Comparison of IMPROVE, modified IMPROVE, IMPROVEDD, Padua and CHA2DS2-VASC risk scores for venous and arterial thrombotic events prediction in hospitalized COVID-19 patients

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Letter to the Editors-in-Chief

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Dear Editor,

Venous thromboembolic (VTE) and arterial thrombotic (AT) events impose a substantial burden of morbidity and have a detrimental impact on mortality of COVID-19 patients [1]. These events occur both in ambulatory and hospital setting and are very challenging to predict and prevent, even using therapeutic thromboprophylaxis with low molecular weight heparins (LMWH) or antiplatelet therapies. There is an increasing pool of evidence deciphering mechanisms of COVID-19 thrombogenicity [2,3] but at the moment there are no therapies available that can completely prevent these events from occurring. Pre-COVID-19 era developed thrombotic risk scores are able to identify patients with increased risk for VTE, nevertheless their predictive properties and risk estimation are uncertain. Thus, we aimed to evaluate predictive properties of several thrombotic risk prediction scores in a large cohort of hospitalized COVID-19 patients.

We retrospectively evaluated 5959 consecutive COVID-19 patients hospitalized in University Hospital Dubrava, Zagreb, Croatia in the period from 3/2020–6/2021. All patients were Caucasian. Data used were recorded as a part of the hospital Registry project (ClinicalTrials.gov identifier: NCT05151094) and were obtained through analysis of electronic and paper medical records. Patients were treated according to the contemporary guidelines with majority of them receiving low molecular weight heparin (LMWH) thromboprophylaxis with various dose intensity and corticosteroids. VTE (deep venous thrombosis (DVT) and pulmonary embolism (PE)) and AT (myocardial infarction (MI), cerebrovascular insult (CVI), peripheral AT (PT) and mesenterial thrombosis (MT)) were considered if documented by objective imaging and laboratory methods. More details on approach, incidence, clinical context and risk factors for VTE and AT in our dataset have been published previously [4]. We considered IMPROVE [5], modified IMPROVE [6], IMPROVEDD [7], Padua [8] and CHA2DS2-VASC [9] risk scores. For arterial events prediction no points were provided for MI and CVI for Padua risk score. Scores were indirectly compared based on their AUC values obtained through ROC curve analysis (*P* values presented in Table 1 represent significance of difference of AUC values from 0.5 value). Cut-offs with the highest Youden index value were shown. P values <0.05 were considered to be statistically significant. Normality of distribution of numerical variables was tested using the Shapiro-Wilk test. Since they were non-normally distributed, they were presented as median and interquartile range (IQR) and were compared between groups using the Mann Whitney *U* test. In cases where median values were same but statistically significant differences were present (due to large sample sizes small absolute differences obtained statistical significance) we added ↑sign adjacent to the group obtaining higher score values. All analyses were performed using the MedCalc statistical software ver 20.014 (MedCalc Software Ltd., Ostend, Belgium).

A total of 5959 patients were analyzed. Patients' characteristics are shown in Supplementary Table S1. Median age was 72 years and median Charlson comorbidity index was 4 points. There were 56.2% males, majority of patients had either severe (70.5%) or critical (15.3%) severity of COVID-19 symptoms at the time of hospital admission. During hospitalization, a total of 1291 (21.7%) patients required high flow oxygen therapy, 1038 (17.4%) required mechanical ventilation and 1359 (22.8%) patients required intensive care unit stay. A total of 2023 (33.9%) patients died. There were 365 (6.1%) documented VTE events, among them 137 (2.3%) DVT and 262 (4.4%) PE. There were 331 (5.6%) AT, among them 102 (1.7%) MI, 142 (2.4%) CVI, 67 (1.1%) PT and 18 (0.3%) MT.

