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A pilot study of application of the Stroke Riskometer mobile app for assessment of the course and clinical outcomes of COVID-19 among hospitalised patients

Merkin A, Akinfieva S, Medvedev ON, Krishnamurthi RV, Gutsaluk A, Reips U-D, Kuliev R, Dinov E, Nikiforov I, Shamalov N, Shafran P, Popova L, Burenchev D, Feigin VL

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A pilot study of application of the Stroke Riskometer mobile app for assessment of the course and clinical outcomes of COVID-19 among hospitalised patients.

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Authors: Alexander Merkin[1,2], Sofya Akinfieva[3], Oleg N. Medvedev[4], Rita Krishnamurthi[1], Alexey Gutsaluk[5], Ulf-Dietrich Reips[2], Rufat Kuliev[5], Evgeny Dinov[6], Igor Nikiforov[7], Nikolay Shamalov[8], Polina Shafran[5], Lyudmila Popova[9], Dmitry Burenchev[5], Valery Feigin[1]

1 Auckland University of Technology, Auckland, New Zealand
2 University of Konstanz, Konstanz, Germany
3 National Centre for Development of Social Support & Rehabilitation, Moscow, Russia
4 The University of Waikato, Hamilton, New Zealand
5 The City Clinical Hospital named after A.K. Eramishantsev, Moscow, Russia
6 Russian Peoples' Friendship University, Moscow, Russia
7 Academy for Postgraduate Education, Moscow, Russia
8 Pirogov Russian National Research Medical University, Moscow, Russia
9 I.M. Sechenov First Moscow State Medical University, Moscow, Russia

Corresponding author: Alexander Merkin (amerkin@aut.ac.nz)
Tel: 64 (0)9 921 9174. Postal Address: Faculty of Health & Environmental Sciences, National Institute for Stroke and Applied Neurosciences, AUT University, Private Bag 92006, Auckland 1142, New Zealand.

Abstract

Introduction: Early determination of COVID-19 severity and health outcomes could facilitate better treatment of patients. Different methods and tools have been developed for predicting outcomes of COVID-19, but they are difficult to use in routine clinical practice.

Methods: We conducted a prospective cohort study of inpatients aged 20-92 years, diagnosed with COVID-19 to determine whether their individual 5-year absolute risk of stroke at the time of hospital admission predicts the course of COVID-19 severity and mortality. The risk of stroke was determined by the Stroke Riskometer mobile application.

Results: We examined 385 patients hospitalised with COVID-19 (median age 61 years). The participants were categorised based on COVID-19 severity: 271 (70.4%) to the "Not severe" and 114 (29.6%) to the "Severe" groups. The median risk of stroke the next day after hospitalisation was significantly higher among patients in the Severe group (2.83, 95% CI 2.35-4.68) vs the Not severe group (1.11, 95% CI 1.00–1.29). The median risk of stroke and median systolic blood pressure (SBP) were significantly higher among non-survivors (12.04, 95% CI 2.73-21.19) and (150, 95% CI 140-170) vs survivors (1.31, 95% CI 1.14-1.52) and (134, 95% CI 130-135), respectively. Those who spent more than 2.5 hours a week on physical activity were 3.1 times more likely to survive from COVID-19. Those who consumed more than one standard alcohol drink a day, or suffered with atrial fibrillation, or had poor memory were 2.5, 2.3, and 2.6 times more likely not to survive from COVID-19, respectively.

Conclusions: High risk of stroke, physical inactivity, alcohol intake, high SBP, and atrial fibrillation are associated with severity and mortality of COVID-19. Our findings suggest that the Stroke Riskometer app could be used as a simple predictive tool of COVID-19 severity and mortality.

Keywords Stroke Riskometer mobile app, Stroke, COVID-19, Co-morbidity, Prediction, Severity

Introduction

In late December 2019 a new COVID-19 pandemic outbreak emerged and spread worldwide, currently affecting over 305 million patients, 5.5 million of whom have died at the time of writing.[1] As the COVID-19 pandemic accelerates, it is necessary to warn people at higher risk of poor COVID-19 outcomes to be particularly stringent in keeping safe and undertaking measures to prevent increased morbidity and mortality related to COVID-19. These measures would reduce the burden on healthcare systems which occur due to the COVID-19 pandemic.[2] Therefore, it is particularly important to know at the earliest possible stage who is at higher risk of poor COVID-19 outcomes. During the COVID-19 pandemic it has quickly become clear that age, sex and a range of risk factors and health conditions, including obesity, diabetes, cardiovascular and pulmonary diseases, are associated with poor COVID-19 outcomes.[3,4]

Stroke is the second most common cause of death and disability in the world,[5] and shares risk factors not only with other non-communicable diseases such as myocardial infarction, vascular dementia, and type 2 diabetes mellitus,[6-8] but also with COVID-19 disease.[9,10] There is also increasing evidence of the association and reciprocal influence between COVID-19 and stroke. Stroke may be one of the risk factors for death from COVID-19,[11,12] while COVID-19 may increase risk of acute stroke,[13-16] and history of stroke is included in prediction models for risk of mortality from COVID-19.[17]

