

# Administration of Statins Can Improve Survival and Coagulation Function in Patients with Severe COVID-19 in Intensive Care Units: A Retrospective Study

**Tian-yu Wu**

Medical School of Nanjing University: Nanjing University Medical School

**Yun Zhou**

Huashan Hospital Fudan University

**Chao-fan Yang**

Medical School of Nanjing University: Nanjing University Medical School

**Wen-ting Ji**

Huashan Hospital Fudan University

**Yong Fang**

Huashan Hospital Fudan University

**Yi-jian Chen** (✉ [chenyijian@fudan.edu.cn](mailto:chenyijian@fudan.edu.cn))

Fudan University Huashan Hospital Institute of Antibiotics

**Yue Zhao**

Medical School of Nanjing University: Nanjing University Medical School

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## Research article

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# Abstract

**Background:** COVID-19 is a global epidemic posing threat to public health. Without specific drugs and therapies, it is important to evaluate the effectiveness of currently applicable drugs. This study was a retrospective analysis of the effect of the administration of statins on survival in patients with severe COVID-19.

**Design:** This study was a retrospective analysis of data collected in the ICU of Tongji Hospital affiliated with Tongji Medical College of Huazhong University of Science and Technology (HUST) during the COVID-19 outbreak. Data from 69 patients with severe COVID-19 treated in the ICU from February to March 2020 were collected for the analysis. Patients with severe COVID-19 were treated with the standard of care at the time, and some patients were also treated with statins.

**Results:** Sixty-four patients with complete records were enrolled in the final stage of analysis. Statin administration had a beneficial effect on the overall survival of the patients. The statin administration cohort had a significantly shorter activated partial thromboplastin time (aPTT) and prothrombin time (PT) according to t-tests. The aPTT and PT were also stable, as shown by locally weighted smoothing (LOESS) analysis. The use of statins combined with corticosteroids, anti-coagulants and anti-hypertensive drugs had a relatively greater effect on survival.

**Conclusions:** Statins can be therapeutic agents that may promote patient survival, possibly by improving coagulation function.

**Trial registration:** HIRB 2020-1119 September 11<sup>th</sup>, 2020, retrospectively registered.

## Background

Emerging pathogens pose threats to public health worldwide. Since the first cluster of coronavirus disease 2019 (COVID-19) patients was reported in Wuhan, China, in December 2019, this disease has caused over 1 million deaths globally(1). Before severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen responsible for COVID-19, was discovered, six coronavirus strains were known to cause human illness, and only 2 strains, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) resulting in mortality(2). Although the main target of SARS-CoV-2 is reported to be the respiratory system, dysfunction in other systems has been reported, including functional impairment of the cardiovascular system(3), renal system(4), and hepatic system(5). Severe COVID-19 cases have imposed a substantial burden on intensive care resources, and many characteristics of COVID-19 remain to be discovered(6). Therefore, it is very important to characterize patients who need to be treated in intensive care units (ICUs) and to evaluate the effectiveness of the current medical management of these patients.

Since the emergence of COVID-19, substantial efforts have been made to provide medical treatments that can inhibit viral replication and increase the probability of survival. While several drugs have been

developed, most are still in Phase-I/II clinical trials and are not yet ready for use in clinical practice(7). As the number of COVID-19 patients has increased, treatment protocols based on current therapies have been released to guide patient management, including respiratory support and drug treatments(8). As the progression of COVID-19 is a complicated pathophysiological process in which many metabolic pathways are affected and disrupted, one plausible strategy is to develop rational treatments to correct the metabolic disorders in patients with severe COVID-19 in the absence of specific, targeted antiviral treatments. A recently published proteomics and metabolomics study showed that lipids, including glycerophospholipids and sphingolipids, are downregulated in patients with severe COVID-19(9). This finding suggested that therapeutic agents targeting lipid metabolism could be effective treatments for COVID-19.

