Thrombosis Update 2 (2021) 100026

Contents lists available at ScienceDirect

Thrombosis Update

journal homepage: www.journals.elsevier.com/thrombosis-update

Antiplatelet therapy in patients with Covid-19: A retrospective observational study

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ARTICLE INFO

Keywords:
Covid-19
Acetylsalicylic acid
Aspirin
Antiplatelet agents
Anticoagulants

ABSTRACT

Introduction: Covid-19 is associated with a high risk of venous thromboembolism. In addition, cases of arterial thromboembolism were also reported. We investigated the effect of antiplatelet therapy on the disease course.
Methods: We evaluated a cohort of inpatients with Covid-19 (n = 152). We recorded the patient's demographic data, their comorbidities, medication use including the use of antiplatelets and anticoagulants, laboratory findings and data about mechanical ventilation. We then separated the patient's outcomes into either being „bad" (dead or referral to higher level of care) or „good" (discharged). Then we evaluated the factors that contributed to the patient needing ventilatory support and to showing typical radiological findings.
Results: In our cohort, 21 patients received ventilatory support whereas 131 did not require the use of ventilators. 127 patients had good outcomes and 25 had bad outcomes. By using multivariate analysis, we found that the need for ventilatory support was the strongest predictor of a bad outcome. All patients who were on ventilators displayed typical radiological findings. The factors predicting the need for ventilatory support were LDH and CRP levels, the presence of cardiac conduction abnormalities as well as chronic lung conditions. Cardiac conduction abnormalities, LDH and CRP levels, and the use of antiplatelets, were factors that predicted typical radiological findings.
Conclusions: There was a higher incidence of typical radiological findings in patients on antiplatelet medication. However, it did not translate into changes in the ventilation requirement or in the outcome. The need for mechanical ventilation was the strongest predictor of a bad outcome.

1. Introduction

The SARS-COV-2 virus infection, commonly known as Covid-19, is associated with a high risk of deep venous thrombosis and pulmonary embolism [1–3]. An enhanced immunological response („cytokine storm") during infection with Covid-19 [4,5] often leads to enhanced platelet activation, thrombotic microangiopathy [6] and clotting [1,7]. In addition, the activated platelets also contribute to neutrophil activation [5]. Prophylactic therapy with anticoagulants is often included in the therapy [1,7,8].

In addition, arterial thromboembolism was reported during some cases of the disease [1,7,9–12]. Testing the effect of acetylsalicylic acid (ASA) was suggested by Violi et al. for Covid-19 pneumonia [7]. This is based on their previous study that ASA treatment ameliorated the course of community-acquired pneumonia and increased the 30-day survival [13]. Treatment with ASA was also proposed by Torrinhas et al. based on its modulatory effect on prostaglandin synthesis and thus being a possibility to accelerate the resolution of the inflammation [14]. ASA was also reported to have direct antiviral effects, for example by up-regulation of type I interferon [5]. There are expert-based recommendations to continue the use of antiplatelet therapy that were started earlier for other indications [5,15,16]. However, as of now, the evidence regarding the effect of ASA or other antiplatelet therapy on Covid-19's severity or outcome is lacking [3].

In this work, we evaluated the effect of antiplatelet therapy on the disease severity and on the disease outcome in a retrospective single-hospital study.

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https://doi.org/10.1016/j.tru.2020.100026
Received 8 July 2020; Received in revised form 22 October 2020; Accepted 22 November 2020

2. Material and methods

We evaluated a cohort of hospital inpatients who were treated for Covid-19 in a single dedicated („Covid") hospital in Selb, Germany, from March 14 to June 15, 2020. The patients were recruited from in-patients after diagnosis with either a nasopharyngeal swab with a positive PCR or after having radiological findings indicating Covid 19; i.e. typical findings of an atypical pneumonia on a chest X-ray or the presence of ground glass opacities on a chest CT scan [17]. We performed routine imaging in all patients according to the standard protocols. This led to n = 166. Patients who had an advanced „do not ventilate" directive in their records (n = 14), were excluded from the analysis. Even though it is an ethically reasonable scenario (respecting the patient's will and providing maximal comfort during possible respiratory failure), it can bring bias into the analysis (such patients could have survived). This led to an analysis of n = 152. The outcomes were recorded as discharged home, deceased or referred to a higher level of care. Referral was done when the patient had a persistent oxygen saturation <85% despite being put on invasive mechanical ventilation with an FiO2 of 100%. The treating facility was the University Hospital in Erlangen in Germany, which is (unlike our hospital) equipped with extracorporeal membrane oxygenation (ECMO) machines.

We collected the following data about the patients: their gender, age at admission, method of diagnosis (nasopharyngeal swab, CT/chest X-ray), presence of diarrhea, length of hospital stay (days), use of common medications: angiotensin II receptor blockers, ACE inhibitors, statins, anticoagulants – a coumarin derivative phenprocoumon or non-coumarin novel oral anticoagulants (NOACs), antiplatelets (ASA or clopidogrel), minimum leukocyte count (thousands per μl), maximum leukocyte count (thousands per μl), presence of D dimers (μg/ml), the maximum level of lactate dehydrogenase (LDH; units/l), minimum levels of C-reactive protein (CRP; mg/l), maximum levels of CRP (mg/l), mechanical ventilation including type (invasive or non-invasive) and troponin levels (positive/negative). The use of coumarins or NOACs were pooled together as oral anticoagulants. We also collected data on the presence or absence of major commorbidites such as cardiac conduction abnormalities, hypertension, diabetes mellitus, COPD or other chronic lung conditions, heart failure or coronary artery disease, malignancies, strokes and chronic limb ischemia.

Since the data was retrieved retrospectively and the patients were anonymized, we did not seek informed consent from the patient regarding data evaluation. Before submission of the paper, we obtained a written approval from the local GDPR commissioner who approved the processing of patients data under the condition that they remain anonymous. Only the lead author had access to the patients' identities.