Median IMPROVE score was 4 points, IQR (1–4), modified IMPROVE score 3 points IQR (1–4), IMPROVEDD 4 points (2–6), Padua score 6 points IQR (4–7) and CHA2DS2-VASC score 3 IQR (2–4). Each of the VTE prediction scores if elevated were significantly associated with higher occurrence of VTE (IMPROVE median 3 vs 2 points, modified IMPROVE median 3 vs 2 points, IMPROVEDD median 5 vs 4 points, Padua median ↑6 vs 6 points in patients with and without VTE, respectively; $P < 0.001$ for all analyses) whereas lower CHA2DS2-VASC score was associated with VTE occurrence (median 3 vs ↑3 points in patients with and without VTE, respectively; $P < 0.001$). All scores if elevated were significantly associated with higher occurrence of AT (IMPROVE median 4 vs 2 points, modified IMPROVE median 4 vs 2 points, IMPROVEDD median 5 vs 4 points, modified Padua without providing points for MI and CVI median ↑6 vs 6 points, CHA2DS2-VASC median 4 vs 3 points in patients with and without AT, respectively; $P < 0.001$ for all analyses).

Comparison of VTE and AT predictive properties of investigated risk prediction scores are shown in Table 1. Regarding VTE, all investigated scores demonstrated modest predictive properties with highest AUC observed for IMPROVEDD score (AUC 0.623, >3 points sensitivity 69%

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Table 1
Predictive properties of IMPROVE, modified IMPROVE, IMPROVEDD, Padua and CHA2DS2-VASC thrombotic risk prediction scores for venous and arterial thrombotic events. Cut-off points with the highest Youden index values were presented.

	Venous thromboembolic events			Arterial thromboses		
	AUC	Sensitivity with 95% CI	Specificity with 95% CI	AUC	Sensitivity with 95% CI	Specificity with 95% CI
IMPROVE	0.596 (0.583–0.608); P < 0.001	>1 point 74 (69–78)	>1 point 43 (42–45)	0.646 (0.634–0.658); *P* < 0.001	>1 point 81 (76–85)	>1 point 44 (42–45)
Modified IMPROVE	0.600 (0.588–0.613); P < 0.001	>1 point 88 (84–91)	>1 point 30 (28–31)	0.653 (0.641–0.665); *P* < 0.001	>3 points 63 (58–68)	>3 points 61 (60–62)
IMPROVEDD	0.623 (0.608–0.637); P < 0.001	>3 points 69 (64–74)	>3 points 49 (48–51)	0.642 (0.627–0.657); *P* < 0.001	>4 points 60 (53–66)	>4 points 62 (61–64)
Padua[a]	0.584 (0.571–0.596); P < 0.001	>4 points 88 (84–91)	>4 points 30 (29–31)	0.614 (0.601–0.626); P < 0.001	>4 points 94 (91–96)	>4 points 30 (29–31)
CHA2DS2-VASC	0.564 (0.551–0.577); P < 0.001	≤3 points 72 (67–77)	≤3 points 40 (39–42)	0.654 (0.642–0.666); P < 0.001	>3 points 61 (55–66)	>3 points 62 (60–63)

[a] Modified Padua score was used for arterial thromboses prediction (without scoring points for acute myocardial infarction and cerebrovascular insult). Abbreviations: AUC – area under curve; CI – confidence interval.

and specificity 49%) followed by modified IMPROVE (AUC 0.600, >1 point sensitivity 88% and specificity 30%), IMPROVE (AUC 0.596, >1 point sensitivity 74% and specificity 43%), Padua (AUC 0.584, >4 points sensitivity 88% and specificity 30%), and CHA2DS2VASC scores (AUC 0.564, ≤3 points sensitivity 72% and specificity 40%) as shown in Fig. 1A. In mutual comparison of ROC curves, IMPROVEDD had significantly higher AUC in comparison to all other scores, whereas other scores had comparable AUC values. Overall higher AUC values were achieved for DVT than for PE prediction, with IMPROVEDD score having highest AUC values for both DVT and PE prediction (DVT AUC 0.650, >3 points sensitivity 75% and specificity 49%; PE AUC 0.603, >2 points sensitivity 89% and specificity 29%).

Regarding AT, CHA2DS2-VASC risk score demonstrated best predictive properties (AUC 0.654, >3 points sensitivity 61% and specificity 62%), followed by IMPROVE (AUC 0.646, >1 point sensitivity 81% and specificity 44%), IMPROVEDD (AUC 0.642, >4 points sensitivity 60% and specificity 62%) and modified Padua risk scores (without providing points for MI and CVI AUC 0.614, >4 points sensitivity 91% and specificity 30%) as shown in Fig. 1B. In mutual comparison of ROC curves, all scores had comparable predictive properties without mutually significant differences. Considering particular type of AT, CHA2DS2-VASC score had best predictive properties for MI (AUC 0.663, >3 points sensitivity 64% and specificity 61%) and CVI (AUC 0.670, >4 points sensitivity 45% and specificity 80%) and IMPROVEDD had best predictive properties for PT (AUC 0.711, >4 points sensitivity 76% and specificity 61%) and MT (AUC 0.573, >3 points sensitivity 29% and specificity 83%).