Developed by the Auckland University of Technology (New Zealand), the free Stroke Riskometer mobile application (the App) is a tool that calculates 5-year absolute risk of stroke (hereinafter "the risk") by specifically assessing the multiple risk factors associated with overall risk of stroke and cardiovascular disease.[6,7,18] The App has been fully validated [19,20] and endorsed by the World Stroke Organization, the World Federation of Neurology, the World Heart Federation and the European Stroke Organisation. It was recently recommended for implementation in all Latin American countries[21] and for world-wide implementation.[22] The wide range of risk factors (socio-demographic, health conditions, lifestyle) covered by the App together with the internationally accepted standard criteria of these risk factors and ease of use of this freely available App makes it suitable for use as a screening tool with or without internet access in virtually any settings including different clinical facilities, place of residence and social institutions.

The overarching aim of this study was to determine whether the risk level of stroke in patients hospitalised with COVID-19 at the time of their hospitalization predict the clinical severity of COVID-19 and its health outcomes (e.g., mortality). We hypothesised that there is a significant difference in the 5 year absolute risk of stroke estimated by the App at baseline (the next day after hospitalisation) between those with combined mild and medium severity of COVID-19, (categorized as "not-severe" , and those with severe (combined severe and extremely severe) COVID-19.

Methods

A quasi-experimental, open-labeled prospective cohort study was conducted at the City Clinical Hospital named after A.K. Eramishantsev and at the Temporary Hospital of the City Clinical Hospital #24, Moscow, Russia. Data collection was carried out from the 1 September through 30 December 2020 during the COVID-19 outbreak in Moscow. The study was approved by the Local Ethics Committee of the Eramishantsev State City Hospital (Nr.9(1)–2020).

Participants

Four hundred and twelve consecutively hospitalised patients with laboratory confirmed COVID-19 were identified within the four-month study period. Study inclusion criteria were: age 20-93 years and ability and willingness to provide an informed consent to participate in the study. Patients who were not able or willing to provide their informed consent because of the severity of their health conditions were excluded from the study. Of the 412 identified potential study participants, 385 (response rate 94.6%) met the inclusion criteria and comprised the final study sample (the study flowchart is shown in Figure 1).

Data collection

The risk of stroke in the study participants was assessed by a trained study team member using the App at baseline (the next day after admittance to the hospital). In order to calculate the risks of stroke the App requires reported input of several demographic and clinical parameters, such as age, sex, ethnicity, SBP, smoking, dietary habits, physical activity, presence of heart disease, family history of stroke and/or heart disease, medication use

for blood pressure lowering, diabetes mellitus, BMI, psychosocial stress, traumatic brain injury, memory problems and dementia (Supplement, Table 4).
To streamline the analysis the answers "Yes, more than 12 months ago" and "Yes, less than 12 months ago" in the App questionnaire were combined into one answer "Yes" to the following questions: "Have you ever been told by a doctor that you have diabetes?", "Have you ever been told by a doctor you have heart or peripheral artery disease?", "Have you ever been told by a doctor that you have left ventricular hypertrophy?", "Have you ever been told by a doctor that you have atrial fibrillation?", "Have you ever been told by a doctor that you have a cognitive problem or dementia?", "Have you ever been told by a doctor that you've had a traumatic brain injury?" and "Have you ever been told by a doctor that you've had a stroke or transient ischemic attack (mini stroke)?". The risk of stroke was calculated based on these data using the validated algorithm embedded into the App.[19]
In addition to the data in the Stroke Riskometer questionnaire (Supplement, Table 4), demographics and clinical data of the participants were collected, including taking anticoagulant medications NOAC (blood thinners) before hospital admission.

Clinical diagnosis & Criteria of COVID-19 outcomes
The study participants underwent regular routine clinical assessments by their physicians and had a series of lung CT scans on admission as well as in the middle of their hospital stay and at the end of the treatment course before hospital discharge (at the discretion of the treating physician). Clinical endpoints comprised of a) individual health outcomes at hospital discharge (survived/non-survived); and b) severity of the course of COVID-19 (mild, moderate, severe, extremely severe). The severity criteria of COVID-19 disease were determined by the result of lung CT scans and the clinical history of the disease during the entire period of hospitalization: duration of fever, respiratory failure, duration of hospitalisation, admittance in intensive care unit (ICU) and treatment needed as well as dynamics of pneumonia. Patients' clinical state and level of severity (mild, moderate, severe, extremely severe) of COVID-19 course were assessed by a clinical panel of certified specialists, which included an internal medicine specialist, a neurologist, a radiologist, and a resuscitator (if needed) in accordance with the "Interim Guidelines for the Prevention, Diagnosis, and Treatment of New Coronavirus Infection (COVID-19)" version 8 [23] and NIH Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.[24] According to these criteria, Mild level of severity was defined as having any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise), but who do not have shortness of breath, dyspnoea, or abnormal chest imaging. Moderate level of severity was defined as showing evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO2) ≥94% on room air at sea level. Severe course was defined as having SpO2 30 breaths/min, or lung infiltrates >50%. And extremely severe level of COVID-19 disease during hospital admission was defined as having respiratory failure, septic shock, and/or multiple organ dysfunction.