For all statistical analyses, we used the Prism 8.4.2 application (GraphPad Software, La Jolla, CA, USA). Continuous variables are shown as being median (interquartile range) and frequency data as absolute frequency (relative frequency). We used multiple logistic regression for most of our analyses. This allows only for two different outcomes. Therefore, we separated the patient's outcomes into either being „bad" (dead or referral to a higher level of care) or „good" (patient was discharged). Similarly, we separated the disease course into „mild" (no need for mechanical ventilation) or „severe" (need for mechanical ventilation). To find the strongest predictors, we considered the significance from the regression and additionally used the Akaike's Information Criterion (AIC) while leaving out a single variable at a time. We provided the parameter's odds ratio with a 95% confidence interval (95% CI). For the analysis of factors influencing the length of hospital stay, we used multiple linear regression. In this case, we provided the parameter estimates β with a 95% CI. A $p < 0.05$ was deemed as being significant, with asterisk marks * $p < 0.05$, ** $p < 0.01$ and ** $p < 0.001$. A "ns" is used for the analyses with $p > 0.05$.

Table 1
A Summary of the Characteristics of our Cohort. The continuous variables are shown as median (interquartile range), frequency data as absolute frequency (relative frequency). The p values show significance based on Fisher's exact test or Chi-square test for relative frequency, or on the Student's t-test for continuous variables, comparing patients using antiplatelet therapy vs. patients without antiplatelet therapy.

Parameters	All Patients	Patients without Antiplatelet Therapy	Patients Using Antiplatelet Therapy	P Value
Gender	Males 75 (49%) Females 77 (51%)	Males 53 (46%) Females 61 (54%)	Males 22 (58%) Females 16 (42%)	0.1193
Age, years	75.5 (22.75)	72.5 (24.8)	80.5 (11.3)	0.0003 ***
Overweight	yes 69 (51%) no 67 (49%)	yes 53 (51%) no 50 (49%)	yes 16 (48%) no 17 (52%)	0.7774
Cardiac Conduction Abnormalities	Atrial fibrillation 37 (25%) Other abnormality 10 (7%) None 104 (69%)	Atrial fibrillation 30 (26%) Other abnormality 5 (4%) None 79 (69%)	Atrial fibrillation 9 (24%) Other abnormality 3 (8%) None 25 (68%)	0.4927
Hypertension	103 (68%)	69 (61%)	34 (89%)	<0.0001 ***
Diabetes Mellitus	51 (34%)	38 (33%)	13 (34%)	>0.9999
Chronic Lung Conditions	COPD 18 (12%) Asthma 2 (1%) Silicosis 1 (1%)	COPD 14 (13%) Silicosis 1 (1%)	COPD 4 (10%) Asthma 2 (5%)	0.0938
Heart Failure or Coronary Artery Disease	52 (34%)	22 (19%)	30 (79%)	<0.0001 ***
Malignancy	29 (19%)	16 (14%)	13 (34%)	0.0015 **
Stroke	15 (10%)	8 (7%)	7 (18%)	0.0309 *
Limb Ischemia	15 (10%)	5 (4%)	10 (28%)	<0.0001 ***
Use of Angiotensin II Receptor Blockers	32 (21%)	22 (19%)	10 (26%)	0.3096
Use of ACE Inhibitors	36 (24%)	22 (19%)	14 (37%)	0.0071 **
Use of Statins	39 (26%)	19 (17%)	20 (53%)	<0.0001 ***
Antiplatelet Medications	Total 38 (25%) ASA 35 (23%) clopidogrel 3 (2%)	n/a	ASA 35 (92%) clopidogrel 3 (8%)	n/a
Anticoagulants	Coumarins 4 (2.6%) NOACs 27 (17.8%)	Coumarins 3 (3%) NOACs 20 (18%)	Coumarins 1 (3%) NOACs 7 (18%)	>0.9999
Nasopharyngeal Swab with a PCR Test	Positive 100 (70%) Negative 43 (30%)	Positive 71 (56%) Negative 37 (34%)	Positive 29 (83%) Negative 6 (17%)	0.0017 **
CT/chest X-ray	Positive 117 (77%) Negative 34 (23%)	Positive 83 (73%) Negative 30 (27%)	Positive 34 (89%) Negative 4 (11%)	0.0063 **
Length of Stay,in days	9.0 (7.0)	9.0 (6.8)	11.5 (8.5)	0.0153 *
Mechanical Ventilation	None 131 (86%) Non-invasive 4 (3%)	None 99 (87%) Non-invasive 4 (4%)	None 32 (84%) Invasive 6 (16%)	0.0661

(continued on next page)

Table 1 (*continued*)

Parameters	All Patients	Patients without Antiplatelet Therapy	Patients Using Antiplatelet Therapy	P Value
	Invasive 18 (12%)	Invasive 11 (10%)		
Troponin	Positive 23 (27%) Negative 61 (73%)	Positive 15 (23%) Negative 49 (77%)	Positive 8 (40%) Negative 12 (60%)	0.0145 *
D-Dimer, μg/ml	1.230 (1.225)	0.91 (1.04)	1.95 (1.68)	0.0048 **
Minimum Leukocyte Count, x 1000 per μl	5.4 (2.8)	5.35 (2.63)	5.90 (3.18)	0.5644
Maximum Leukocyte Count, x 1000 per μl	8.3 (5.7)	7.90 (5.50)	9.95 (5.45)	0.5957
Maximum Lactate Dehydrogenase Level, units/l	401 (225)	394 (234)	425 (239)	0.4940
Minimum CRP Level, mg/l	16.5 (33.7)	16.5 (33.5)	18.5 (31.8)	0.3046
Maximum CRP Level, mg/l	85.5 (131)	84.0 (126)	100.0 (169)	0.0564
Patient Outcomes	Discharged 127 (84%) Referred 6 (4%) Deceased 19 (13%)	Discharged 91 (80%) Referred 5 (4%) Deceased 18 (16%)	Discharged 30 (79%) Referred 1 (3%) Deceased 7 (18%)	0.8751

