SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

The International Survey of Acute Coronary Syndromes (ISACS) COVID-19.

In response to the COVID-19 crisis, ISACS-TC (International Survey of Acute Coronary Syndromes in Transitional Countries; NCT01218776)[37] has promoted a new registry including the existing and additional centres from the same geographic areas to support clinical research to prevent, and treat the COVID-19 illness. (International Survey of Acute Coronavirus Syndromes-COVID-19 [ISACS COVID-19], NCT05188612)

The characteristics of each active enrolling centre are described below.

Characteristics of centers included in ISACS COVID-19, stratified by country

Center name	City	Total capacity	ICU capacity	Center type
Italy				
IRCCS Azienda Ospedaliero-Universitaria di Bologna, St Orsola University Hospital	Bologna	≥450	0-20	Academic Hospital
AOU Policlinico "Gaetano Martino"	Messina	≥450	20-60	Academic Hospital
Macedonia				
University Clinic for infectious diseases	Skopje	0-150	0-20	Academic Hospital
University Clinic for cardiology	Skopje	0-150	0-20	Academic Hospital
PHI Specialised Hospital for Geriatric and Paliative medicine	Skopje	150-300	0-20	Non-Academic Hospital
Institute of Respiratory Diseases in Children - Kozle	Skopje	0-150	0-20	Non-Academic Hospital al
Specialized hospital for prevention, treatment and rehabilitation of cardiovascular diseases	Ohrid	0-150	0-20	Non-Academic Hospital
Serbia				

Hospital Medical Center Bezanijska kosa	Belgrade	150-300	20-60	Academic Hospital
Clinic for Anesthesia, Covid Hospital Batajnica,	Belgrade	≥450	≥60	Non-Academic Hospital
University Clinical Center Nis	Nis	≥450	≥60	Academic Hospital
Institute for Cardiovascular Diseases Dedinje	Belgrade	0-150	20-60	Academic Hospital
Clinical Center of Serbia	Belgrade	≥450	≥60	Academic Hospital
Institute for cardiovascular Diseases Sremska Kamenica	Novi Sad	150-300	20-60	Academic Hospital
Clinical Hospital Center Dragiša Mišović	Belgrade	300-450	20-60	Academic Hospital
Romania				
Emergency Clinical Hospital of Bucharest	Bucharest	≥450	20-60	Academic Hospital
Croatia				
University Hospital Centre Zagreb	Zagreb	≥450	≥60	Academic Hospital
University Hospital Dubrava	Zagreb	≥450	20-60	Academic Hospital

Definition of conventional risk factors and pre-existing comorbidities

Smoking habits were self-reported. We defined current smokers as individuals who smoked 100 cigarettes in his or her lifetime and who smoked cigarettes, cigars, and cigarillos at the time of the index event. Participants who have smoked at least 100 cigarettes in their lifetime but who were not active smokers at the time of the index event were labelled as former smokers regardless of time since they quit.[38] Former smokers were defined as those patients who had a history of tobacco smoking, but were not active smokers at the time of the index event. Hypertension, hypercholesterolemia, and diabetes mellitus were assessed by documentation of medical history prior to admission in the database. Obesity was defined as a BMI ≥ 30.0 kg/m2 according to World Health Organization.[39]. Chronic Kidney disease was defined as a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration creatinine equation or need for dialysis.[40]. Active cancer was defined as cancer diagnosed within the previous six months, recurrent,

regionally advanced or metastatic cancer, anti-cancer treatment administered within six months, or haematological cancer with incomplete remission.[41] Diagnosis of dementia was based on clinical evaluation. It required a history of cognitive decline and impairment in daily activities, with corroboration from a close friend or family member, and a mental status examination by a clinician to delineate impairments in memory, language, attention, visuospatial cognition, executive function, and mood.[42] The types of chronic lung conditions that were diagnosed in our population included exclusively asthma and chronic obstructive pulmonary disease.

Data on laboratory values

All participants underwent venous blood sampling on hospital admission. Reference values are reported below.