Data analyses
Descriptive statistics were produced for all variables. Normality of distributions of continuous variables was assessed by visual examination of histograms, analyses of skewness and kurtosis, and the Shapiro-Wilk test. To examine differences between less and more severe courses of COVID-19 we combined patients with mild and moderate severity into the Not severe COVID-19 group while participants with severe and extremely severe courses of COVID-19 were allocated into the Severe group of COVID-19. The Stroke Riskometer algorithm accounts for demographic differences such as age and sex. For this reason, these demographic variables were not included in the group comparison to minimise Type I error and to prevent controlling for the same factor twice. To determine whether the risk level of stroke in COVID-19 patients predict their mortality, participants were divided into two independent groups based on the clinical outcome of COVID-19: Survived or Non-survived. Survival function was evaluated by the Kaplan-Meier method. [25] The risk of stroke estimates was not normally distributed and, therefore, non-parametric tests were used to determine whether the risk of stroke in COVID-19 patients at the time of their hospitalization significantly predict the clinical severity of COVID-19. The Chi-square test was used for independent samples to compare categorical variables. The Fisher's exact test was used whenever the number of one group was five or less. Independent-Samples Mann-Whitney U Test was used for independent samples to compare two quantitative variables. Statistical significance was determined by $p<0.05$.

Funding
No external funding was received for this project.

Results

The majority of participants (n=271, 70.4%) had no severe course of COVID-19, and 114 (29.6%) patients had a severe course of COVID-19. During the period of hospital admission 39 (10.1%) patients died, all of them belonged to the Severe group of COVID-19. Descriptive statistics of each of the groups are presented in the Supplement, Tables 1, 2 and 3.

The median age of the participants was 61 years (95% CI 59-64), more than half (n=261, 67.8%) were males, more than 75% had either a body mass index (BMI) of ≥ 25 or systolic (upper) blood pressure (SBP) of ≥ 120, or both. About one third of the participants (125, 32.5%) smoked cigarettes and one third (130, 33.8%) spent at least 2.5 hours a week on physical activity. There were 70 (18.2%) participants who consumed more than one standard alcohol drink daily. The majority of the participants (348, 90.4%) did not use New Oral Anticoagulants (NOAC) before contracting COVID-19 and being admitted to the hospital.

The median age of the participants in the Severe group was significantly higher compared to the Not severe group (70 years, 95% CI 68-73 vs 56 years, 95% CI 54-59) accordingly to Mann-Whitney U Test (Z=-7.327, p<0.001, r=-0.373 (medium effect size)). We found no significant difference by sex between the severity groups (Pearson Chi-Square 0.615 p=0.433) or Severe group and a random sample (n=114) from the Not-severe group of the same size (Pearson Chi-Square 0.521 p=0.470).

The risk of stroke was higher in the Severe group compared to the Not severe group (Z=-6.886, p<0.001, r=-0.351 (medium effect size)) (Figure 2) with a calculated median risk of stroke of 1.11 (95% CI 1.00-1.29) in the Not severe group and 2.83 (95% CI 2.25-4.49) in the Severe group.

The median risk of stroke was 1.31 (95% CI 1.14-1.52) among survivors of COVID-19 and 12.04 (95% CI 2.73-21.19) among non-survivors. Figure 3 demonstrates that the median values of risks of stroke amongst the non-survivors were significantly higher than those in the survivors as evidenced by the Mann-Whitney U Test (Z=-5.298, p<0.001, r=0.270).

It was found that the median age was significantly higher in non-survivors than in survivors: median age 73 years old (95% CI 68-81) vs median age 60 years old (95% CI 58-63), respectively (Z=-4.089, p<0.001, r=-0.208). Those participants who spent more than 2.5 hours a week on physical activity were 3.1 times more likely to survive the disease (OR=3.1, (95%CI 1.3–7.5)). Participants who consumed more than one standard alcohol drink a day were 2.5 times more likely not to survive from COVID-19 compared to those who did not consume alcohol (Odds Ratio (OR)=2.5, 95% CI 1.2–5.2). Participants who suffered with atrial fibrillation were 2.3 times more likely not to survive (OR=2.3, 95% CI 1.0–5.2) and participants who had poor memory were 2.6 times more likely not to survive COVID-19 (OR=2.6, 95% CI 1.3–5.1). SBP was significantly higher among non-survivors (median 150, 95% CI 140-170) compared to survivors (median 134, 95% CI 130-135) in accordance with the Mann-Whitney U Test (Z=-4.019, p<0.001, r=-0.205). For other risk factors assessed by the App, there were no significant differences between the Survive and Non-survive groups (Supplement, Table 1, 2).