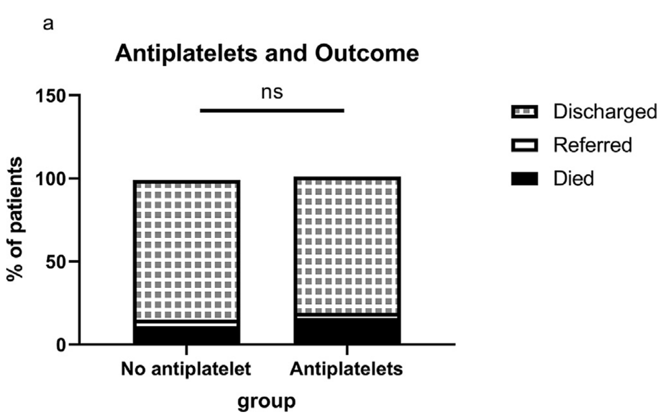

Fig. 1a. Outcomes of patients with/without antiplatelet medications.

3. Results

3.1. Cohort characteristics

In our final cohort (n = 152), 21 patients required ventilatory assistance whereas 131 did not. 127 patients had good outcomes (were discharged) and 25 had bad outcomes – six patients were referred to a higher level of care and 19 patients died. Among the deceased patients, 12 of them received mechanical ventilation and 7 died without ventilatory support. Notably, all referred patients had been ventilated prior to the referral and all of the ventilated patients had initial chest CT/X-rays which were indicative of Covid 19. . A total of 117 patients had typical findings on the chest CT/X-ray, whereas 34 had negative imaging results; the data from the images are unavailable for one patient. Of the 152 patients, 103 had arterial hypertension, 51 had diabetes mellitus, 52 had coronary artery disease and/or heart failure, 15 had a history of stroke, 15 had chronic limb ischemia, 18 had COPD plus 2 patients with asthma

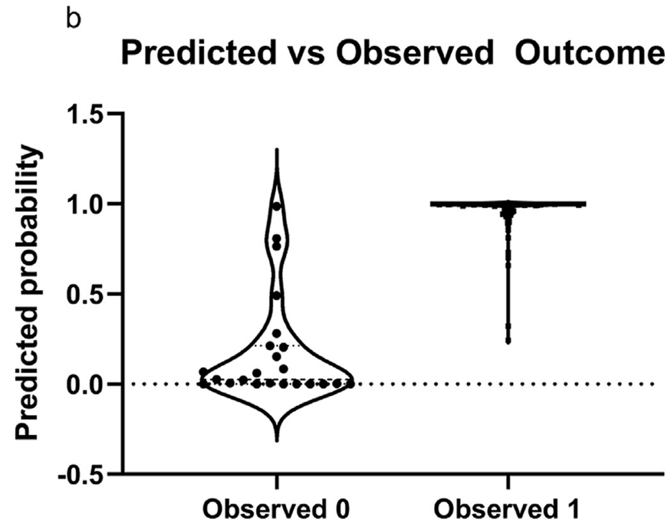

Fig. 1b. A violin plot of the predicted vs the observed outcomes (0 = death or referral to higher level of care, 1 = discharge from the hospital).

plus 1 with pulmonary silicosis and 29 patients had a malignancy. 38 patients were using antiplatelet medication; of those, 35 were receiving ASA and 3 were receiving clopidogrel. Detailed descriptive statistics are provided in Table 1.

3.2. Disease outcome

When evaluating the percentage of patients with good or bad outcomes, with or without antiplatelet medications, a higher percentage of patients on antiplatelet medications tended to do worse than the patients who were not on antiplatelet medication (19% vs. 15%, $p = 0.4908$; Fig. 1a).

However, this result is for illustration purposes only as patients on antiplatelet medication were older (80.5 vs. 72.5 years, $p < 0.001$) and had a higher proportion of cardiovascular comorbidities, especially heart failure or coronary artery disease (79% vs. 19%; $p < 0.001$) than those without it (Table 1). Therefore, we performed a multiple logistic regression which takes all other factors into account.

We were not able to complete the analysis with all of the parameters as not all patients had all of the data that we needed. Therefore, we had to omit the data on obesity, diarrhea, D-dimers and troponin, as these were not available in all patients. Then, after omitting the data on the nasopharyngeal swabs, the analysis was completed with the following parameters: gender, age, imaging results, the use of angiotensin II receptor blockers, the use of ACE inhibitors, the use of statins, the minimum leukocyte count and maximum leukocyte counts, the maximum LDH levels, the minimum CRP levels, and maximum CRP levels, the need for mechanical ventilation, the presence/absence of cardiac conduction

Table 2
Predictors of disease outcome (hospital discharge vs. death or referral to a higher level care). Variables with an odds ratio smaller than 1 contributed to a bad outcome.

Variable	Odds Ratio	95% CI	P Value	P Value Summary
Mechanical Ventilation	0.00141	1.56×10^{-6} to 0.0499	0.0058	**
Minimum CRP Levels	0.938	0.867 to 0.982	0.0349	*
Maximum LDH	0.990	0.975 to 0.998	0.0502	ns
Chronic Lung Disease	0.0201	0.000115 to 0.624	0.0571	ns
Diabetes Mellitus	0.0687	0.000908 to 1.38	0.1242	ns
Male Gender	0.0989	0.00239 to 1.41	0.1252	ns

Table 3
The predictors of disease severity as defined by a need for mechanical ventilation (1 = required mechanical ventilation, 0 = did not require mechanical ventilation). Variables with an odds ratio greater than 1 contributed to the need for mechanical ventilation.

Variable	Odds Ratio	95% CI	P Value	P Value Summary
Maximum LDH Levels	1.01	1.00 to 1.02	0.0029	**
Maximum CRP Levels	1.01	1.00 to 1.03	0.0371	*
Cardiac Conduction Abnormalities	12.6	1.34 to 185	0.0377	*
Use of Anticoagulants	0.0361	0.000457 to 0.853	0.0732	ns
Chronic Lung Conditions	7.57	0.816 to 98.3	0.0857	ns

abnormalities, the presence/absence of arterial hypertension, if the patients were diabetic, the presence/absence of chronic lung disease, the presence/absence of chronic heart failure/coronary artery disease, the presence/absence of any malignancies, any history of strokes, presence/absence of chronic limb ischemia, the use of antiplatelet therapy and the use of oral anticoagulants.