Statins are therapeutic agents that inhibit 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR). HMGCR is the key enzyme in the cholesterol biosynthesis pathway and in the biosynthesis pathways of prenylation agents, which are important in the posttranslational modification of multiple proteins and are capable of influencing protein trafficking and the activation of the Ras family(10). Since protein trafficking and interference in many cell signaling pathways are key factors in the life cycle of various viruses, statins have been proposed as antiviral therapies. With regard to influenza, statins have been proposed as therapies due to their disruption of multiple signal transduction pathways (STAT3, Rho/Rho kinase pathways, etc.)(11). A population-based study suggested that in patients infected with influenza viruses, treatment with statins is as efficacious as targeted therapy with oseltamivir or ribavirin(12). Statins have been shown to be effective against Ebola virus by disrupting glycoprotein processing(13). In the era of COVID-19, although the evidence regarding the effectiveness of statin therapy is limited, an *in silico* study showed that statins could directly interact with the main protease (Mpro), which suggests a direct inhibitory effect of statins on SARS-CoV-2(14). However, statins are known to have a myopathic effect and can induce diabetes mellitus(15). Therefore, it is very important to evaluate statin use in patients with severe COVID patients to provide better guidance for clinical practice.

## Methods

### Participants and study design

In this retrospective study, patients treated in the ICU of Tongji Hospital affiliated with Tongji Medical College of Huazhong University of Science and Technology (HUST) from February to March 2020 due to COVID-19 were enrolled in the analysis. These patients were admitted to the ICU when their oxygenation index was lower than 200, they experienced a disturbance of consciousness and/or the functions of organs other than those in the respiratory system were impaired. These parameters ensured that the baseline characteristics of these patients were wellbalanced. The data were collected after receiving the approval from the Ethics Committee of the medical school of Fu Dan University. We applied for exemption from the need to obtain informed consent for the use of data from nonsurviving patients and patients who could not be contacted after three attempts.

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# Data collection and preprocessing

The case histories were accessed, and the relevant information was collected using a standardized form and stored for further analysis. Information that could be used to personally identify individual patients, including names and identification numbers, were anonymized using a coding system. Basic data, including sex, age, survival status, follow-up duration, medical history, pulse, temperature, respiration rate, blood pressure, and oxygen saturation, were collected from the medical records. Biometric data, including blood test results, metabolic indexes (the levels of glucose, urea, creatine, and total cholesterol), hepatic function parameters (the levels of alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase), cardiac injury markers (the levels of high-sensitivity troponin, creatine kinase-MB, and N-terminal B-type natriuretic peptide), coagulation function parameters (the international normalized ratio (INR), prothrombin time, thrombin time, and D-dimer level) were collected from the laboratory reports. Drug use information was collected from the medical order records. The patients were then grouped according to the drugs used for further parallel analysis of the effect of statin administration.

The Acute Physiology And Chronic Health Evaluation II (APACHE II) score was used to represent the severity disease and the degree of associated damage(16). An experienced clinician who was directly involved in the care of these patients was asked to calculate the APACHE II score for each patient at the time of admission to the ICU and at the time of peak disease severity. The data from the patients who met our criteria were then stored in a database for further analysis.

## Data analysis

Julia and R programming languages were used for data analysis due to their excellent performance and stability. For each patient, the biometric values at the time of admission to the ICU were analyzed. Simple two-sided t-tests and Mann-Whitney tests were used to detect differences between the drug treatment groups. The peak values of the other biometric data, which reflected the worst condition of the patients, and the drug use information were integrated into the in-depth statistical analysis. Patients who were not severely ill according to their APACHE II score and those with missing drug treatment records or laboratory reports were excluded. To ensure the relevance of our conclusion to real-world clinical practice, no other exclusion criteria were applied.

The survival analysis was performed with the R package survminer(17). Cox regression was conducted to eliminate the possible interference of confounding covariates that were found to be significantly different between the drug treatment groups. Kaplan-Meier curves were then generated for the different drug treatment groups. In the survival analysis, the follow-up time was defined as the period from admission to the ICU to death or discharge from the ICU. Based on the drugs that were associated with improved survival, patients were classified into drug-use and control groups. Two-sided t-tests were conducted to compare the baseline information between the groups to ensure that the baseline information was

balanced. Then, to detect the effects of drug use on biometric values and organ function, two-sided t-tests and Mann-Whitney tests were conducted to evaluate the differences in laboratory test results between the groups. To better characterize the change in the distribution, density was plotted to show the width of the distribution. Alocally weighted regression (LOESS) model was utilized to visualize the dynamic changes in the parameters.

## Results

### Participants and pivotal analysis

We reviewed the records of 69 patients treated in the E3 area of the hospital's ICU from February to March. During the patient selection process, 4 patients were excluded, including 1 patient without severe COVID-19, 1 patient without confirmation of the diagnosis of COVID-19, and 2 patients with incomplete medical records. Therefore, 64 patients were included in the analysis(**Fig 1**).

