Peer Review Comments

#Reviewer 1:

Q1: Propensity score matching or adjustment can be added as a supplementary file

A: Thank you for your warm comments, Absolutely, we can submit it as a supplementary file

#Reviewer 2

Q2: In the manuscript, 38 patients took daily Aspirin before hospitalization. However, according to the propensity analysis they performed following several suggestions from reviewers and editors, there were 47 patients on the aspirin-taking arm. Did the authors allow duplication when they performed propensity analysis?

A: Thank you so much for being thorough with our manuscript. It is duly appreciated. I have attached the changed tables below.

Q3: Propensity matching is not quite suitable in a study with a small sample size, as the authors replied. However, did they try the inverse weighting technique as well? That could be the solution to assimilate the baseline characteristics in the two groups and enhance the generalizability of this study. I still do not understand why the variables the authors included in the logistic Regression are supposed to improve the prediction performance of the statistical model.

A: We have tried the inverse weighting technique, and we can include that in the supplementary file as well. The results, however, are not impressive. The various variables were used for log regression because these were the medications used by the patients. Given this was a retrospective study initiated at a time when steroids, remdesivir was not used. We used daily drugs that most of our patients in the ICU were like Aspirin, warfarin, NOACs. Data was just coming out about the hypercoagulability; hence we used the commonly used blood thinners. I hope this makes sense.

The inverse probability weighting table is below at the end of this document, as requested by you.

Propensity Score Matching

Propensity Score Matching (PMS) is essential as it ensures groups of subjects are matched equally on all factors.

Logistic Regression is commonly used for estimating propensity scores. To calculate the propensity scores.

$$e\text{^}xi = \frac{1}{1 + e^{-(\alpha+\beta 1X1+\beta 2X2+\ \beta 3X3+\ \beta 4X4+\ \beta 5X5+\ \beta 6X6)}}$$

Where;

α is the constant intercept

β_i are the regression coefficients

Xi explanatory variables;

X1=Aspirin

X2=Warfarin

X3=NOACS

X4=P2Y12

X5=HTN

X6=DM

1.1 Logistic Model using ICU admission as Y.

Table1: Output results of Logistic Regression Analysis

		# Iter	20		Alpha	0.05	
	coefficient	*s. e.*	*Wald*	*p-value*	*exp(b)*	*lower*	*upper*
intercept	-0.45044	0.332171	1.838826	0.175089	0.637351		
aspirin	-1.00047	0.46281	4.67307	0.030639	0.367707	0.378575	2.269164
warfarin	0.382791	0.733339	0.272467	0.601681	1.466372	0.179321	3.701697
NOACs	-0.15984	0.616872	0.067143	0.795543	0.852277	0.229824	2.520831
P0Y10	1.098044	0.908435	1.461005	0.22677	2.998296	0.142169	5.14458
HTN	0.213851	0.424561	0.253712	0.614473	1.238438	0.259028	1.790559
DM	0.018183	0.432623	0.001767	0.966474	1.01835	0.187667	1.05208

The results of the logistic model were discussed earlier. However, Aspirin is statistically significant in predicting ICU admission since its P-value is <0.05.

1.2 Propensity Score Matching Model

To estimate the propensity score model, we have;

Treatment as Aspirin

Independent Variables are: Warfarin, NOACS,P2Y12,HTN,DM

Outcome =ICU admission

Table 2; Output results of Propensity Score Matching Analysis

	coeff	*s.e.*	*Wald*	*p-value*	*exp(b)*	*lower*	*upper*
intercept	-1.97905	0.460885	18.43873	1.75E-05	0.1382		
Warfarin	0.631805	0.757552	0.69557	0.404276	1.881002	0.426148	8.302681
NOACs	0.257214	0.596261	0.186086	0.666194	1.293321	0.401946	4.161451
P2Y12	-1.17267	1.124333	1.087827	0.296953	0.30954	0.034173	2.803827
HTN	1.27439	0.510448	6.233079	0.012539	3.57652	1.315125	9.726449
DM	0.612198	0.426062	2.064607	0.150754	1.84448	0.80022	4.251466