We found that the need for ventilatory assistance was the strongest predictor of bad outcomes with an odds ratio of 0.00141 (with a 95% confidence interval 1.56×10^{-6} to 0.0499, $p = 0.0058$). This was followed by minimum CRP levels, maximum lactate dehydrogenase (LDH) levels, chronic lung disease, diabetes mellitus and male gender. A summary of these factors is provided in Table 2. The other parameters analyzed did not have any significant influence and their omission did not improve the prediction as calculated by AIC. Specifically for the use of antiplatelet medications, the odds ratio was 2.25 (95% CI 0.0456 to 270; $p = 0.6887$).

Using only variables from Table 2, we obtained an area under the ROC curve of 0.9593 and a Tjur's R squared value of 0.7140. When using all variables, the area was 0.9852 and the $R2 = 0.7854$. A violin plot of the predicted vs. the observed outcomes is provided in Fig. 1 b.

3.3. Disease severity

Since the need for mechanical ventilation was the strongest predictor of an unfavorable outcome, we analyzed it further. We were not able to analyze the subset of mechanically ventilated patients by multivariate analysis due to a low n value (21 ventilated patients). Therefore, we sought the factors that predicted the need for mechanical ventilation instead.

We separated the disease according to its clinical course into mild (no need for mechanical ventilation) and severe (a need for mechanical ventilation). The percentage of patients requiring mechanical ventilation was nonsignificantly higher in patients using antiplatelet medication than in those without it (16% vs. 13%, $p = 0.5469$). Again, this comparison is more for illustration with more detailed statistics to follow.

Again, to complete the analysis, we omitted the data on obesity, D-dimers, troponin levels, data on nasopharyngeal swabs, and the presence of diarrhea to obtain a maximal n number. We also had to skip the data on chest CT/X-rays due to a phenomenon of a quasi-perfect separation: all mechanically ventilated patients had positive imaging results. The analysis was completed with the following parameters: gender, age, the use of angiotensin II receptor blockers, the use of ACE inhibitors, the use of statins, the minimum leukocyte count and maximum leukocyte counts, the minimum and maximum LDH levels, the minimum and maximum CRP levels, the presence of cardiac conduction abnormalities, the presence/absence of arterial hypertension, if the patient was diabetic, the presence/absence of chronic lung disease, the presence or absence of chronic heart failure/coronary artery disease, if any malignancies are

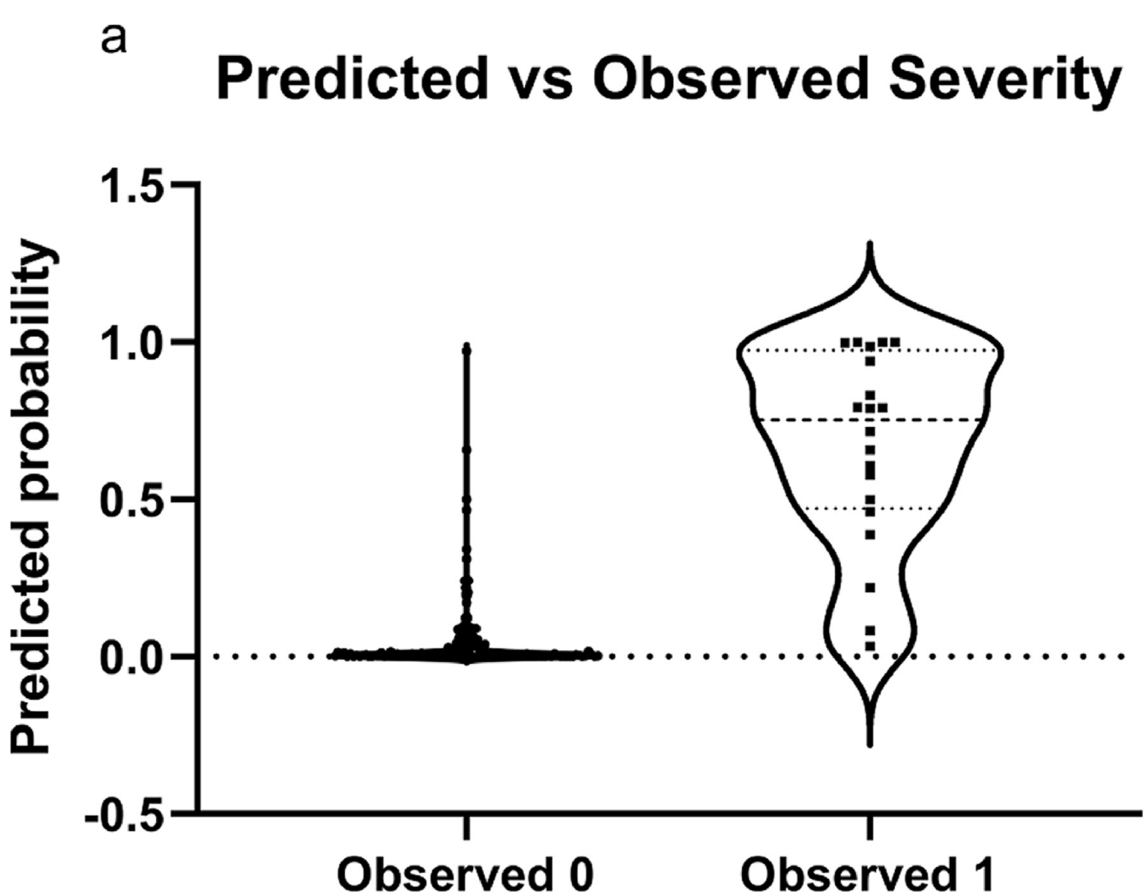

Fig. 2a. A violin plot of the Predicted vs the Observed Severity (1 = severe: required mechanical ventilation, 0 = mild: no need for mechanical ventilation).