Preliminary statistical analysis detected no significant differences in the survival of patients administered chloroquine, broad-spectrum antiviral drugs and antibiotics. However, statins administration was associated with significantly improved survival in patients with severe COVID-19 after adjustment for confounders (**Fig 2**), and the statins administration cohort had an adjusted hazard ratio (HR) for mortality of 0.34 compared with the control cohort( $p=0.02$ ).

Therefore, we found 11 patients with statins therapy(20mg atorvastatin qd/10mg rosuvastatin qd) prescribed to them in the ICU without previous statins application, while the other 53 were not prescribed with statins therapy. The analysis of the baseline laboratory parameters revealed no significant differences in any of the indexes, indicating that the baseline characteristics were well balanced(**Table S1**). Pearson's chi-square test did not show any significant differences, which meant that the two groups did not differ other than in the use of statins(**Table S2**).

### Statins and coagulation

#### Statins may improve prognosis by improving coagulation function

To investigate the effect of statins on patients with severe COVID-19, two-sided t-tests were conducted to determine the differences in biometric variables between the two groups. However, no differences were identified in physiological indexes, blood test results, liver function parameters, metabolic function parameters or cardiac function parameters between the statins group and the control group. However, three key indexes of coagulation, namely, the PT( $p=0.003$ , \*\*), INR( $p=0.005$ , \*\*) and aPTT( $p=0.005$ , \*\*), were significantly less in the statin group than in the control group(Fig 3(A), 3(B)). The differences in these three indexes suggest that the functionality of the intrinsic and extrinsic coagulation pathways was improved in the statin group. In addition, the distribution of the peak values were visualized with density plots in the two groups(Figure 3(C), 3(D)).

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## Dynamic profiles of coagulation function in the two groups

As the administration of drugs was initiated after the patients were admitted to the ICU, it was possible to investigate the dynamic changes in the biometric indexes. A LOESS model was used to characterize the changes in the PT, INR and aPTT because the distributions of the mean values over time did not adhere to standard distributions. PT trended upward over time in the statin group, while there was no clear trend in the control group (Figure S1(A)). However, in contrast with the stable change over time in the PT, which reflects the function of the extrinsic pathway, the statin group maintained a stable level of the aPTT, which reflects the function of the intrinsic pathway. In contrast, the aPTT rose sharply in the control group over time (Figure S1(B)).

## Combination therapy with statins and other drugs could maximize the survival benefit

Further analysis of the effect of the use of combinations of drugs on survival was conducted to identify the treatment strategy that could maximize survival in patients with severe COVID-19. HRs for mortality according to drug combinations are shown in **Table 1**. The Cox regression analysis showed that the combined use of statins and systemic corticosteroids, anticoagulants or antihypertensive drugs was associated with significantly reduced mortality (Figure S2). It can be inferred that these drugs enhanced the anti-inflammatory and anticoagulant effects of statins, leading to improved survival.

## Discussion

In the context of the rapidly spreading global COVID-19 pandemic, effective strategies for managing patients with severe COVID-19 involving currently available drugs are urgently needed. Statins are widely used in clinical practice; therefore, they represent a therapeutic option that would be readily available and inexpensive. This study evaluated the effect of the administration of statins on survival and various biometric indexes in patients with severe COVID-19, with additional analyses of combination therapy with statins and other drugs.

As indicated by the overall survival analysis, statins were associated with prolonged survival in patients with COVID-19. This result agrees with the findings in a recently published proteomics and metabolomics study, which showed that COVID-19 patients have severe disturbances in lipid metabolism and suggested that agents that can regulate lipid metabolism, including statins, are potential therapeutic options(9). Analysis of the biometric data suggested the importance of the anticoagulant effect of statins, which was consistent with the finding in a previous study that showed that statins can influence the gene expression of clotting factors(18). There have also been many reports on the anti-coagulant effects of statins. Coli et al. reported that statins can inhibit tissue factor (TF) in cultured human macrophages by preventing the production of mevalonate, thereby preventing the geranylgeranylation of proteins related to the activity of TF (19). It has also been found that statins can increase protein C promoter activity by loading [MathJax]/jax/output/CommonHTML/jax.js ac1, thus exerting anticoagulant effects(18). As statins can

inhibit the Rho pathway, they can mitigate platelet activation that is dependent on the Rho pathway(20). Moreover, the platelet activating factor(PAF) is an important factor in the formation of microthrombin in the process of DIC and plays a significant role in the development of DIC(21). It was also indicated that statins can inhibit the PAF both in vitro and in vivo(22).