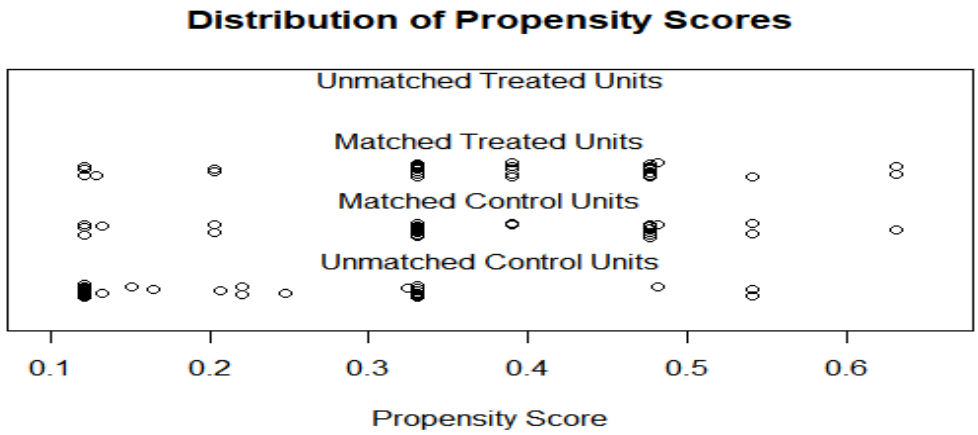
From the above Model;

Individuals with P2Y12 are less likely to receive Aspirin, while individuals with Warfarin, Noacs, P2Y12, HTN, and DM are likely to receive Aspirin.

1.3 Estimation of Propensity Scores

Propensity scores are estimated from the Propensity Model. The figure below represents the distribution of Propensity Scores.

Figure 1: Distribution of Propensity Scores



From the above figure, unmatched treated units had no cases while Matched control units and Matched treated units show that most patients were in the lower (0.1-0.5) part of the propensity scores; however, few patients are in the higher range (0.5 to 0.6)

1.4; To run the propensity score matching, we use a library (MatchIt)

In our case, we match using the nearest neighbor method and ratio=1. Table 2,3,4 provides summary tables that include means and standard deviations for all Data, balance for matched data, and percent balance improvement, respectively.

Table 3: Summary of Balance for All Data

	Means Treated	Means Control	Std. Mean Diff.	Var. Ratio	eCDF Mean	eCDF Max
distance	0.3802	0.2778	0.7942	0.7485	0.2172	0.3289
Warfarin	0.1026	0.0575	0.1486	.	0.0451	0.0451
NOACs	0.1538	0.1034	0.1397	.	0.0504	0.0504
P2Y12	0.0256	0.0575	-0.2014	.	0.0318	0.0318
HTN	0.8462	0.5747	0.7523	.	0.2714	0.2714
DM	0.4615	0.2644	0.3955	.	0.1972	0.1972

Table 4: Summary of Balance for Matched Data

Summary of Balance for Matched Data:

	Means Treated	Means Control	Std. Mean Diff.	Var. Ratio	eCDF Mean	eCDF Max
distance	0.3802	0.3734	0.0527	1.0566	0.0080	0.0769
Warfarin	0.1026	0.0513	0.1690	.	0.0513	0.0513
NOACs	0.1538	0.1026	0.1421	.	0.0513	0.0513
P2Y12	0.0256	0.0256	0.0000	.	0.0000	0.0000
HTN	0.8462	0.8718	-0.0711	.	0.0256	0.0256
DM	0.4615	0.4359	0.0514	.	0.0256	0.0256

	Std. Pair Dist.
distance	0.0540
Warfarin	0.1690
NOACs	0.2843
P2Y12	0.0000
HTN	0.0711
DM	0.0514