Reference values for laboratory testing

	Reference values
Laboratory findings on hospital admission	
Leukocyte count, (10^9/L)	4.0-11.0
Hemoglobin, (g/dL)	Male=13.5 - 17.2
	Female=11.8 – 15.8
Platelet count, (10^9/L)	160 - 370
Serum creatinine levels, (mg/dL)	0.50 – 1.20
Peak laboratory findings during hospitalization	
C-reactive protein, (mg/dL)	<0.5
Aspartate aminotransferase, (U/L)	Male <50, Female <35
Alanine aminotransferase, (U/L)	Male <50, Female <35
Lactate dehydrogenase, (U/L)	<248
D-dimer, (ng/mL)	<0.55

Multiple Imputation using Chained Equation (MICE) algorithm

Multiple Imputation using Chained Equation (MICE) algorithm is an efficient and popular method to fill in missing data where each missing value on some records is replaced by a value obtained from

related cases in the whole set of records. Thus, imputation for clinical features was conducted using the chained equations across other features.[19] More specifically, MICE algorithm sequentially imputes the missing values of clinical features based on both observed values and previously imputed values. This sequential imputation is conducted via chained equations.

We tried multiple imputations using the MICE algorithm for the initial analyses to address the uncertainty in the imputation process. More specifically, we generated multiple imputed datasets and check whether the conclusions are consistent across the different imputed datasets. If the conclusions are consistent across multiple imputed datasets, we use a single imputed dataset (by MICE algorithm) as the final dataset to report the results of statistical analyses in the paper.

Inverse Propensity Score Weighting Analysis

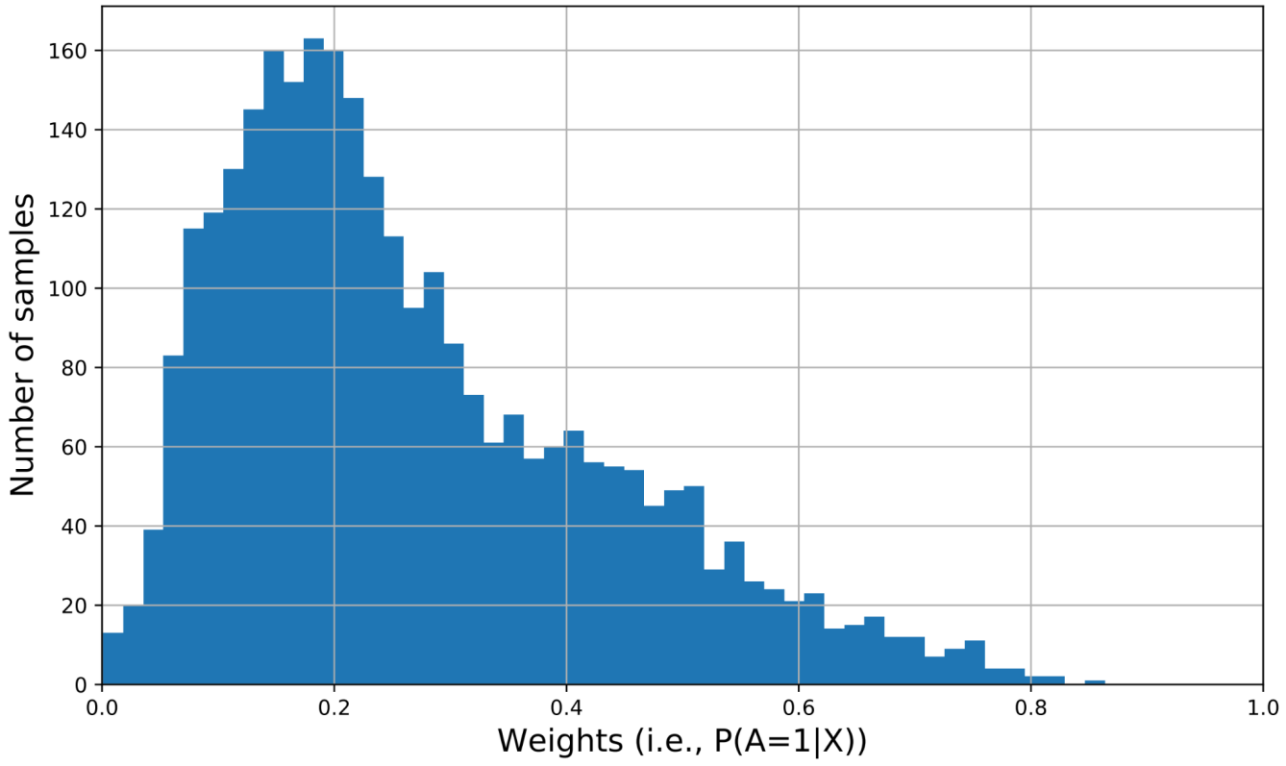
We used Inverse Propensity Score Weighting (IPW) to balance the distribution of covariates between two patient groups. Note that we use Logistic Regression to estimate the propensity scores ({P}(Z=1 | x)) If *e* denotes the estimated propensity score (i.e. e=\hat{P}(Z=1 | x), where the patient x is included in patient group 1; then, 1-e = \hat{P}(Z=0 | x)), then the original sample is weighted by the following weights: Z/e+(1−Z)/ 1−e where Z represents the patient group. For instance, women (Z=1) are assigned a weight equal to the reciprocal of the propensity score (1/e), while men (Z=0) are assigned a weight equal to the reciprocal of one minus the propensity score (1/1-e). The weighting procedure for each sample balances the covariate distributions between two patient groups.[20]

