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Derivation and Validation of a Novel Prediction Model to Identify Low-Risk Patients With Acute Pulmonary Embolism

Running Title : Model for Low- risk Acute Pulmonary Embolism

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ABSTRACT

Accurate identification of low-risk patients with acute pulmonary embolism(PE) who may be eligible for outpatient treatment or early discharge can have substantial cost saving benefit. The purpose of this study was to derive and validate a prediction model to effectively identify PE patients at low risk of short term mortality, right ventricular (RV) dysfunction, and other non-fatal outcomes. This study analysed data from 400 consecutive patients with acute PE. We derived and internally validated our prediction rule based on clinically significant variables that are routinely available at initial examination, that were categorized and weighted using coefficients in the multivariate logistic regression. The model was externally validated in an independent cohort of 82 patients. The final model (HOPPE score) consisted of 5 categorized patient variables (1,2,or 3 points, respectively):systolic blood *p*ressure(>120,100-119,<99;mmHg), diastolic blood *p*ressure(>80,65-79,<64;mmHg), *h*eart rate (<80,81-100,>101;beats/min), arterial partial pressure of *o*xygen (>80,60-79,<59;mmHg), and modified *E*CG score (<2,2-4,>4). The 30- day mortality rates were 0% in low risk(0-6 points), 7.5%-8.5 in intermediate risk(7-10), and 18.2-18.8% in high risk(≥ 11) patients across the derivation and validation cohorts. In comparison to the previously validated PESI score, the HOPPE score had a higher discriminatory power(AUC 0.74 vs 0.85, p=0.033) and significantly improved both the discrimination(integrated discrimination improvement,p=0.002) and reclassification(net reclassification improvement,p=.003) of the model for short term mortality. In conclusion, the HOPPE score accurately identifies acute PE patients at low risk of short term mortality, RV dysfunction, and other non fatal outcomes. Prospective validation of the prediction model is necessary before implementation in clinical practice.

KEYWORDS: Acute Pulmonary Embolism, Mortality, Outpatient, Right Ventricular Dysfunction, Score

INTRODUCTION

Prognostic assessment of patients with acute pulmonary embolism (PE) is crucial in guiding therapeutic decision making and helping clinicians determine the appropriateness of ambulatory treatment or early hospital discharge. There is increasing evidence supporting the use of low-molecular-weight heparin in outpatient treatment of patients with low risk PE. [1,2] Accurate identification of those patients who may be theoretically eligible for outpatient treatment or early discharge can have substantial cost saving benefit.[3] Although several prognostic models have been derived and validated in patients with acute PE, they are over-dependent on comorbidities, which represent a spectrum of disease and are clinically difficult to classify as binary parameters. [4-8] The purpose of this study was to derive and validate a clinical prediction rule based on simple clinical information that is routinely collected in emergency departments to effectively identify PE patients at low risk of short term mortality, right ventricular dysfunction (RVD), and other non - fatal complications. In addition, this study wanted to compare the prognostic ability of this prediction model with the previously validated Pulmonary Embolism Severity (PESI) score.

METHODS

We retrospectively analyzed the data of all consecutive inpatients and outpatients with confirmed acute pulmonary embolism between January 2011 and March 2015 at a tertiary care hospital in Chennai, India. Eligibility for this study required patients to be more than 18 years of age and have acute pulmonary embolism confirmed by an intraluminal filling defect on CT pulmonary angiography (CTPA). The study was approved by the institutional review board and ethics committee of our hospital.

The baseline clinical variables necessary to derive our prediction rule were abstracted using a standardized form from the hospital database. All patients had been examined in the

emergency department and during hospitalization in the intensive care unit. Information was obtained regarding demographics, comorbidites, (malignancy, chronic lung disease, congestive heart failure), and recent events leading to pulmonary embolism (PE) (trauma, surgery). A modified ECG score with adjusted variables and point values was utilized (Tachycardia – 2, Incomplete Right bundle branch block (RBBB) – 1, Complete RBBB – 3, T wave inversion in V1-V3 – 4, $S_1Q_3T_3$– 4) .[9,10] Two blinded investigators independently assess the ECG parameters and discrepancies were resolved by consensus.

The patients were required to undergo trans-thoracic echocardiography within 24 hours after diagnosis of PE to assess the presence of right ventricular dysfunction (RVD). RVD was defined in echocardiography as the presence of two or more of the following criteria: RV>30mm or RV/LV end-diastolic ratio > 1 (apical 4-chamber view); dyskinesia or hypokinesia of the right ventricular free wall; hypokinesia of the infundibular RV region with normal contraction of the RV apex; tricuspid annular plan systolic excursion (TAPSE)<15mm; RV/atrial gradient >30mmHg.[11-13] Utilizing the CT pulmonary angiogram, the pulmonary artery obstruction index (PAOI) was calculated according to the Qanadli score (0-100% obstruction), taking into consideration the number of occluded segmental arteries and estimated degree of occlusion of each vessel.[14]

The primary outcome used to derive and validate the prediction rule was all-cause 30-day mortality after diagnosis of acute pulmonary embolism. Secondary endpoints were 1) In-patient mortality, 2) RVD, diagnosed by echocardiography, 3) nonfatal cardiogenic shock and aborted cardiorespiratory arrest. Outcomes were assessed by using patient or proxy phone interviews and/or review of the hospital medical records.