Since disseminated intravascular coagulopathy (DIC) has been shown to be as one of the most common symptoms and leading causes of death in patients with severe COVID-19, the anticoagulant activity of statins may be very helpful in the medical management of these patients by slowing the exhaustion of clotting factors (23). Interestingly, the dynamic profiling showed that although statins did reverse coagulopathy, they stabilized the indexes, including the PT and aPTT, with a more pronounced effect on the latter. Although the extrinsic pathway is known to be the starting point of DIC, the role played by the intrinsic pathway is unknown. The factor XII-dependent pathway was reported to be associated with prognosis of patients with DIC (24). Therefore, the stabilizing effect of statins on the aPTT suggests that they can improve the function of the intrinsic pathway, thereby improving the prognosis of patients with severe COVID-19.

We then explored the various combinations of other drugs with statins and found that the simultaneous administration of statins with systemic corticosteroids, anticoagulants, and antihypertensive drugs resulted in significantly lower mortality in patients with severe COVID-19. This may be due to enhancement of the anti-inflammatory, anti-coagulation and cardiovascular protection effects of statins by drugs in these three classes. Corticosteroids, including dexamethasone, have been used because of their anti-inflammatory and immunomodulatory effects. A recent clinical trial of dexamethasone reported that corticosteroids reduced mortality(25), making the combined use of corticosteroids and statins more rational. Anti-coagulants are included in the standard protocol for the management of DIC, and the anti-clotting effect can be enhanced by the addition of statins. The enhanced effect of the combined use of anti-hypertensive drugs with statins may be due to the effect of statins on cardiomyopathy(15).

## Limitation

Given that this retrospective study was observational and not controlled, it was necessary to ensure that the baseline parameters were well balanced between the groups. First, the data were from the ICU in a single center, which meant that regional differences could not be considered. Second, as the standardized records started at the time of admission to the ICU from other wards or other hospitals, the medical history before ICU admission strongly depended on verbal patient self-reported data, which may have affected the baseline analysis. Third, the sample size was limited, as is often true for single-center studies, we have to warn that there were only 11 patients with statins admission found in the data we obtained. Therefore, sample population may not be representative of all patients with severe COVID-19. The limited sample size also affected feature extraction. Large-scale cohort studies or randomized clinical trials are still needed to verify these findings.

In conclusion, statins can be a valid therapeutic option for the management of patients with severe COVID-19 in the ICU due to their effects on survival, which may be attributable to their stabilization of coagulation. Statins combined with anticoagulants, antihypertensive drugs and systemic corticosteroids were observed to have a better effect on promoting the survival.

## Abbreviations

COVID-19: Corona Virus Disease 2019

ICU: intensive care unit

aPTT: activated partial thromboplastin time

PT: prothrombin time

LOESS: locally weighted smoothing

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

MERS-CoV: Middle East respiratory syndrome respiratory syndrome coronavirus

HMGCR: 3-hydroxy-3-methylglutaryl-CoA reductase

Mpro: main protease

HUST: Huazhong University of Science and Technology

APACHE: the Acute Physiology And Chronic Health Evaluation

INR: international normalized ratio

## Declarations

### Ethics approval and consent to participate

This work was conducted with the approval of the Ethics Committee of Huashan Hospital affiliated with Fudan University (registration number: HIRB 2020-1119). As some of the patients were deceased or could not be contacted, we applied for an exemption from the need to obtain informed consent for the use of these patients' data. The exemption from the consent was agreed by the Ethics Committee of Huashan Hospital affiliated with Fudan University.

### Consent for publication

Not applicable.

## Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to regulation of the ethics approval for the sake of privacy of the patients, but are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interests.

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## Author's contributions

YZ obtained, initially coded and interpreted the data with the help of WTJ, YF and YJ. TYW rearranged the data and conducted whole analysis process with the help of YZ and YCF, while supervised by YZ and YJC for rationality of the analysis. TYW and YZ drafted the manuscript, with YZ and YJC substantively revised. All the authors have approved the submitted version and agreed to be personally accountable for the author's own contributions.

## Acknowledgements

Not applicable.