In details, we computed the propensity scores using logistic regression: (i) coefficients of the terms were used, (ii) we did not use the interaction terms between variables, (iii), we checked that the distributions of each feature were well distributed between two groups after inverse propensity score weighting using standardized differences.

Coefficients of terms used in the propensity score estimation	
Intercept	-1.2251
Female sex	-0.0182
Age, mean (SD)	0.0075
Cardiovascular risk factors	
Diabetes	0.1927
Hypertension	-0.1072
Hypercholesterolemia	0.1835
Current smoking	0.1686
Former smoking	0.2187
Obesity	0.0956
Comorbidities	
Chronic kidney disease	0.3288
Chronic lung conditions	0.1004
Active cancer	0.0480
Dementia	0.0837
Clinical features on admission	
X-ray/ CT signs of interstitial pneumonia	-0.2536
WBC count on admission, 10^9/L [mean (SD)]	-0.0269
Hb on admission, g/dL [mean (SD)]	-0.0227
Platelet count on admission, 10^9/L [mean (SD)]	0.0008
Serum creatinine on admission, mg/dL [mean (SD)]	-0.1404
CRP, mg/dL [mean (SD)]	-0.0087
D-dimer, ng/mL [mean (SD)]	0.0067
AST, U/L [mean (SD)]	0.0003
ALT, U/L [mean (SD)]	-0.0007

LDH, U/L [mean (SD)]	-0.0003
In-hospital treatment	
Darunavir	0.0804
Lopinavir/Ritonavir	-0.7288
Remdesivir	-0.1317
Hydroxychloroquine	1.0842
Corticosteroids	0.0255
Oral anticoagulants	-0.2066
Heparin	0.1816
Antiplatelet treatment	-0.5033
β-lactam antibiotics	0.9770
Sulfonamides	-0.2771
Diuretics	-0.7265

The weight distributions (P(A=1|X)) is described below in terms of the histogram



Inverse probability of treatment weighting method can potentially result in unstable and biased estimates if some of the weights are very high. To avoid excessive weights, we compared results with other methods for handling confounding. We included probability of treatment variables in a multivariable model. We also used XGBoost, a decision-tree-based ensemble machine learning algorithm, as an alternative multivariable model for estimating the probability of treatment. Conclusions from theses analyses were the same as our current results. Further, we created a threshold for weights to avoid the impacts of the outliers (we use 0.01 as threshold). Therefore, the inverse probability of treatment weighting analyses presented in the current analysis were quite stable.

Computation of Relative Risk and its Confidence Interval

In a two-group cohort study, the risk ratio (RR, also called relative risk), is usually applied to compare risks of a health event between two independent binomial populations that differ by a demographic characteristic (i.e. sex, age) or by the level of exposure to a specific drug or risk factor. In such types of studies, data can be summarized in a confusion matrix as follows:

	Risk of Designated Outcome		
	Yes	**No**	**Total**
Exposed	a	b	a+b (H_1)
Unexposed	c	d	c+d (H_0)
Total	a+c	b+d	

Where H_1 and H_0 correspond to the total number of exposed and unexposed patients, respectively, whereas a and c represent the number of exposed and unexposed patients at risk for the designated outcome, respectively.

