considered to be the one causing the most severe infections with highest mortality rate (Gottlieb *et al.*, 2022; Wrenn *et al.*, 2022).

The role and prevalence of comorbidities such as hypertension, diabetes mellitus, obesity, cancer, chronic kidney disease etc. have been studied since the beginning of the pandemic to ascertain their impact on the severity and outcome of the disease. Studies also suggest a correlation between age and mortality, where older patients are at a higher risk in terms of lethal disease outcome. Results showed that

both, comorbidities and age, can affect the mortality (Bonanad *et al.*, 2020; Sanyaolu *et al.*, 2020; Ng *et al.*, 2021).

The primary goal of this study was to analyse the length of hospitalisation of COVID-19 patients and disease outcome in relation to comorbidities, age and gender. Additionally, the influence of treatment with Remdesivir and vaccination was studied.

## MATERIALS AND METHODS

The study was conducted at Rīga East University Hospital clinic “Gaiļezers”, and its duration was one year starting from 1 November 2020.

The data was obtained from patient medical records and a unique profile for each patient was created including the age, gender, comorbidities, vaccination status and whether specific treatment with Remdesivir was received.

The comorbidities considered in this study were primary arterial hypertension, coronary artery disease, atrial fibrillation, type 2 diabetes, chronic kidney disease, cerebrovascular disease, neurodegenerative disease, oncological disease, bronchial asthma, liver disease and obesity.

IBM SPSS Statistics software was used to analyse whether the abovementioned factors had an influence on hospitalisation length and mortality.

## RESULTS

In the study period there were 802 patients with COVID-19 pneumonia. 44.3% (355) were male patients and 55.7% were female, with median age 71 (IQR = 60–81). 171 (21.3%) of all patients had a lethal disease outcome.

There was a weak correlation between the age and duration of hospitalisation with older patients having a longer hospitalisation ( $r_s = 0.134$ ;  $p < 0.001$ ) (Fig. 1).

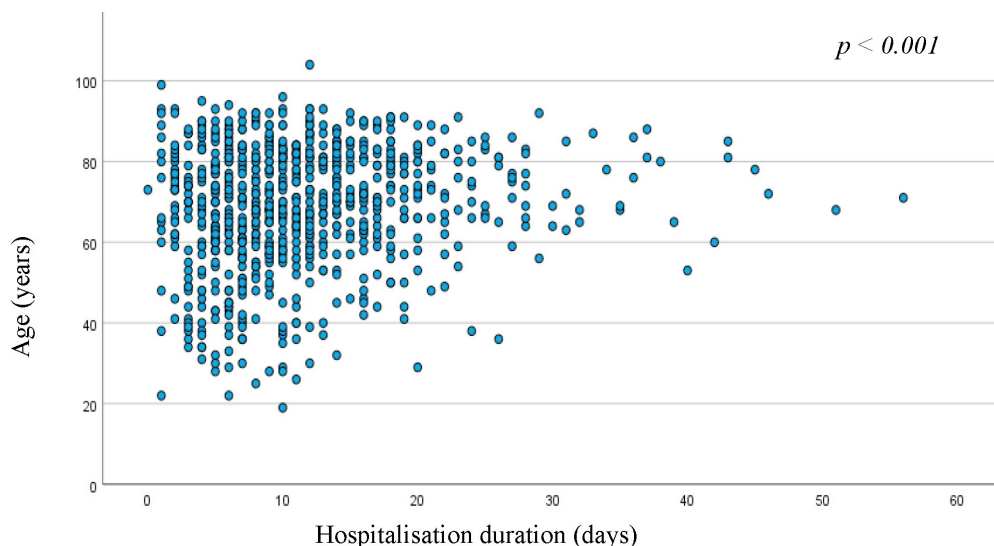


Fig. 1. Correlation between age and hospitalisation duration.

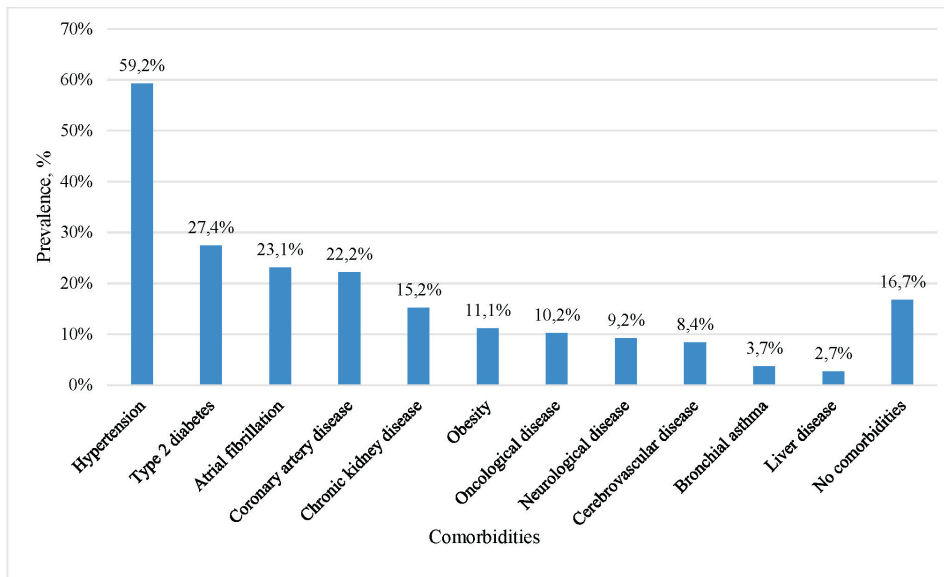


Fig. 2. Prevalence of comorbidities.