The median duration of hospital admission of all the participants was 13.0 days (95% CI 12-14). The median number of days patients spent in hospital before discharge was 12 (95% CI 11.15-12.85) for participants from the Not severe group and 19 (95% CI 17.60-20.40) for participants from the Severe group. The difference between the groups was significant according to the Log Rank criterion (Mantel-Cox) at p-value<0.001. The Kaplan-Meier survival curve (Figure 4) represents how many days patients spent in hospital before discharge, depending on the severity of COVID-19. Those patients who belonged to Not severe group were discharged from the hospital faster than those with who had a more severe course of the disease.

All non-survivors belonged to the Severe group. The median number of days non-survivors spent in hospital before death was 27 (95% CI 24.46-29.54).

The risk of stroke in the Severe group was higher than in the Not severe group. The difference of risk of stroke was significant according to the Log Rank criterion (Mantel-Cox) at p-value<0.001. Figure 5, the Kaplan-Meier survival curve represents the risk of stroke among patients with COVID-19.

Discussion

Our study findings suggest that the risk of stroke calculated by the App is significantly higher in patients with fatal and severe COVID-19 compared to those with a not severe course of the disease. We also found that elevated SBP, alcohol consumption of more than one standard alcohol drink per day, and medical history of atrial fibrillation and memory loss were associated with fatal COVID-19 outcomes during hospital admission. At the same time, physical activity of more than 2.5 hours per week served as a protective factor from death from

COVID-19. These findings are in line with other studies, which found that those people who had severe COVID-19 or fatal health outcome, also had elevated SBP, older age,[26] as well as an increased risk of acute stroke.[13,16] We found significant differences across estimates of stroke risk between groups of the participants with varying severity of COVID-19 with higher risk of stroke in the group with more severe COVID-19 than in the group with milder course of COVID-19. These findings emphasise that the Stroke Riskometer app could have clinical utility for estimating the stroke risk factor-related cumulative risk of adverse outcomes due to COVID-19. We anticipate our findings demonstrated potential applicability of the App as a risk assessment tool for prediction of severity and individual health outcomes of COVID-19 disease in routine clinical practice.

As would be expected, the Survival analysis shown that those patients with a higher severity of COVID-19 were admitted longer in hospital. A timely prediction may help to allocate a sufficient number of beds and prevent overwhelming of healthcare system, and possibly reduce costs of treatment. And potentially this predictive tool could be developed based on the App.

Our study had several limitations. Due to the relatively small number of the study participants and small number severe and fatal cases of COVID-19, the study was focused on descriptive analysis and non-parametric tests were used for determining the differences between risk of stroke scores and COVID-19 outcomes. For the same reason, it was impossible to conduct the regression analysis or to identify the exact cut-off point for the risks of stroke to be used for reliable prediction of the severity and mortality of COVID-19 and to reliably determine associations of some relatively rare risks of the course of COVID-19 disease. On the same grounds, the binary classification of using the App for predicting COVID-19 severity and outcome was also not considered. This limitation would be adjusted in the future studies. In addition, our study was confined to hospitalised patients with COVID-19. However, the inclusion of a wide age range of consecutively admitted patients with laboratory confirmed COVID-19 strengths the generalisability of our findings.

All of this paves the way for future research focused on establishing cut-off scores of stroke risks associated with different COVID-19 severity levels. These cut-off scores might need further cross-cultural validation using more heterogeneous samples varying on demographic factors, such as our team has already done, using generalisability theory.[20]

In summary, our study suggests that the Stroke Riskometer app could be a useful screening tool for prediction of the severity and individual health outcomes of COVID-19. However, the current quasi experimental study design may not allow causal interpretation of the results. Determining the risk of stroke threshold to predict COVID-19 severity requires further research on a larger and more socio-demographically divergent sample.

The App potentially could be a suitable and convenient tool for rapid screening and assessment of possible severity and clinical outcomes of COVID-19. Using the App could allow clinicians to assess the patient's medical history quickly and comprehensively and would promote rapid clinical decision making and reduce workload of clinicians.

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Statement of Ethics

The study was approved by the local Ethics Committee of the Eramishantsev State City Hospital (#9(1)–2020). Written informed consent was obtained from each participant and registered in the electronic health records.

Conflict of Interest Statement

Valery Feigin, Rita Krishnamurthi and Alexander Merkin declare that the free Stroke Riskometer app is copyrighted and owned by Auckland University of Technology, New Zealand. The other authors declare no conflict of interest.

Funding Sources

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Author Contributions

Alexander Merkin: research design & translation, analysis, draft paper, writing, editing.
Sofya Akinfieva: Russian recruitment, analysis, draft paper, writing, editing.
Oleg N. Medvedev: analysis, writing, editing.
Rita Krishnamurthi: draft paper, writing, editing.
Alexey Gutsaluk: Russian recruitment, analysis, writing, editing.
Ulf-Dietrich Reips: draft paper, writing, editing.
Rufat Kuliev: Russian recruitment, analysis, writing, editing.
Evgeny Dinov: translations, analysis, writing, editing.
Igor Nikiforov: translations, analysis, writing, editing.
Nikolay Shamalov: draft paper, writing, editing.
Polina Shafran: Russian recruitment, analysis, writing, editing.
Lyudmila Popova: Russian recruitment, analysis, writing, editing.
Dmitry Burenchev: Russian recruitment, analysis, writing, editing.
Valery Feigin: research conception, design, writing, editing.