RR is defined as the ratio between the risk of outcome in exposed patients (H_1) and the risk of outcome in unexposed patients ($H_{0,}$) which can be summarized as:

$$RR = \frac{\left({}^{a}/_{H_1}\right)}{\left({}^{c}/_{H_0}\right)}$$

When applying this equation to an IPTW balanced population, ${}^{a}/_{H_1}$ will be assigned a weight equal to the reciprocal of the propensity score $\left(\frac{1}{e}\right)$ and ${}^{c}/_{H_0}$ will be weighted by the reciprocal of one minus the propensity score ($\frac{1}{(1-e)}$).

In order to compute the lower and upper (1-α) confidence limit RR_L for RR, we operate in the assumption of log normal distribution.[43] In particular, the variate $\log\frac{\left({}^{a}/_{H_1}\right)}{\left({}^{c}/_{H_0}\right)} = \log {}^{a}/_{H_1} - \log {}^{c}/_{H_0}$ is approximately normally distributed with approximate mean log(RR) and estimated variance $\frac{1-\left({}^{a}/_{H_1}\right)}{a} + \frac{1-({}^{c}/_{H_0})}{c}$.

It follows that RR_L can be computed by solving the following equation:

$$\frac{\left[\log(\frac{{}^{a}/_{H_1}}{{}^{c}/_{H_0}}) - \log(RR_L)\right]}{\left[\frac{1-\left({}^{a}/_{H_1}\right)}{a} + \frac{1-({}^{c}/_{H_0})}{c}\right]^{1/2}} = z_{1-\alpha}$$

Where $z_{1-\alpha}$, is the 100(1-α) percentage point of the N(O, 1) distribution

Comparison of means and prevalences in the weighted sample

To evaluate the balance of the baseline covariate distributions between treatment and control groups, standardized difference (SD) is widely used in inverse probability of treatment weighting (IPTW) framework. For the baseline analysis, we use standard SD which is defined as follows: $\frac{m_t - m_c}{\sqrt{\frac{s_t^2 + s_c^2}{2}}}$ for continuous variables and $\frac{m_t - m_c}{\sqrt{\frac{m_t(1-m_t)+m_c(1-m_c)}{2}}}$ for binary variable where m_t, m_c are sample mean of the

variables for treatment and control group, and s_t^2, s_c^2 are sample variance of the variables for treatment and control group, respectively. For IPTW analysis, we use weighted SD where m_t, m_c are replaced to weighted sample mean of the variables for treatment and control group, and s_t^2, s_c^2 are replaced to weighted sample variance of the variables for treatment and control group, respectively. Weights are determined by the inverse probability of treatment received. In general, 0.1 is the reasonable threshold to determine whether two distributions are balanced (i.e., if SD > 0.1, the baseline covariate is imbalanced).[21]

Interaction test

The comparison of two estimated quantities, each with its standard error, is a general method that can be applied widely. We compared the risk ratios of primary and secondary outcomes from subgroups stratified by use of azithromycin. These measures were always analyzed on the log scale because the distributions of the log ratios tend to be closer to normal than of the ratios themselves. If the estimates are *E*1 and *E*2 with standard errors SE(*E*1) and SE(*E*2), then the difference *d*=*E*1 - *E*2 has standard error SE(*d*)=Ö[SE(*E*1)2 + SE(*E*2)2] i.e., the square root of the sum of the squares of the separate standard errors. The ratio *z*=*d*/SE(*d*) gives a test of the null hypothesis that in the population the difference *d* is zero, by comparing the value of *z* to the standard normal distribution. The 95% confidence interval (CI) for the difference is *d*-1.96SE(*d*) to *d*+1.96SE(*d*).[11] Bland and Altman are explicit in explaining that the method they describe only applies to comparisons of two independent estimates.[22] As documented in our interaction test results, the two groups are "disjoint" and each estimate (both mean and confidence interval of RR) is independently computed. For example, as can be observed in **Table S5**, Group 1 is represented by patients with preexisting cardiovascular disease and Group 2 by patients without preexisting cardiovascular disease. The two groups are completely disjoint and there are no common individuals. Furthermore, the mean and confidence interval of RR for each group was computed independently as shown in Table 3 and Table 4. Therefore, those are

not relied on the same covariate adjustment. As such, the two estimates were independent as required by the interaction test proposed by Bland and Altman.