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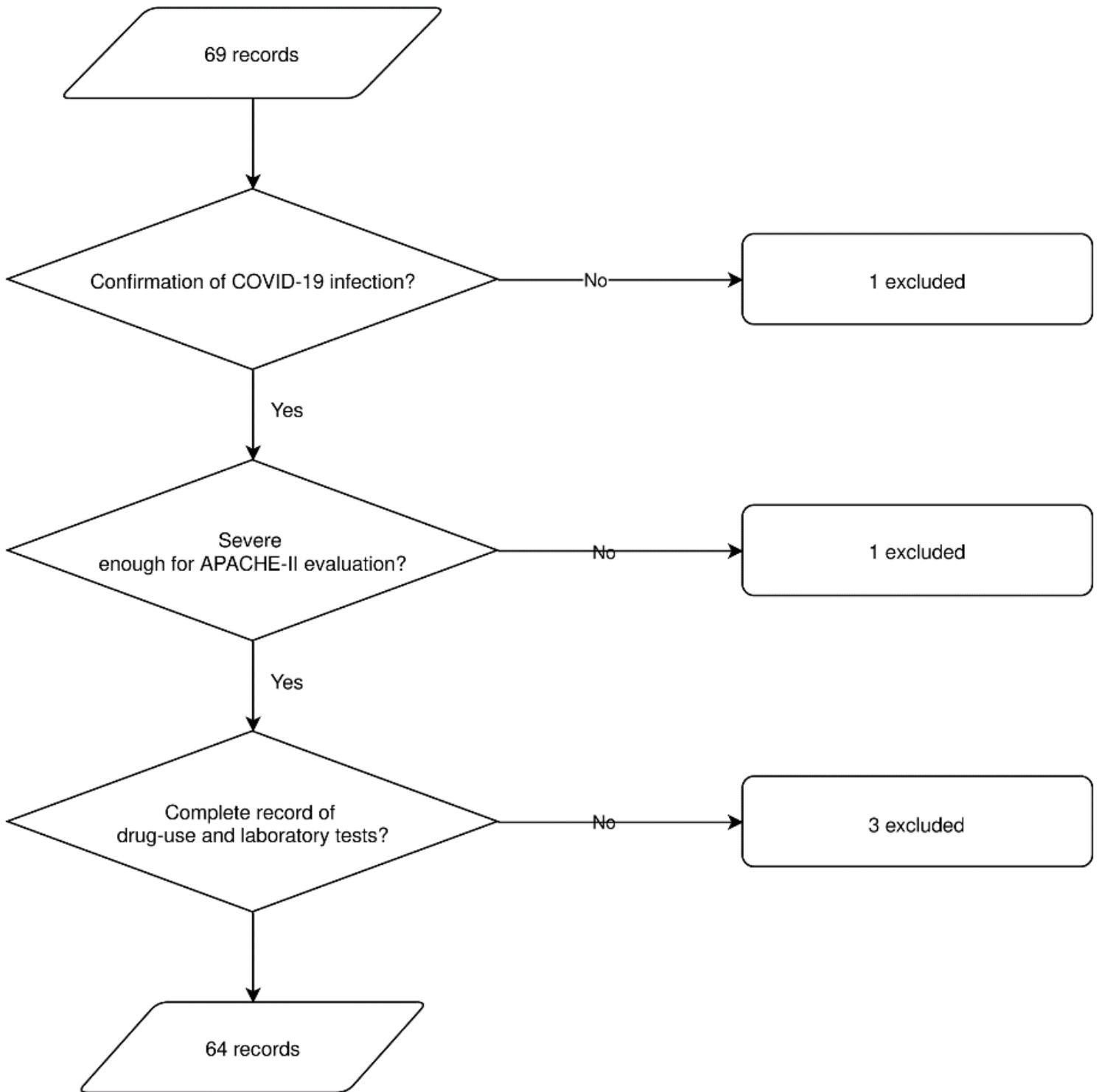
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## Tables