There are several important points that need to be considered. Our results based on 5959 mostly severe and critical COVID-19 patients from a dedicated tertiary institution suggest that although all VTE prediction scores were significantly higher in patients with than without COVID-19 associated thrombotic events (and CHA2DS2-VASC was significantly lower in patients with VTE and higher in patients with AT when compared to patients without events), neither of the investigated scores demonstrated acceptable VTE nor AT discrimination properties. There are substantial differences regarding VTE and AT, as well as between AT subsets. In comparison to other scores, D-dimer based IMPROVEDD had significantly better, although overall modest properties for VTE discrimination. All scores had somewhat better properties for DVT then PE discrimination which might reflect the challenges of PE diagnosis in COVID-19 patients that might be not sufficiently stable to undergo diagnostic procedures. DVT evaluation is more easily performed and often unexpectedly high event rates are encountered if screening of asymptomatic patients can be utilized [10]. In contrast to VTE that associates with more severe COVID-19 presentation and high functional impairment, AT seem to be associated with milder severity of COVID-19 symptoms and more clear clinical presentation, often in the context of previously established chronic metabolic comorbidities [4]. Thus, it is not surprising that CHA2DS2-VASC score based on comorbidities seems to perform best for prediction of MI and CVI.

Limitations of our work are single center experience and retrospective study design. Our findings are representative of a high output tertiary COVID-19 center and might not translate into other clinical contexts.

In conclusion, predicting VTE and AT in hospitalized COVID-19 patients cannot be relied on pre-COVID era developed risk scores. D-dimer

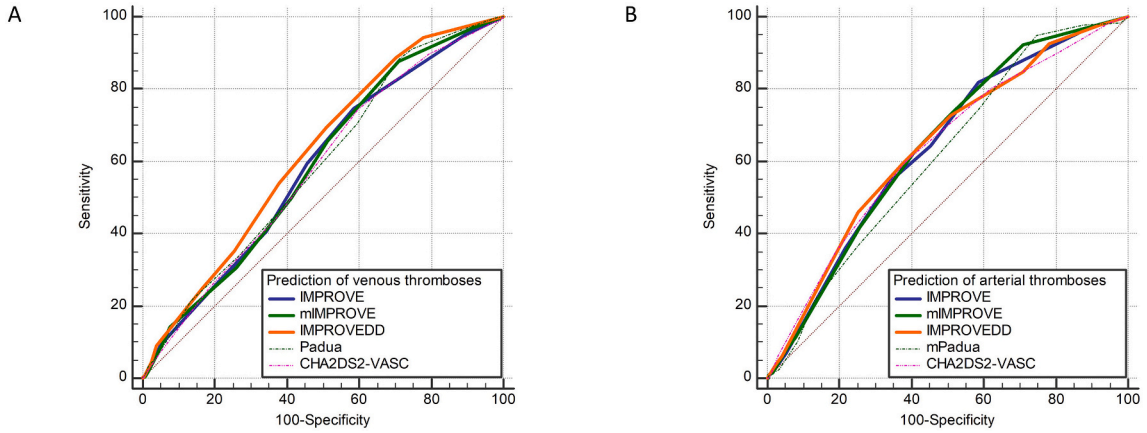

Fig. 1. Receiver operating characteristic (ROC) curves of IMPROVE, modified IMPROVE, IMPROVEDD, Padua and CHA2DS2-VASC risk scores for prediction of A) venous and B) arterial thrombotic events.

based score (IMPROVEDD) had best diagnostic properties regarding VTE in comparison to other scores, whereas comorbidities based CHA2DS2-VASC score performed best regarding AT. Our results highlight the needs for development of new thrombotic risk prediction scores specific for COVID-19 and to increase measures of systematic screening of patients for thrombotic events.

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Ethical approval

Study was approved by the University hospital Dubrava review board (nm. 2021/2503–04).

Declaration of competing interest

None.

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