SUPPLEMENTAL RESULTS

Interaction tests

We tested **(Table S5)** whether there is a significant interaction between risk ratios (azithromycin users versus non-users) for 30-day mortality derived from separate analyses: patients with and without preexisting cardiovascular disease. We obtained the logs of the risk ratios and their confidence intervals (rows 2 and 4). As 95% confidence intervals were obtained as 1.96 standard errors (SE) either side of the estimate, the SE of each log relative risk was obtained by dividing the width of its confidence interval by 2×1.96 (row 6). The estimated difference in log relative risks was *d*=E1- E2= 0.50 (row 7) and its standard error 0.23 (row 8). From these two values, we tested the interaction and estimated the ratio of the relative risks (with confidence interval). The test of interaction was the ratio of *d* to its standard error: z= 2.22, which gave a P value 0.01 when we referred it to a table of the normal distribution (row 10). The estimated interaction effect was exp =1.65 (row 11). The confidence interval for this effect was 0.06 to 0.94 on the log scale (row 9). Transforming back to the relative risk scale, we got 1.06 to 2.57 (row 12). We repeated the interaction test for the outcomes of acute heart failure **(Table S6).**

Table S1. Outcomes stratified by use of azithromycin

Outcome	Azithromycin N=793	No Azithromycin N=2,141	Standardized difference
Primary outcome: 30-day mortality, n (%)	134 (16.9)	483 (22.6)	-0.1426
Risk Ratio (95% CI)	0.70 (0.56 - 0.86)		-0.1426
Secondary outcome: AHF, n (%)	68 (8.6)	185 (8.6)	-0.0023
Risk Ratio (95% CI)	0.99 (0.74 - 1.33)		-0.0023

Table S2. Outcomes stratified by use of azithromycin; patients with prior cardiovascular disease

Outcome	Azithromycin N=292	No Azithromycin N=774	Standardized difference
Primary outcome: 30-day mortality, n (%)	77 (26.4)	228 (29.5)	-0.0689
Risk Ratio (95% CI)	0.86 (0.63 - 1.16)		-0.0689
Secondary outcome: AHF, n (%)	48 (16.4)	134 (17.3)	-0.0233
Risk Ratio (95% CI)	0.94 (0.65 - 1.35)		-0.0233

Table S3. Outcomes stratified by use of azithromycin; patients without prior cardiovascular disease

Outcome	Azithromycin N=501	No Azithromycin N=1,367	Standardized difference
Primary outcome: 30-day mortality, n (%)	57 (11.4)	255 (18.7)	-0.2048
Risk Ratio (95% CI)	0.56 (0.41 - 0.76)		-0.2048
Secondary outcome: AHF, n (%)	20 (4.0)	51 (3.7)	0.0136
Risk Ratio (95% CI)	1.07 (0.63 - 1.81)		0.0136

Table S4. Inverse probability of treatment weighting: clinical factors associated with outcomes. Results stratified by use of azithromycin or absence of antibiotic treatment

	Azithromycin N=793	**No Antibiotics N=775**	**Standardized difference**
Female sex	44.1	45.2	-0.02
Age, mean (SD)	64.8 (16.0)	64.8 (16.3)	0.005
Cardiovascular risk factors			
Diabetes	24.9	24.8	0.002
Hypertension	62.0	62.2	-0.005
Hypercholesterolemia	32.5	32.0	0.01
Current smoking	9.6	9.6	-0.0008
Former smoking	15.4	15.3	0.002
Obesity	21.6	21.4	0.003
Comorbidities			
Chronic kidney disease	12.9	12.0	0.02
Chronic lung conditions	10.8	10.7	0.003
Active cancer	14.4	14.7	-0.008
Dementia	11.9	12.0	-0.003
Clinical features on admission			
X-ray/CT signs of interstitial pneumonia	54.5	54.0	0.01
Lab testing			
WBC count on admission, 10^9/L [mean (SD)]	8.3 (4.59)	8.3 (6.4)	-0.01
Hb on admission, g/dL [mean (SD)]	12.8 (2.2)	12.9 (2.2)	-0.04
Platelet count on admission, 10^9/L [mean (SD)]	229.6 (114.3)	234.5 (103.3)	-0.04
Serum creatinine on admission, mg/dL [mean (SD)]	1.3 (1.5)	1.1 (1.1)	0.05
CRP, mg/dL [mean (SD)]	9.4 (8.7)	9.0 (8.6)	0.04
D-dimer, ng/mL [mean (SD)]	3.4 (7.6)	3.4 (8.2)	-0.007
AST, U/L [mean (SD)]	90.9 (285.6)	94.7 (305.3)	-0.01
ALT, U/L [mean (SD)]	76.1 (150.8)	78.9 (191.6)	-0.01
LDH, U/L [mean (SD)]	447.2 (543.5)	445.6 (474.5)	0.003
In-hospital treatment			
Darunavir	0.8	0.3	0.06