Table 1: HR values according to Cox regression for the use of drug combinations

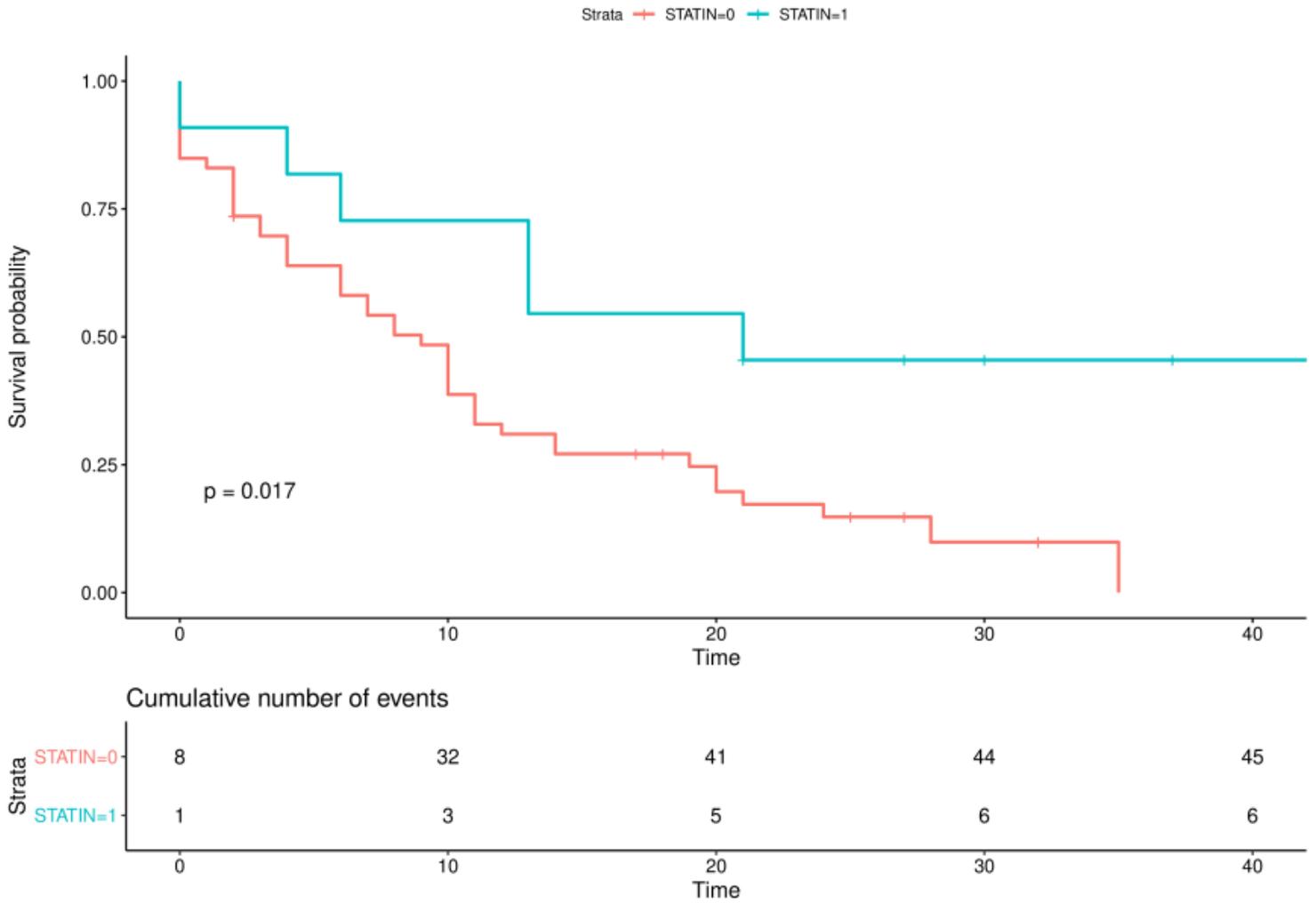
Drugs	HR	95%CI	P-value
Statins &traditional Chinese medicine	0.37	(0.05, 2.77)	0.335
Statins &respiratory regulation drugs	0.36	(0.13, 1.01)	0.051
Statins &vasoactive drugs	0.65	(0.20, 2.10)	0.475
Statins &broad-spectrum antivirals	0.51	(0.07, 3.70)	0.505
Statins &antifungals	3.78e-8	(0, +∞)	0.996
Statins &antibiotics	0.39	(0.14, 1.10)	0.075
Statins &systemic corticosteroids	0.24	(0.06, 0.98)	0.046(*)
Statins &immunoglobulins	0.19	(0.03, 1.40)	0.104
Statins &anticoagulants	0.30	(0.11, 0.86)	0.025(*)
Statins &antihypertensives	0.18	(0.04, 0.74)	0.018(*)
Statins &insulin	0.50	(0.15, 1.62)	0.247