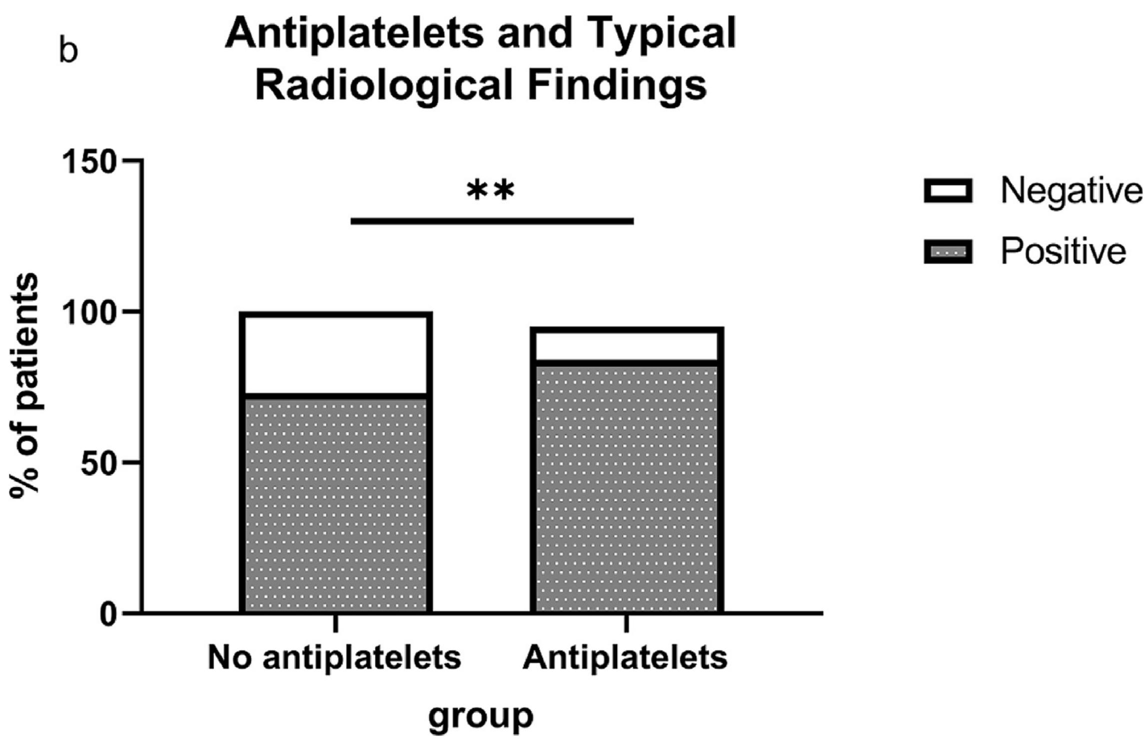

Fig. 2b. Percentage of typical radiological findings in patients without and with antiplatelet medication.

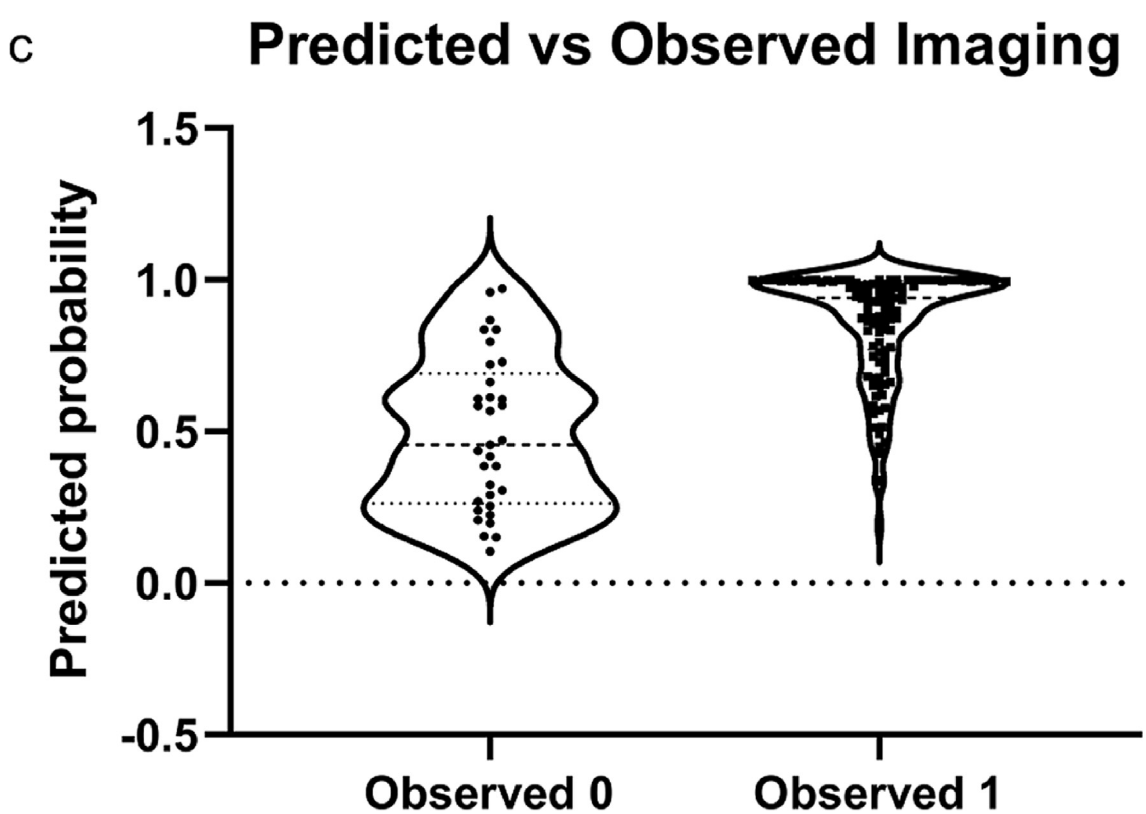

Fig. 2c. A violin plot of the Predicted vs the Observed Imaging (0 = negative chest CT/X-rays, 1 = positive chest CT/X-rays).

present, any history of strokes, the presence/absence of chronic limb ischemia, the use of antiplatelet therapy and the use of oral anticoagulants.