Lopinavir/Ritonavir	1.7	1.9	-0.01
Remdesivir	12.7	10.9	0.05
Hydroxychloroquine	18.2	16.2	0.05
Corticosteroids	56.6	55.5	0.02
Oral anticoagulants	11.1	11.3	-0.006
Heparin	77.7	78.1	-0.007
Antiplatelet treatment	21.4	21.9	-0.01
Diuretics	27.0	26.7	0.005
Outcomes			**P value**
Primary outcome: 30-day mortality	17.1	16.9	0.903
Risk Ratio (95% CI)	1.02 (0.78 – 1.32)		0.903
Secondary outcome: AHF	10.0	6.7	0.019
Risk Ratio (95% CI)	1.54 (1.07 – 2.22)		0.020

Data are reported as % or mean (SD), unless otherwise stated.

Abbreviations: AHF=Acute heart failure; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; CRP= C-reactive protein; CT=computed tomography; Hb= Hemoglobin; LDH= Lactate dehydrogenase; WBC=White blood cells

Table S5. Interaction test: calculations for comparing two estimated risk ratios (Azithromycin users versus non-users) for 30-day mortality using inverse probability of treatment weighting: preexisting cardiovascular disease vs no prior cardiovascular disease

		Group 1 **[Pre-existing cardiovascular disease]** **(Patients n = 1,064)**	**Group 2** **[No prior cardiovascular disease]** **(Patients n = 1,867)**
1	**RR**	0.94	0.57
2	**log RR**	-0.06	-0.56
3	**95% CI for RR**	0.69 – 1.28	0.42 – 0.79
4	**95% CI for log RR**	-0.37-0.25	-0.87-(-0.24)
5	**Width of CI**	0.62	0.63
6	**SE (=width / (2*1.96))**	0.16	0.16
	Difference between log risk ratios		
7	**d (=$E_1 - E_2$)**	0.50	
8	**SE (d)**	0.23	
9	**CI (d)**	0.06-0.94	
10	**Test of Interaction**	2.22 **(P value: 0.01)**	
	Ratio of risk ratios		
11	**RRR (=exp(d))**	1.65	
12	**CI (RRR)**	1.06-2.57	

Table S6. Interaction test: calculations for comparing two estimated risk ratios (Azithromycin users versus non-users) for acute heart failure using inverse probability of treatment weighting: preexisting cardiovascular disease vs no prior cardiovascular disease

		Group 1 **[Pre-existing cardiovascular disease]** **(Patients n = 1,064)**	**Group 2** **[No prior cardiovascular disease]** **(Patients n = 1,867)**
1	**RR**	1.48	1.23
2	**log RR**	0.39	0.21
3	**95% CI for RR**	1.06 – 2.06	0.75 – 2.04
4	**95% CI for log RR**	0.06-0.72	-0.29-0.71
5	**Width of CI**	0.66	1
6	**SE (=width / (2*1.96))**	0.17	0.26
	Difference between log risk ratios		
7	**d (=$E_1 - E_2$)**	0.19	
8	**SE (d)**	0.31	
9	**CI (d)**	-0.42-0.79	
10	**Test of Interaction**	0.60 **(P value: 0.27)**	
	Ratio of risk ratios		
11	**RRR (=exp(d))**	1.20	
12	**CI (RRR)**	0.66-2.19	

Table S7. Inverse probability of treatment weighting: acute respiratory failure and acute kidney injury in the overall population stratified by use of azithromycin.

