

Variables associated with bleeding and thrombotic outcomes among patients admitted to the hospital with COVID-19 and elevated D-dimer: insights from the ACTION randomised clinical trial

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Background: In the ACTION trial, therapeutic anticoagulation did not show benefit on mortality, days of hospitalization and oxygen therapy at 30 days among patients with COVID-19. However, this strategy was associated with higher rate of bleeding and a potential reduction in the rate of clinical thrombotic events. The current analysis evaluated which variables were independently associated with both outcomes in order to help the identification of the risk for thrombotic and hemorrhagic events among patients with COVID-19.

Methods: A total of 615 patients hospitalized with COVID-19 and elevated D-dimer levels were randomly assigned to prophylactic anticoagulation (mainly in-hospital heparin) or a therapeutic strategy that used in-hospital rivaroxaban 20 mg daily for stable patients, or enoxaparin 1 mg/kg twice daily for unstable patients, followed by rivaroxaban through 30 days. One patient withdrew consent and was not included in the analysis. The current analysis tested baseline clinical characteristics and laboratorial exams one by one with independent logistic regressions for the composite of bleeding (major bleeding and clinically relevant nonmajor bleeding) and thrombotic events (venous thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events). Significant variables ($p < 0.05$) were selected to adjust several multiple logistic models. Final models were chosen based on Akaike information criterion and therapeutic anticoagu-

lation was included in the final model based on the primary results of the trial.

Results: The model for bleeding events showed an accuracy of area under the curve (AUC) of 0.635 (table 1) while the model for thrombotic events had an AUC of 0.725 (table 2). Level of respiratory support (especially invasive ventilation) was associated with both outcomes in the multivariable analysis (tables 1 and 2). Beyond respiratory support, level of creatinine and history of coronary disease were also independently associated to the risk of thrombotic events. When the utilization of therapeutic anticoagulation (mainly with rivaroxaban) was included in the multivariable analysis, this variable was strongly associated with higher risk of bleeding (model AUC of 0.718) but was not associated with lower rate of thrombotic events (Tables 1 and 2).

Conclusion: Since the variables associated with higher risk of thrombotic events are similar to the variables associated to bleeding complications, the selection of patients with better balance of risk vs. benefit to use therapeutic anticoagulation in COVID-19 still a challenging decision. Coronary disease and creatine may help to identify patients at higher risk of thrombotic complications while the use of therapeutic dose of direct oral anticoagulant increased the risk of bleeding in almost 4 times among patients hospitalized due to COVID-19.

Table 1. Multiple model for bleeding events (with or without therapeutic anticoagulation)

Variables	OR	CI 95%	p-value
NIV or HFNC vs Catheter or Oxygen Mask	2.307	0.836; 6.365	0.1063
Tracheal intubation vs Catheter or Oxygen Mask	3.142	1.117; 8.845	0.0301
Age	1.020	0.994; 1.046	0.1326

AUC = 0.635

Variables	OR	CI 95%	p-value
NIV or HFNC vs Catheter or Oxygen Mask	2.305	[0.824; 6.453]	0.1117
Tracheal intubation vs Catheter or Oxygen Mask	2.829	[0.987; 8.103]	0.0529
Age	1.020	[0.994; 1.047]	0.1234
Group (therapeutic)	3.789	[1.610; 8.913]	0.0023

AUC = 0.718

Table 2. Multiple model for thrombotic events (with or without therapeutic anticoagulation)

	OR [IC 95%]	P value
Intercept	1 (Ref)	
Catheter or oxygen mask vs No Oxygen	3.29[1.21; 8.83]	0.0193
NIV / HFNC vs No Oxygen	7.24[2.15; 24.17]	0.0014
Tracheal intubation vs No Oxygen	7.03[1.95; 25.18]	0.0028
Creatinin	1.01[1.00; 1.02]	0.0076
Coronary Disease	3.67[1.32; 10.29]	0.0130

AUC = 0.725

Catheter or oxygen mask vs No Oxygen	3.32[1.22; 8.95]	0.0185
NIV / HFNC vs No Oxygen	7.32[2.18; 24.68]	0.0013
Tracheal intubation vs No Oxygen	7.32[2.03; 26.57]	0.0024
Creatinin	1.01[1.00; 1.02]	0.0071
Coronary Disease	3.63[1.31; 10.17]	0.0133
Therapeutic group	0.68[0.38; 1.24]	0.2098