This time, the maximum LDH activity was the strongest predictor of having a severe disease course: odds ratio 1.01 (95% CI 1.00 to 1.02, p = 0.0029), followed by maximum CRP, the presence of cardiac conduction abnormalities and a chronic lung condition. On the other hand, the use of oral anticoagulants appears to predict a mild course of the disease (Table 3). The other parameters analyzed did not significantly contribute to the disease course and their omission did not improve the prediction as

Table 4
Predictors of positive imaging results (1 = positive chest CT/X-ray, 0 = negative chest CT/X-ray). Variables with odds ratio greater than 1 contributed to the likelihood of having a positive imaging.

Variable	Odds Ratio	95% CI	P Value	P Value Summary
Cardiac Conduction Abnormalities	12.8	2.10 to 126	0.0119	*
Maximum LDH Levels	1.01	1.00 to 1.02	0.0120	*
Maximum CRP Levels	1.02	1.00 to 1.03	0.0204	*
Use of Antiplatelets	12.1	1.41 to 167	0.0354	*
Use of ACE Inhibitors	0.218	0.0378 to 1.09	0.0714	ns
Use of Angiotensin II Receptor Blockers	0.249	0.0423 to 1.27	0.1042	ns

calculated by the AIC. Specifically for the use of antiplatelet medications, the odds ratio was 0.781 (95% CI 0.0253 to 17.0, p = 0.8777). When using all variables, we obtained an area under the ROC curve of 0.9669 and a Tjur's R squared value of 0.6172. A violin plot of the predicted vs. Observed Severity is provided in Fig. 2a.

We then separated the patients into those with a negative chest CT/X-ray and those with a positive chest CT/X-ray. The percentage of patients with positive radiological findings was higher in patients using antiplatelet medications than in those without it (84% vs. 73%, p = 0.0066; Fig. 2 b). Again, this comparison is more for illustration due to the associated comorbidities of the patients on antiplatelet medications.

To complete the multivariate analysis and to obtain the maximum n number, we omitted the data on obesity, D-dimers, troponin levels and the presence of diarrhea. Last, we omitted the data on nasopharyngeal swabs since this was often complementary with the chest CT/X-rays (the patient had either a positive PCR or a positive imaging diagnosed for Covid-19).

The analysis was completed with the following parameters: gender, age, the use of angiotensin II receptor blockers, the use of ACE inhibitors, the use of statins, the minimum leukocyte count and maximum leukocyte counts, the minimum and maximum LDH levels, the minimum and maximum CRP levels, the presence of cardiac conduction abnormalities, the presence/absence of arterial hypertension, if the patient was diabetic, the presence/absence of chronic lung disease, the presence or absence of chronic heart failure/coronary artery disease, if any malignancies are present, any history of strokes, the presence/absence of chronic limb ischemia, the use of antiplatelet therapy and the use of oral anticoagulants.

This time, the presence of cardiac conduction abnormalities was the strongest predictor of radiological positivity: the odds ratio was 12.8 (95% CI 2.10 to 126, p = 0.0119), followed by maximum LDH levels, maximum CRP levels and the use of antiplatelet medications. Specifically for the use of antiplatelet medications, the odds ratio was 12.1 (95% CI 1.41 to 167, p = 0.0354). On the other hand, the use of ACE inhibitors or angiotensin II receptor blockers appeared to be a predictor of negative imaging results (Table 4). The other analyzed parameters did not significantly contribute to the likelihood of having positive imaging results and their omission did not improve the prediction as calculated by the AIC.

When using all of the variables, the area under the ROC curve was 0.8827 with a Tjur's R squared value of 0.3688. A violin plot of the Predicted vs. the Observed Imaging is provided in Fig. 2c.