A positive correlation was found with age and disease outcome — the median age of patients who died during hospitalisation was 79 (IQR 71–85) and those discharged — 68 years (IQR 58–79;  $p < 0.001$ ).

The most prevalent of comorbidities was primary arterial hypertension (59.2%), followed by type 2 diabetes (27.4%) and atrial fibrillation (23.1%) (Fig. 2).

Binary Logistic regression (Nagelkerke pseudo  $r^2 = 0.246$ ) showed that the age of the patient had the strongest impact on lethal disease outcome (Wald = 70.1;  $p < 0.001$ ).

Gender also had an influence on disease outcome (Wald = 8.802;  $p = 0.003$ ) — male patients had 1.804 times higher risk of lethal disease outcome than female patients (95% CI = 1.222 – 2.665).

Primary arterial hypertension had an inverse effect on lethal disease outcome (Wald = 29.839;  $p < 0.001$ ) — less lethal outcomes in patients with hypertension.

Chronic kidney disease showed an influence on disease outcome close to reaching statistical significance (Wald = 3.29;  $p = 0.071$ ).

None of the other comorbidities showed statistically significant influence on disease outcome ( $R^2 = 0.246$ ) using the regression model. Apart from age and gender factors, the following comorbidities reached statistical significance: chronic kidney disease ( $p < 0.001$ ), primary arterial hypertension ( $p < 0.001$ ), cerebrovascular disease ( $p = 0.024$ ) and neurological disease ( $p = 0.041$ ). However, the quality criteria of this model were very low (Nagelkerke pseudo  $r^2 = 0.082$ ).

A difference in disease outcome in terms of treatment with Remdesivir was observed. Of the patients who survived, 32.6% had received Remdesivir therapy, whereas only 12.3% of those who died had received Remdesivir ( $p < 0.001$ ).

It was observed that patients who had received initial vaccination course had shorter length of hospitalisation compared to those non-vaccinated — Me = 8 days (IQR = 5–13) vs Me = 10.5 (IQR = 6–15.75), although statistical significance was not reached ( $p = 0.067$ ).

Vaccination status did not have an impact on disease outcome ( $p = 0.55$ ).

## DISCUSSION

The present study showed a significant link between age and lethal disease outcome, where older patients had higher risk. Similar conclusions were reached in a meta-analysis where 611,158 patients from 17 studies were analysed (Bonanad *et al.*, 2020). Unlike that study, the present study did not have a subdivision in age groups (< 29, 30–39, 40–49, etc.) and therefore a specific age threshold, when mortality increases more rapidly and whether such was present at all (in the previous study, the age group of 50–59 to 60–69) was not identified. A larger group of patients would make the search for this threshold more useful and statistically significant.

A weak correlation between age and hospitalisation duration was identified, where older patients tended to have longer hospitalisation. Consequently, there is strong evidence that older patients are a higher risk group that should be prioritised and a different approach might be required to possibly prevent a worse disease outcome (Bonanad *et al.*, 2020).

According to the results, gender also had an influence on disease outcome. The study included 355 male patients (44.3%) and the results showed that male patients had 1.804 times higher risk of lethal disease outcome than female patients. The same conclusion was made in another meta-analysis of 63 countries (Geldsetzer *et al.*, 2022). To ensure that the results are indeed related to COVID-19 disease, it would be necessary to compare them with male all-cause

mortality in Latvia. According to the previously mentioned meta-analysis, where such comparison was carried out, it could be predicted that increased mortality among male patients in Latvia also was directly linked to COVID-19, although further detailed analysis are required for confirmation.

None of the comorbidities except primary arterial hypertension in the present cohort had a statistical significance on disease outcome. The data about the influence of comorbidities on disease outcome remains controversial. Many studies indicate that comorbidities are very prevalent in patients hospitalised with COVID-19, drawing conclusions that comorbidities are linked to a higher risk of hospitalisation and developing severe disease, although data regarding their actual effect on mortality are very debatable (Sanyaolu *et al.*, 2020; Singh *et al.*, 2020). Results seem to vary depending on how many factors were analysed simultaneously — studies analysing just the influence of comorbidities on disease outcome tend to have more statistically significant results, whereas the role of comorbidities becomes less significant when demographic factors such as age and gender are also added (Bhaskaran *et al.*, 2021; Kompaniyets *et al.*, 2021; Péterfi *et al.*, 2022).