Data Availability Statement
All data generated or analysed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Figure Legend

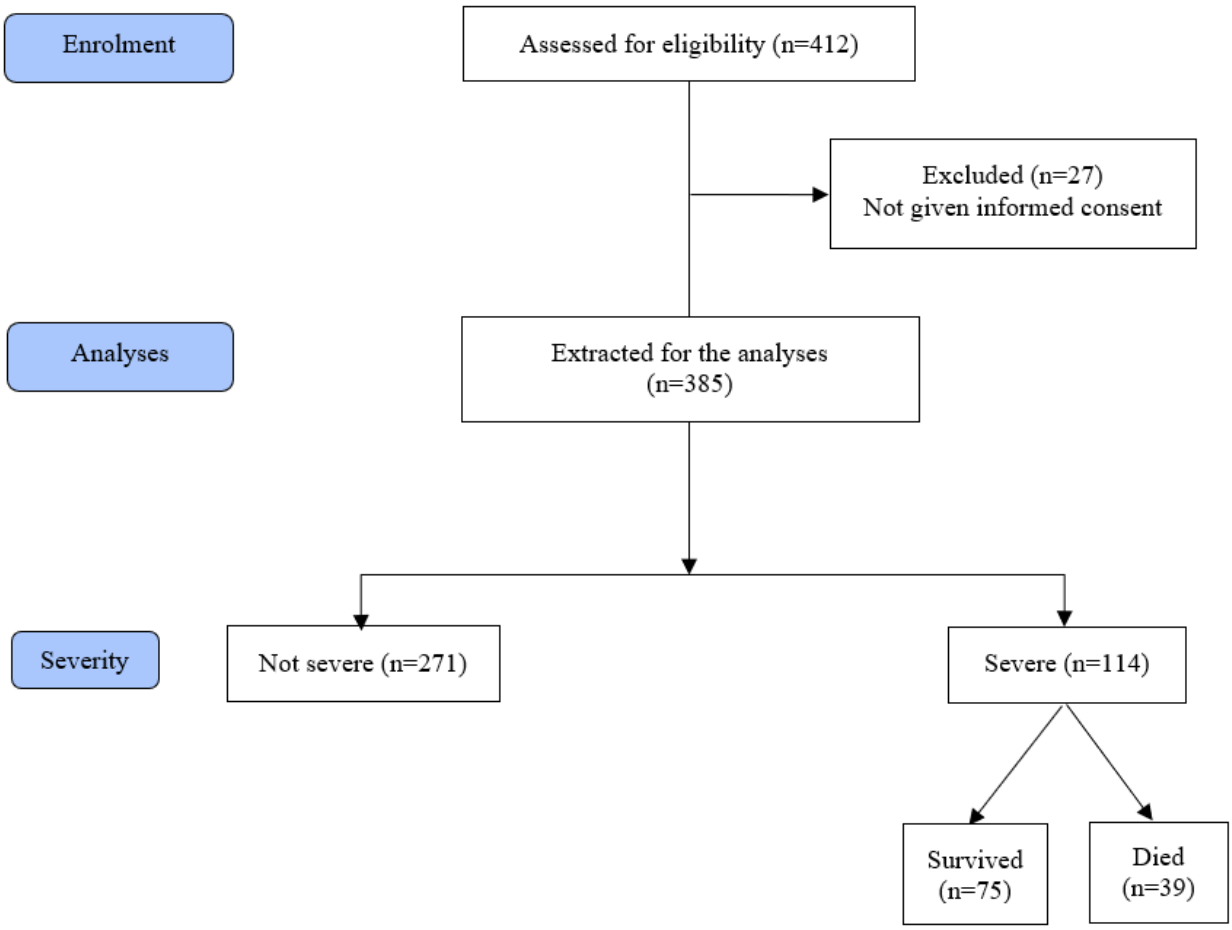
Figure 1. Consort flow diagram for recruitment of participants.

Figure 2. Risk of stroke distribution in the severity groups.
Error Bars 95% CI.

Figure 3. Risk of stroke distribution in the outcome groups.
Error Bars 95% CI.

Figure 4. Unadjusted Kaplan-Meier survival estimates (days since hospitalisation to discharge).