	Azithromycin N=792	**No Azithromycin N=2,141**	**Standardized difference**
Female sex	42.5	43.0	-0.01
Age, mean (SD)	65.0 (15.6)	64.8 (15.9)	0.01
Cardiovascular risk factors			
Diabetes	25.5	25.5	-0.001
Hypertension	64.7	62.7	0.04
Hypercholesterolemia	31.5	29.0	0.05
Current smoking	10.4	9.7	0.02
Former smoking	14.0	15.0	-0.03
Obesity	23.4	23.2	0.01
Comorbidities			
Chronic kidney disease	13.8	12.4	0.04
Chronic lung conditions	11.7	12.1	-0.01
Active cancer	14.3	14.3	0.002
Dementia	10.2	11.0	-0.03
Clinical features on admission			
X-ray/ CT signs of interstitial pneumonia	65.2	66.4	-0.02
Lab testing			
WBC count on admission, 10^9/L [mean (SD)]	8.4 (4.4)	8.5 (6.6)	-0.02
Hb on admission, g/dL [mean (SD)]	13.0 (2.1)	13.0 (2.1)	-0.02
Platelet count on admission, 10^9/L [mean (SD)]	231.5 (113.9)	231.7 (106.7)	-0.002
Serum creatinine on admission, mg/dL [mean (SD)]	1.3 (1.5)	1.2 (1.0)	0.07
CRP, mg/dL [mean (SD)]	11.1 (9.9)	11.0 (10.0)	0.01
D-dimer, ng/mL [mean (SD)]	4.0 (9.8)	3.9 (8.5)	0.02
AST, U/L [mean (SD)]	97.6 (271.9)	107.9 (370.9)	-0.03
ALT, U/L [mean (SD)]	80.9 (118.7)	87.9 (267.3)	-0.05

LDH, U/L [mean (SD)]	500.9 (533.2)	532.1 (596.1)	-0.06
In-hospital treatment			
Darunavir	1.2	1.0	0.02
Lopinavir/Ritonavir	2.6	2.4	0.01
Remdesivir	9.9	10.3	-0.01
Hydroxychloroquine	16.8	16.9	-0.002
Corticosteroids	62.6	64.5	-0.04
Oral anticoagulants	11.6	10.8	0.03
Heparin	81.5	83.1	-0.04
Antiplatelet treatment	24.9	21.7	0.08
β lactam antibiotics	45.5	47.8	-0.05
Sulfonamides	2.5	1.8	0.05
Diuretics	40.9	40.4	0.01
Outcome			**P value**
Secondary outcome: ARF	48.1	52.4	0.040
Risk Ratio (95% CI)	0.84 (0.71 – 0.99)		0.040
Secondary outcome: AKI	13.1	17.3	0.004
Risk Ratio (95% CI)	0.72 (0.57 – 0.92)		0.010

Data are reported as % or mean (SD), unless otherwise stated.

Abbreviations: AKI=Acute kidney injury; ALT=Alanine aminotransferase; ARF=Acute respiratory failure; AST=Aspartate aminotransferase; CRP=C-reactive protein; CT=computed tomography; Hb= Hemoglobin; LDH= Lactate dehydrogenase; WBC=White blood cells

Table S8. Inverse probability of treatment weighting: acute respiratory failure and acute kidney injury in patients with preexisting cardiovascular disease stratified by use of azithromycin.