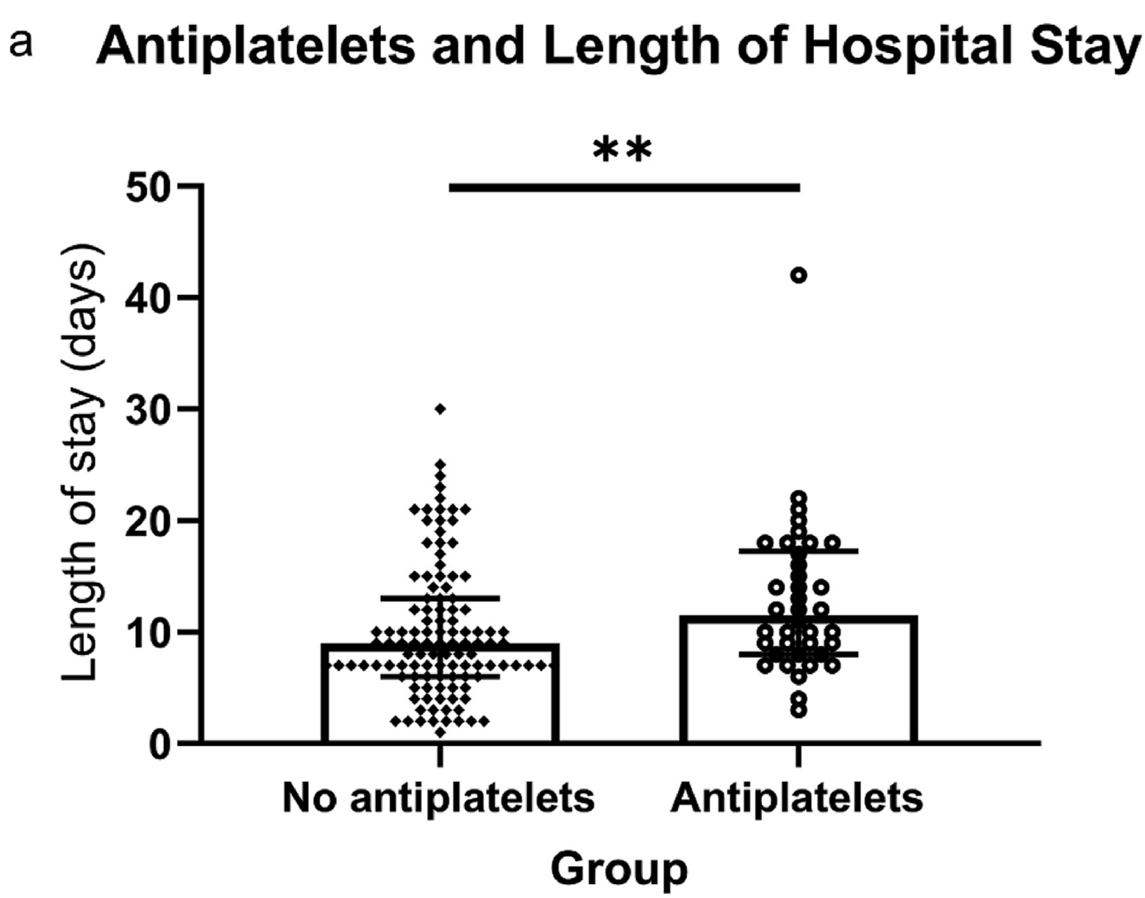

Fig. 3a. Length of hospital stay in patients without and with antiplatelet medication.

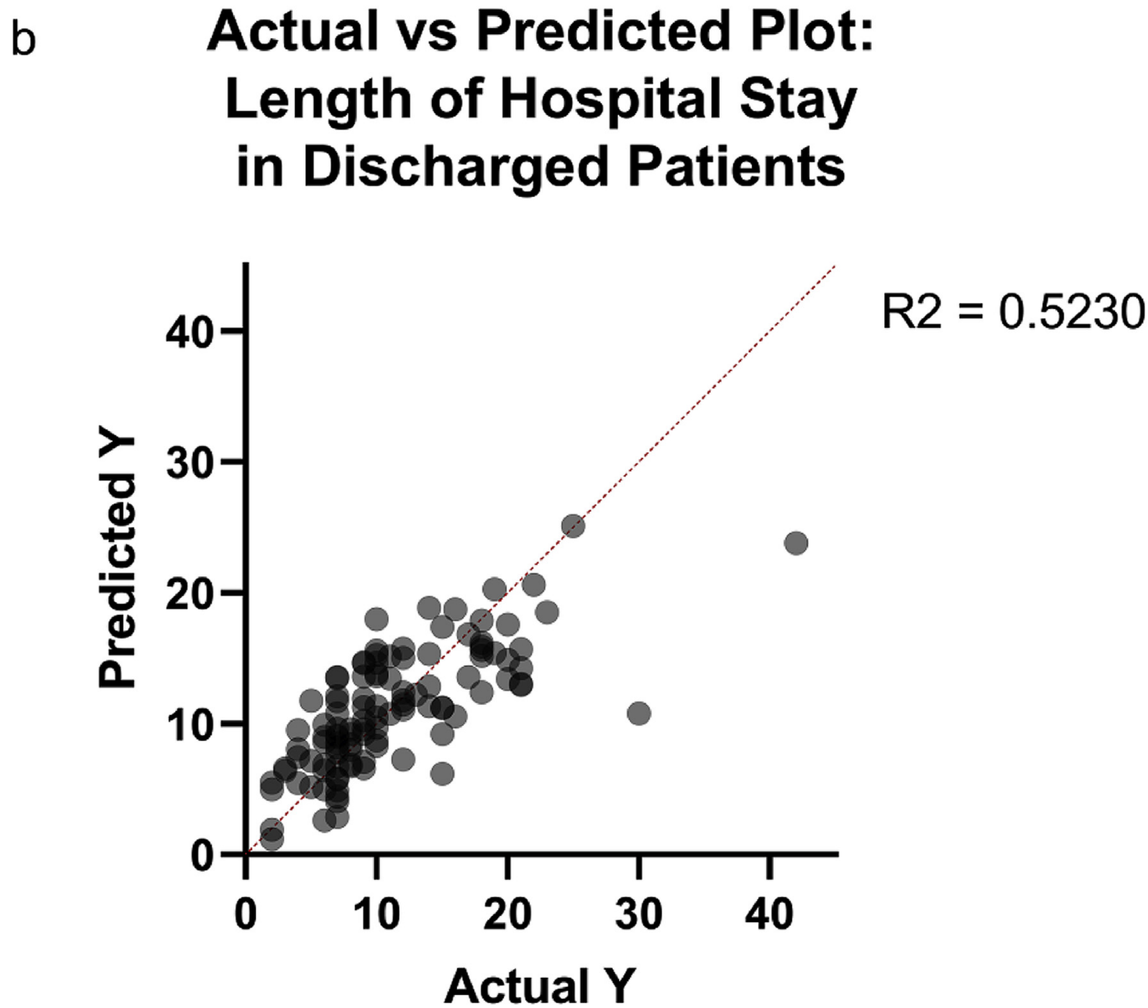

Fig. 3b. Prediction of length of hospital stay in discharged patients.

3.4. *The length of hospital stay*

Finally, we analyzed the length of hospital stays. The patients using antiplatelet medication had significantly longer hospital stays than those without it: 11.5 (9.25) vs 9.0 (7) days, p = 0.0078 (Fig. 3a). Again, this is compounded by their higher age with a higher proportion of commorbidities and is further analyzed by multiple linear regression.

The analysis was completed with the following parameters: gender, age, the use of angiotensin II receptor blockers, the use of ACE inhibitors, the use of statins, the minimum leukocyte count and maximum leukocyte counts, the minimum and maximum LDH levels, the minimum and maximum CRP levels, the presence of cardiac conduction abnormalities, the presence/absence of arterial hypertension, if the patient was diabetic, the presence/absence of chronic lung disease, the presence or absence of chronic heart failure/coronary artery disease, if any malignancies are present, any history of strokes, the presence/absence of chronic limb ischemia, the use of antiplatelet therapy and the use of oral anticoagulants.