Figure 5. Unadjusted Kaplan-Meier survival estimates (the risk of stroke).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Analyses
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Severity
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Survived
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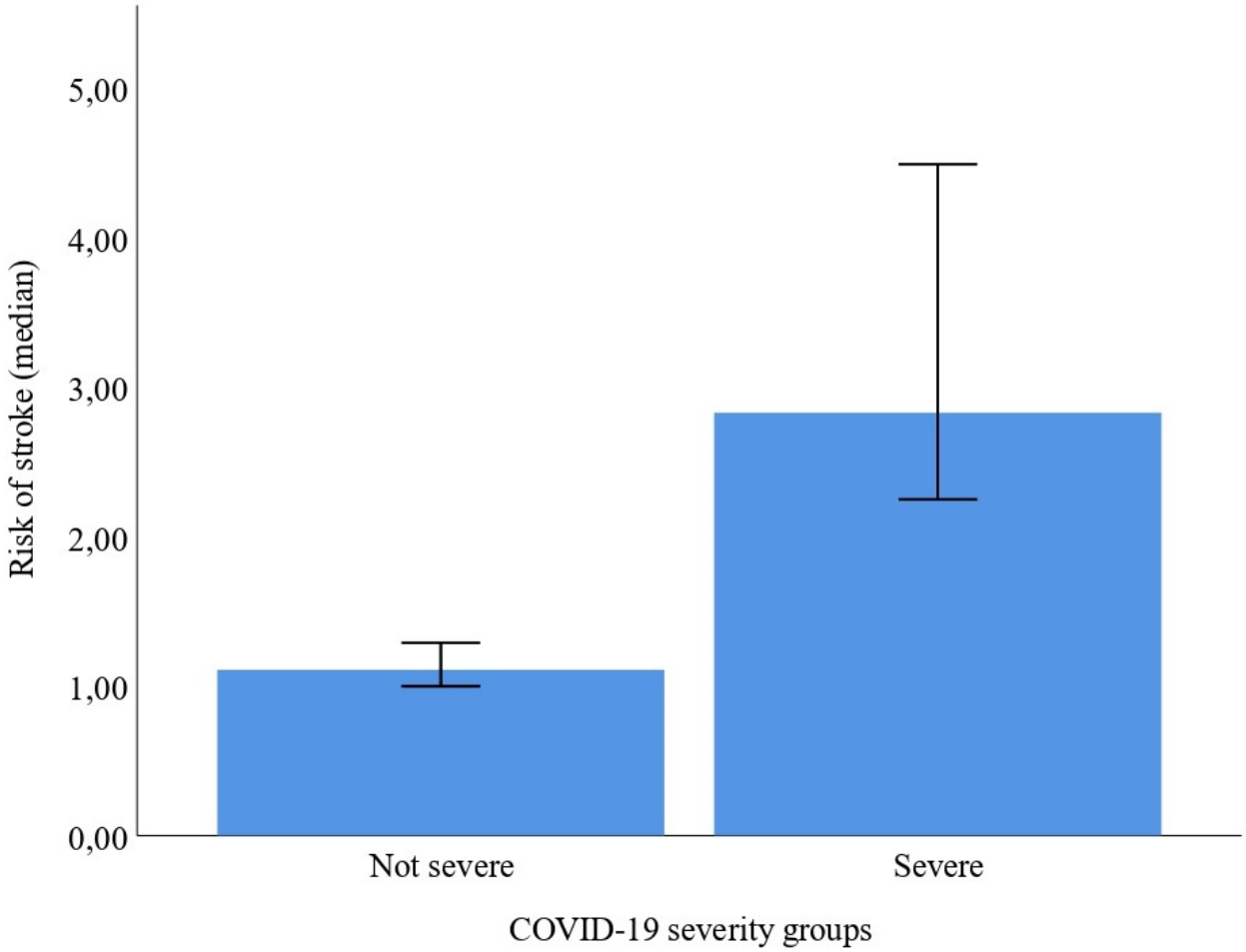