## Figures



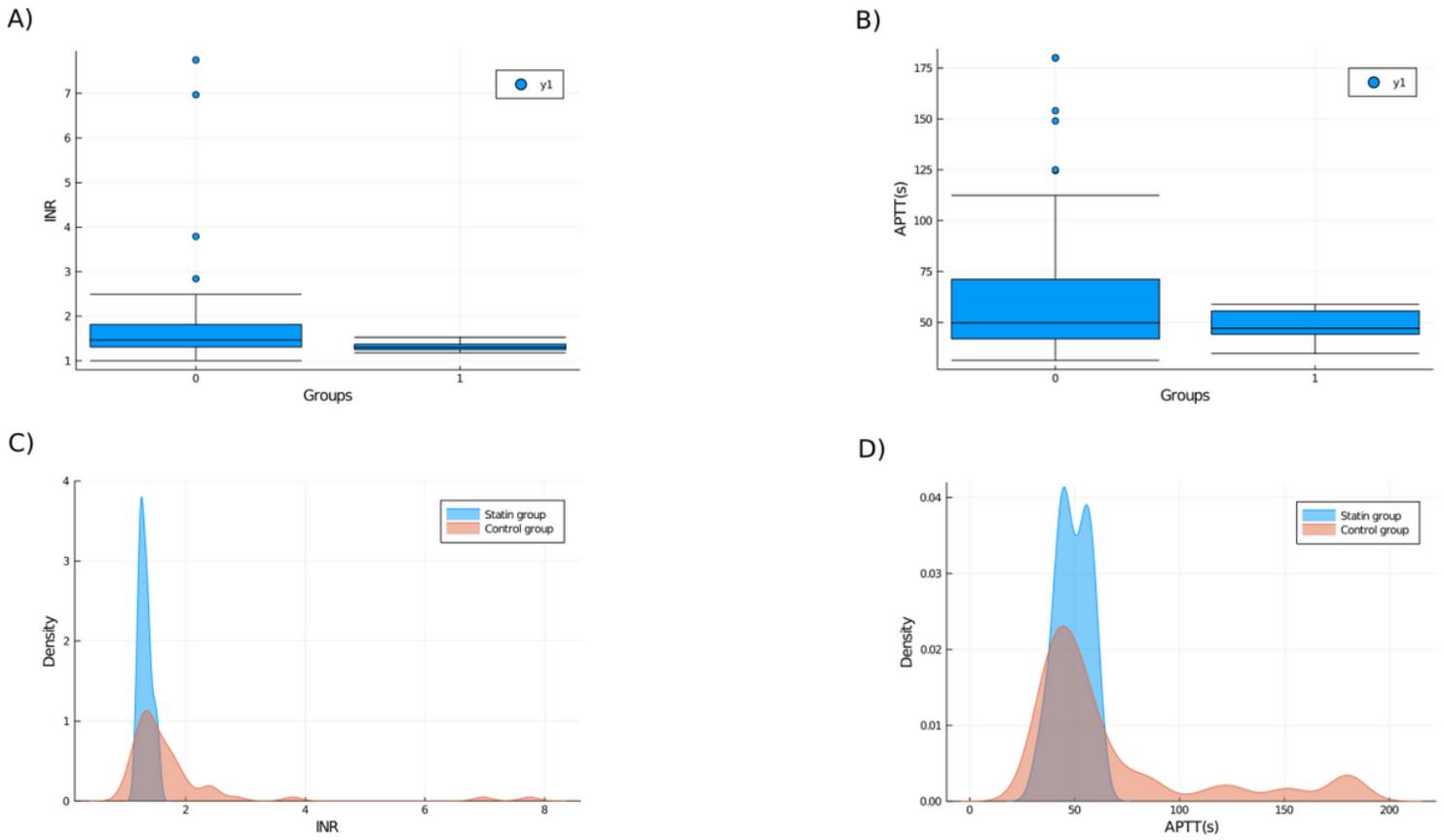
**Figure 1**

Patient enrollment diagram



**Figure 2**

Kaplan-Meiersurvival analysis of the statin group and control group



**Figure 3**

Profiling of the coagulation function between the control group and the statins administration group

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [FigS1.pdf](#)
- [FigS2.pdf](#)
- [SupplementaryMaterial.docx](#)