This time, the patient age, maximum levels of CRP and the positivity of nasopharyngeal swab tests, were predictors of longer hospital stays. On the other hand, minimum CRP levels were associated with shorter hospital stays. The use of antiplatelet medication did not seem to influence the length of hospital stays: β = 1.663, 95% CI -1.639 to 4.964, p = 0.3207.

As death in severely ill patients may distort the distribution of the length of hospital stay [18], we then analyzed the factors affecting the length of hospital stays in a subset of patients who were discharged home. The results were similar to the analysis of the entire cohort. Additionally, the need for mechanical ventilation was identified as a factor that contributed to longer hospital stays (Table 5). This time, the R squared value was at 0.5230 (Fig. 3b). Again, the use of antiplatelet medications did not influence the length of hospital stay: β = 1.553, 95% CI -2.280 to 5.385, p = 0.4228.

Table 5
Predictors of length of the hospital stay: discharged patients only. Variables with β greater than 0 prolong hospital stay.

Variable	β estimate	95% CI	P Value	P Value Summary
Age	0.186	0.0963 to 0.275	<0.0001	***
Minimum CRP Level	−0.101	−0.153 to −0.0479	0.0003	***
Maximum CRP Level	0.0323	0.0144 to 0.0502	0.0005	***
Positivity of the Nasopharyngeal Swab Test	3.53	1.23 to 5.83	0.0030	**
Need for Mechanical Ventilation	6.01	−0.729 to 12.8	0.0798	ns

4. Discussion

In our study, we were not able to find any influence of antiplatelet medications on the disease outcome. Even though such a benefit would be pathophysiologically plausible, the patients who were being treated with antiplatelet therapy did not do any better than the patients without antiplatelet therapy even after adjusting for confounding factors. Interestingly, there was a significant contribution of the use of antiplatelet medications to the imaging results being positive, even after adjusting for other factors by means of multivariate analysis. However, this did not translate into either differences in the requirement for mechanical ventilation nor to death or referral to a higher level of care.

We found the need for mechanical ventilation as the strongest predictor of disease outcome. This is in accord with the work of Paranjpe et al. [19], who observed high in-hospital mortality rates in Covid-19 patients who required mechanical ventilation. In accord with other authors, high levels of C-reactive protein were found to predict a poor prognosis [4,17] as did maximum lactate dehydrogenase levels [4,20–25]. Chronic lung disease and diabetes mellitus were identified by other teams in predicting unfavorable outcomes in Covid-19 patients [20,25]. A high prevalence of chronic lung conditions and diabetes mellitus was also found in an autopsy study of deceased Covid-19 patients by Edler et al. [2].

Notably, we found that patients using oral anticoagulants, either coumarins (phenprocoumon) or the newer non-coumarin novel oral anticoagulants (NOACs), had a significantly lower chance to require mechanical ventilation. Similarly, other authors suggested that therapeutic anticoagulation (rather than prophylactic), might be necessary during Covid-19, possibly by preventing microvascular thrombosis [16,19,26–28]. However, this did not translate into changes of the rates of bad outcomes, i.e. death or referral in patients using oral anticoagulants. This is in accord with the work of Klok et al. who reported a lower incidence of thromboembolic disease in patients who were already using oral anticoagulants than in the controls; however, they did not find any difference in the survival rate [29]. A possible explanation for this is that in a previous study, it was found that there was a survival benefit only in patients with sepsis-induced coagulopathy, but not in all patients [27].

Last, patients using ACE inhibitors or angiotensin II receptor blockers, had a lower chance of having positive radiological imaging tests than those who didn't. Similarly, Meng et al. identified a lower rate of severe diseases in patients using renin-angiotensin-aldosterone system inhibitors [30]. However, this did not translate into differences in the need for mechanical ventilation nor in the rate of bad outcomes which is in accord with a large population-based study by Fosbøl et al. [31].

There were some limitations to our study. First, our study was retrospective and the patients were receiving ASA or clopidogrel due to their already present cardiovascular diseases. This factor should have been accounted for by the use of multiple regression, which can separate the effect of antiplatelet medications from the potentially confounding factor of the comorbidities. Still, the character of our study did not allow for the randomization of patients.

Second, even though 117 of our patients had positive chest CT/X-rays, most of them did not require mechanical ventilation. There were only 21 patients who were mechanically ventilated in our study. This does not grant us sufficient statistical power to analyze any effect of antiplatelet medications in this subset of patients with the most severe course of Covid-19. This is in sharp contrast to the study in the use of ASA in community-acquired pneumonia, where the authors included one thousand and five patients [13]. Also in the study of venous and arterial thromboembolic events, where the authors reported arterial thrombotic events in 3.7% of the patients, all of the 184 Covid-19 patients were at the ICU [1]. So even though we did not determine that patients using antiplatelet therapy fared any better than patients without antiplatelet therapy, we do not preclude its possible beneficial effects in the most severe cases, as proposed by Viecca et al. [32].

Third, the length of hospital stay might have been distorted by quarantine measures as well as non-medical reasons, e.g. patients from a nursing home who could not be discharged even in the case of a negative control swab test.

5. Conclusions

The use of antiplatelet medications had no effect on the disease outcome in our study. There was a higher amount of positive radiological findings in patients on antiplatelet medications, which did not translate into either a need for mechanical ventilation or into a bad outcome. Instead, the need for mechanical ventilation was the strongest predictor of a poor outcome. The use of ACE inhibitors or angiotensin II receptor blockers, seemed to lower the incidence of positive radiological findings and the use of oral anticoagulants decreased the need for mechanical ventilation; however, none of these translated into any differences in the outcomes for the patients. The other identified factors predicting bad outcomes were minimum CRP, maximum lactate dehydrogenase, the presence of chronic lung disease, the presence of diabetes mellitus and male gender.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank Dr. Cyrus Rasti, MD, for the language correction of the manuscript.

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