Nevertheless, the present study results showed that chronic kidney disease was likely to have the highest negative influence on disease outcome and was close to reaching statistical significance ( $p = 0.071$ ). Chronic kidney disease was also identified as the most prominent comorbidity leading to death in another meta-analysis of eight studies regarding the influence of comorbidities on mortality, but hypertension, oncological disease and diabetes were also linked to lethal disease outcome (Ng *et al.*, 2021). The difference most likely was due to the fact that in the present cohort demographic factors were also included in the regression model and hence the role of comorbidities became less significant. To test the theory, age and gender factors were excluded from the model and as a result chronic kidney disease and some other comorbidities suddenly showed statistical significance. However, the new model quality criteria were so low, such that it was decided not to conclude anything from those results. The present study included 122 patients with chronic kidney disease and a larger group of patients is necessary to gain more precise results.

The most unpredicted result obtained was in the hypertension group. Similar to other studies (Sanyaolu *et al.*, 2020; Ng *et al.*, 2021), hypertension was the most prevalent comorbidity, being present in 28.3% (475) of the patients. But unlike the meta-analysis containing 12 studies, where hypertension was considered as a risk factor for increased mortality (Du *et al.*, 2021), the present study results showed a reverse effect on disease outcome with a statistical significance. Those results could partially be explained by the common use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) in the hypertension group. Another study showed a decreased risk of severe COVID-19 disease among patients using ACE inhibitors or ARBs (Hipsisley-Cox *et al.*, 2020). As these

drugs are commonly used for many patients with hypertension worldwide, it does not quite explain why the present study results were different. The present study does not contain data on how many patients of those who had hypertension used ACE inhibitors or ARBs. A more detailed analysis with additional factors is definitely required to explain these controversial results.

Regarding specific therapy in this cohort, some patients did not receive Remdesivir as they did not qualify for such treatment (beginning of treatment should not exceed ten days after the onset of symptoms) or the treatment with Remdesivir was contraindicated. Those patients were not excluded in this study and this may have affected the results. When the initial treatment began after the onset of symptoms, the data was not analysed, and, according to other studies on the efficiency of Remdesivir, this factor seems to have an influence on disease outcome. The present study results showed that such treatment might have a positive effect on disease outcome, as out of patients who survived, a significantly higher number of patients had received therapy with Remdesivir (32.6%) compared to those with a lethal disease outcome (12.3%).

There was no evidence that vaccinated patients had an influence on disease outcome, but vaccinated persons had a shorter hospitalisation duration. Unfortunately, it did not reach statistical significance, but the  $p$  value was close — 0.067. Vaccination was introduced late in the study period, so a higher number of patients could have resulted in statistical significance. It is known that vaccines do not exceed 95% efficiency, so it is possible that some part of the hospitalised patients were the ones who did not gain the anticipated immunity. In that case, evaluating the general efficiency of vaccination in such patients would not be appropriate.

## ETHICS

The study was conducted in accordance to the Declaration of Helsinki ethical standards. Riga East University Hospital Support Foundation Ethics Committee provided approval for the study.

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## PĀRSKATS UN IZNĀKUMI AR COVID-19 PNEIMONIJU STACIONĒTIEM PACIENTIEM RĪGAS AUSTRUMU KLĪNISKAJĀ UNIVERSITĀTES SLIMNĪCĀ

Covid-19 pandēmija vēl joprojām ir slogs medicīnas aprūpes sistēmai visā pasaulē, ietekmējot tās spēju nodrošināt pirmās nepieciešamības palīdzību. Kaut arī ir pieejama specifiska terapija un profilakse, SARS-CoV-2 vīruss laika gaitā turpina krāt mutācijas, negatīvi ietekmējot vakcīnu efektivitāti un izraisot jaunus slimības uzliesmojumus, kas rezultējas ar pacientu hospitalizācijas pieaugumu. Pirmie pētījumi liecina, ka mirstību no Covid-19 ietekmē pacientu vecums un konkrētas blakusslimības. Šī pētījuma mērķis ir analizēt pacientus, kas stacionēti ar Covid-19 pneimoniju, ņemot vērā vecumu, dzimumu un blakusslimības. Papildus tika pētīta Remdesivir terapijas un vakcinācijas ietekme uz hospitalizācijas ilgumu un slimības iznākumu. Rezultāti norāda, ka letālu slimības iznākumu galvenokārt ietekmē pacienta vecums un dzimums, kur gados vecākiem pacientiem un vīriešiem ir augstāks risks. Mazāk letālu iznākumu bija pacientiem ar primāru arteriālu hipertensiju. Citām blakusslimībām nebija statistiski nozīmīgas ietekmes uz slimības iznākumu. Pacientu grupā, kas izdzīvoja, Remdesivir terapiju bija saņēmuši vairāki nekā grupā ar letālu slimības iznākumu. No rezultātiem var secināt, ka gados vecāki pacienti un vīrieši ir riska grupa sliktākam slimības iznākumam. Terapijai ar Remdesivir ir pozitīva ietekme uz slimības iznākumu, kaut arī ir nepieciešama tālāka detalizēta analīze.