Died
(n=39)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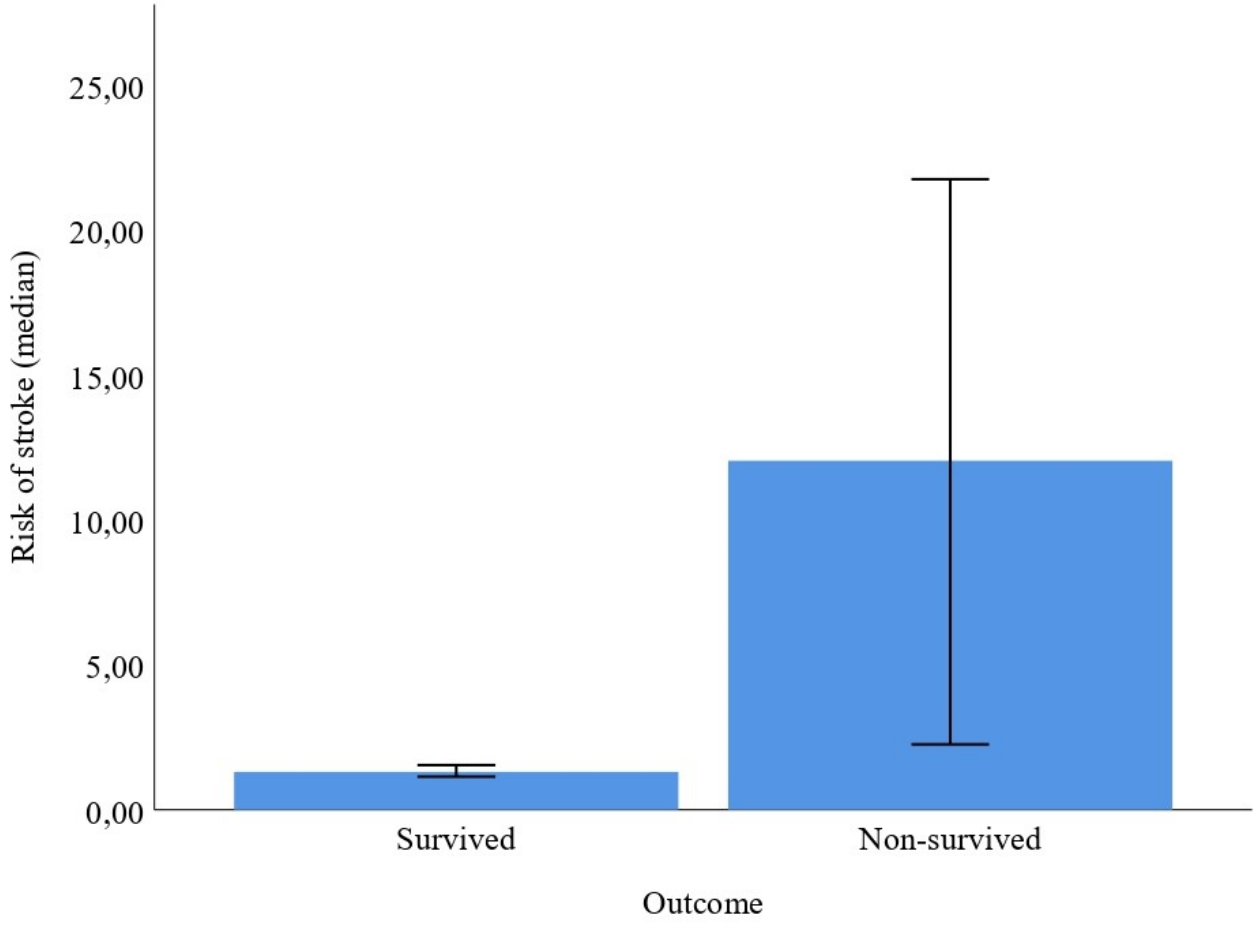
Risk of stroke (median)
Not severe
Severe
COVID-19 severity groups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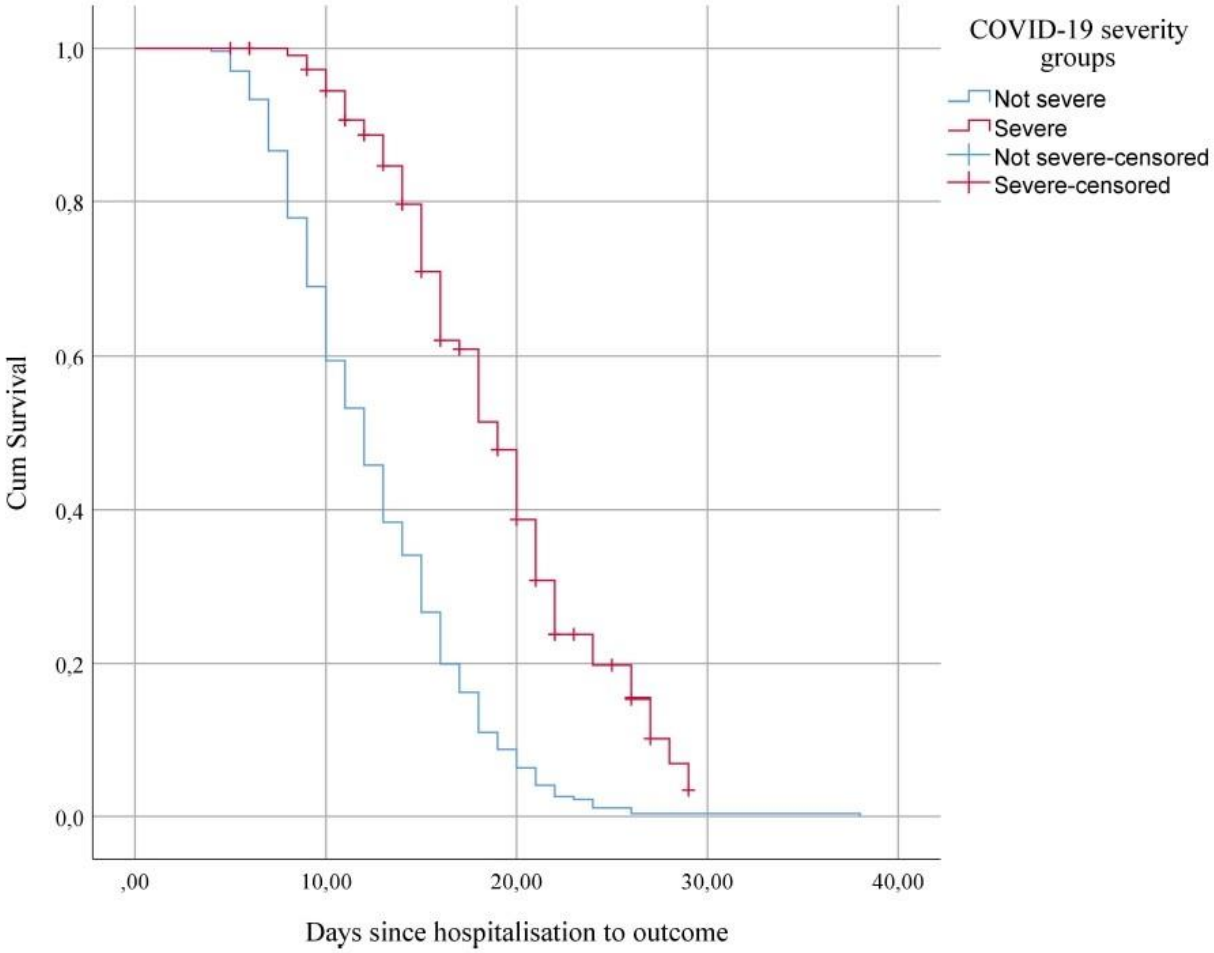
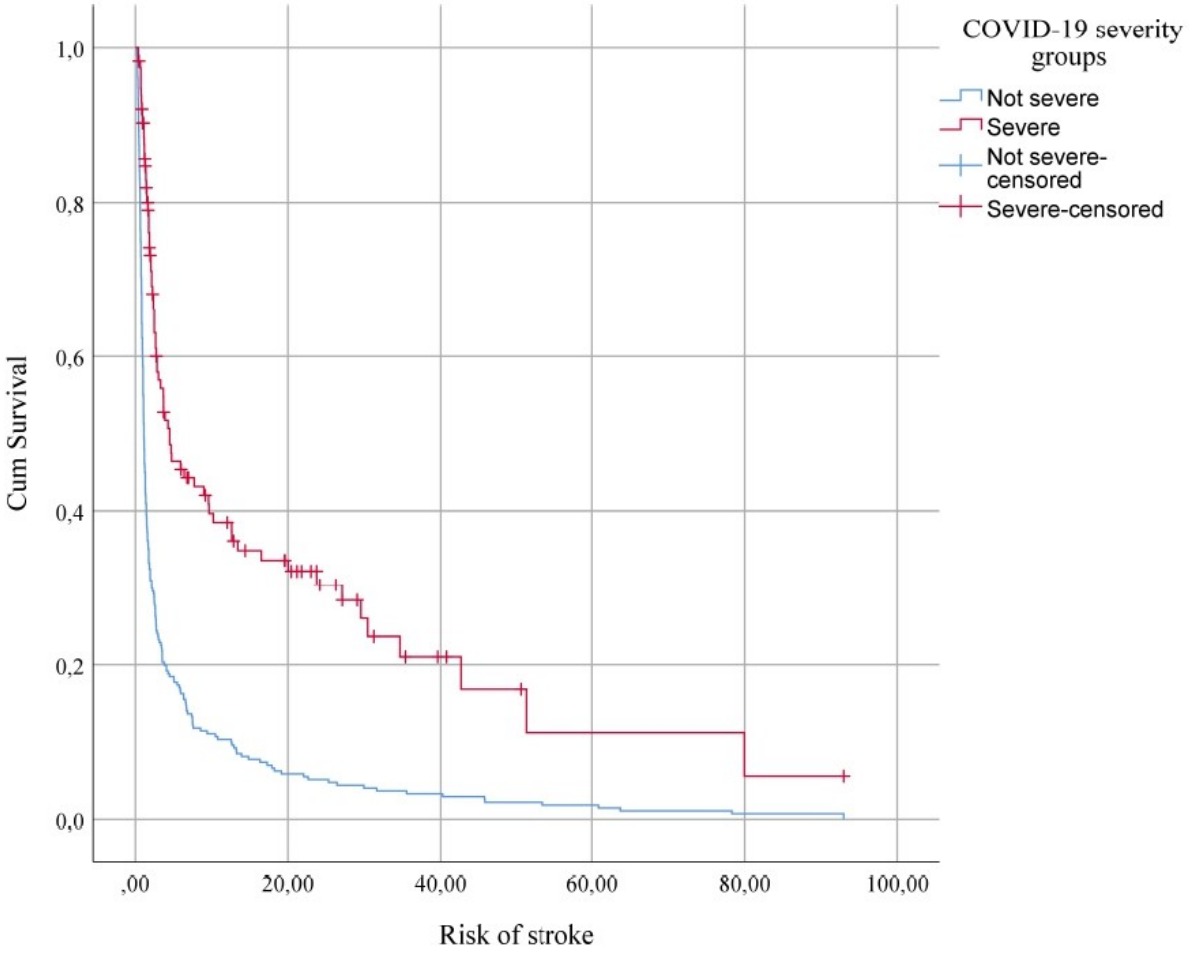
Survived
Non-survived
Outcome


COVID-19 severity groups
Not severe
Severe
Not severe-censored
Severe-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
10,00
20,00
30,00
40,00
Days since hospitalisation to outcome


COVID-19 severity groups
Not severe
Severe
Not severe-censored
Severe-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
20,00
40,00
60,00
80,00
100,00
Risk of stroke