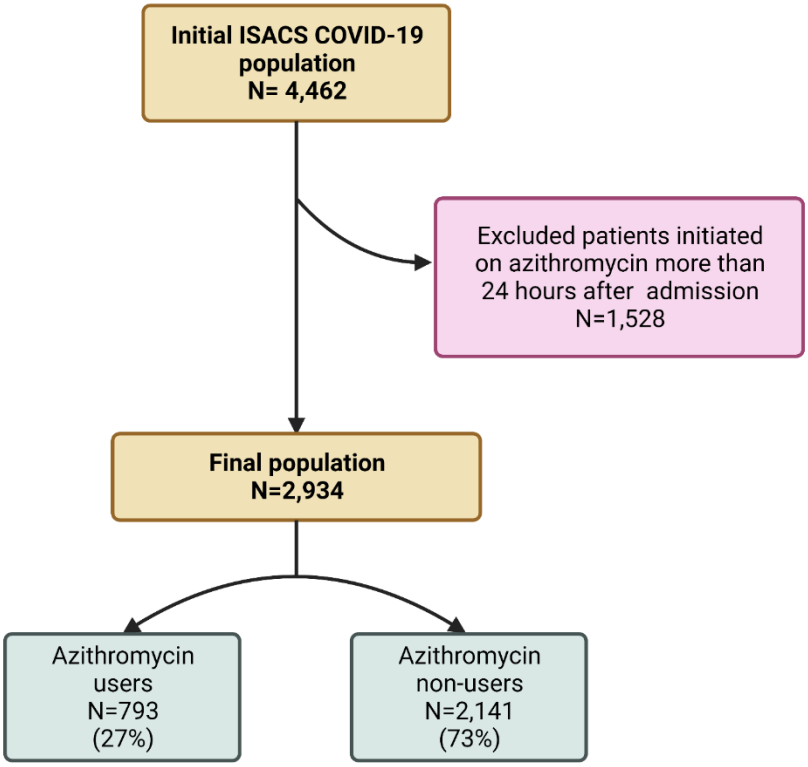
	Azithromycin N=290	**No Azithromycin N=774**	**Standardized difference**
Female sex	42.9	43.3	-0.008
Age, mean (SD)	71.3 (11.9)	72.4 (11.8)	-0.05
Cardiovascular risk factors			
Diabetes	36.0	35.8	0.005
Hypertension	84.7	83.4	0.03
Hypercholesterolemia	48.8	45.5	0.06
Current smoking	9.0	9.3	-0.008
Former smoking	20.7	21.2	-0.01
Obesity	28.7	27.2	0.03
Comorbidities			
Chronic kidney disease	21.3	22.6	-0.03
Chronic lung conditions	19.3	17.2	0.05
Active cancer	15.9	14.9	0.02
Dementia	15.4	18.5	-0.08
Clinical features on admission			
X-ray/CT signs of interstitial pneumonia	61.8	61.8	-0.0002
Lab testing			
WBC count on admission, 10^9/L [mean (SD)]	8.8 (4.6)	8.9 (5.2)	-0.02
Hb on admission, g/dL [mean (SD)]	12.5 (2.1)	12.6 (2.2)	-0.05
Platelet count on admission, 10^9/L [mean (SD)]	230.0 (101.7)	226.2 (102.3)	0.03
Serum creatinine on admission, mg/dL [mean (SD)]	1.2 (1.1)	1.3 (1.3)	-0.08
CRP, mg/dL [mean (SD)]	11.1 (10.1)	11.3 (9.9)	-0.01
D-dimer, ng/mL [mean (SD)]	4.0 (7.1)	4.1 (8.3)	-0.02
AST, U/L [mean (SD)]	131.9 (463.9)	135.4 (506.3)	-0.007
ALT, U/L [mean (SD)]	80.4 (134.2)	95.7 (187.5)	-0.06
LDH, U/L [mean (SD)]	493.3 (652.4)	537.4 (611.5)	-0.06

In-hospital treatment			
Darunavir	0.8	0.7	0.02
Lopinavir/Ritonavir	2.0	1.6	0.02
Remdesivir	13.0	11.4	0.04
Hydroxychloroquine	13.8	13.5	0.01
Corticosteroids	58.9	62.3	-0.07
Oral anticoagulants	20.8	19.9	0.02
Heparin	76.9	80.0	-0.07
Antiplatelet treatment	37.2	35.5	0.03
β lactam antibiotics	48.2	49.3	-0.02
Sulfonamides	3.2	1.9	0.08
Diuretics	49.6	48.8	0.01
Outcome			**P value**
Secondary outcome: ARF	47.6	57.7	0.003
Risk Ratio (95% CI)	0.67 (0.51 – 0.87)		0.003
Secondary outcome: AKI	13.6	23.2	<0.001
Risk Ratio (95% CI)	0.52 (0.36 – 0.76)		<0.001

Data are reported as % or mean (SD), unless otherwise stated.

Abbreviations: AKI=Acute kidney injury; ALT=Alanine aminotransferase; ARF=Acute respiratory failure; AST=Aspartate aminotransferase; CRP=C-reactive protein; CT=computed tomography; Hb= Hemoglobin; LDH= Lactate dehydrogenase; WBC=White blood cells.

Figure S1. Study flow chart.



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