Table 5: Percent Balance Improvement

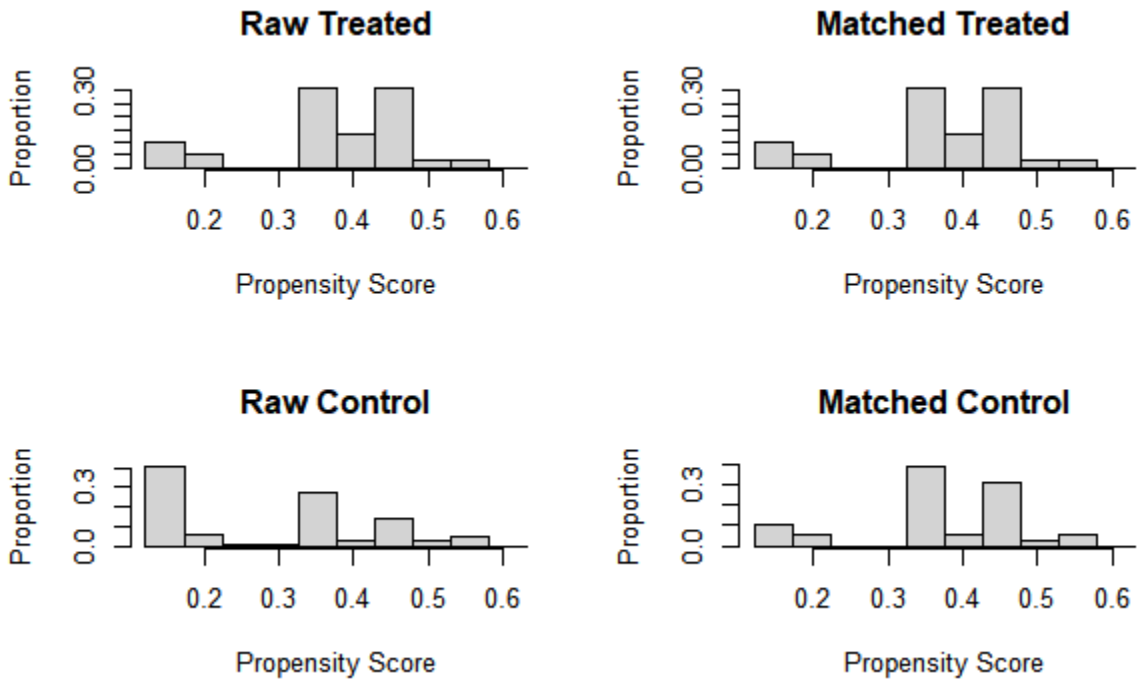
	Std. Mean Diff.	Var. Ratio	eCDF Mean	eCDF Max
distance	93.4	81	96.3	76.6
Warfarin	-13.7	.	-13.7	-13.7
NOACs	-1.8	.	-1.8	-1.8
P2Y12	100.0	.	100.0	100.0
HTN	90.6	.	90.6	90.6
DM	87.0	.	87.0	87.0

Table6:Summary of the matched observations

Categories	Number	Matched	Percentages	Unmatched	Percentages
1	38	38	100%	0	0%
0	87	38	45%	49	55%

All individuals in the treated group were matched to the control group from the table above.

Figure 2: Histogram presentation of propensity scores



1.5: Inverse Probability Weighting (IPW)

IPW analysis involves using predicted probability from Logistic Model as weights.

Using propensity scores to weight observations, we use;

$$\frac{\mathbf{Treatment}}{\mathbf{propensity}} + \frac{\mathbf{1-Treatment}}{\mathbf{1-propensity}}$$

The table below shows Regression output using weights, Y being ICU admission.

Table7: Output results of Inverse Probability Weighting

To ease interpretation of coefficients of the model, we include exponential of coefficients summary table as shown below.

	Coef	std.error	statistic	p.value
(Intercept)	0.7023935	0.275849	-1.28063353	0.200322418
Aspirin	0.4074902	0.2840699	-3.16027269	0.001576215
Warfarin	2.5253771	0.5304515	1.74641854	0.080738251
NOACs	0.9512181	0.4419046	-0.11317353	0.909892981
P2Y12	6.6365531	0.7712036	2.45407655	0.014124691
HTN	1.0212066	0.306786	0.06840226	0.945465426
DM	0.9460828	0.3062912	-0.18095574	0.85640232