Of the 400 patients who met our inclusion criterion, we randomly selected 300 (75%) for the derivation sample and 100 (25%) for the internal validation sample. To derive our

prediction rule, we used variables that were readily accessible by an emergency physician and previously shown to be associated with short-term mortality in acute pulmonary embolism (PE). We performed univariate analysis to select predictor variables for the multivariate model, using a cut off of $p<0.20$. Continuous variables that were statistically significant were then categorized, choosing the most discriminative cut-off points. We included variables that were statistically significant in a logistic regression model. After removing non-statistically significant variables, a regression coefficient for each significant variable in the final model was calculated. Similar to previous studies, we explored candidate models in an attempt to find models that identified a low-risk group with a membership of at least 20% of the total derivation sample and a 30-day mortality of < 1%.[15-17] An external validation was performed in an independent patient population using data from 82 patients with acute PE at another tertiary care hospital. Follow up information was obtained by medical records review and phone interview of patients

A descriptive analysis was performed using relative frequencies for categorical variables and means (SD) for continuous variables. We used the chi squared or Fisher exact test to compare categorical variables. The Mann- Whitney and Kruskal- Wallis tests were used for continuous parameters. Inter-observer agreement between the ECG parameters of both blinded observers was assessed by the kappa statistic using Fleiss' agreement scale. We compared mortality rates in each of the three risk classes across the derivation and validation cohorts with the use of chi-square statistics. We used a receiver operating characteristic (ROC) curve to estimate the discriminatory power of our rule to predict 30-day mortality across both the derivation, internal and external validation cohorts. In order to assess the predictive accuracy of our prediction rule, we compared the sensitivity, specific, positive and negative predictive values and likelihood ratios across both cohorts. Correlation between the Qanadli score for PAOI and the prediction model was assessed using Spearman's rank

correlation coefficient. In addition, to compare the discriminative value of our prediction model and the PESI score, we calculated the net reclassification improvement(NRI) and integrated discrimination improvement(IDI) as described by Pencina et al.[18] For all analysis, a two- tailed P value <0.05 was used to define statistical significance.

RESULTS

The baseline patient characteristics of the derivation, internal and external validation sample are shown in Table 1. The mean age of the evaluable population was 54 years, and 54.5% were males. The kappa statistic assessing the inter-observer agreement was between 0.82-0.86 for all the ECG parameters. Thirty day mortality in the derivation, internal and external validation samples were 9.0%, 9.0%, and 8.5%, respectively.

We found 5 patient variables to be independently associated with 30-day mortality in pulmonary embolism: systolic blood pressure, diastolic blood pressure, heart rate, PaO_2 (arterial partial pressure of oxygen), modified ECG score. These numerical variables were each categorized into 3 groups; systolic blood *p*ressure (>120, 100-119, <99), diastolic blood *p*ressure (>80, 65-79, <64), *h*eart rate (<80, 81-100, >101), Pa*O*2 (>80, 60-79, <59), and modified *E*CG score (<2, 2-4,>4). We included all 15 variables in a logistic regression model shown in Table 2, and assigned points for the risk score according to the regression coefficients obtained. The final prediction rule (HOPPE score) and optimal cut off values were used to quantify the association of each of these variables with 30 day mortality. The prediction rule classified similar proportions of patients in three risk classes across the derivation and internal validation samples (Table 3). In the derivation sample, 30 day mortality was 0% in the low risk group, 7.5% in the intermediate risk group, and 18.8% in the high risk group (Table 4). The secondary outcomes of in-patient mortality, right ventricular

dysfunction (RVD), non-fatal cardiogenic shock and cardiorespiratory arrest showed a similar trend across all the risk classes.

As shown in Table 4, there were no significant differences in 30-day mortality, RVD, nonfatal cardiogenic shock or cardiorespiratory arrest in the risk classes among the three study samples. In addition, when assessing the discriminatory power of the HOPPE score for 30-day mortality, there no significant difference (p=0.32) in the area under the ROC curves between the derivation (AUC=0.85,95% CI 0.70-0.93), internal (AUC 0.84, 95%CI 0.68-0.92) and external validation (AUC=0.83, 95% CI 0.67-0.93) cohorts.

When categorized as low risk vs. higher risk (intermediate and high risk groups), the HOPPE score had a high sensitivity and high negative predictive value for predicting 30-day mortality and RVD (Table 5). The specificity (45-48%) and positive predictive value (21-23%) were low due to the fact that the prediction rule was designed to identify low risk patients.

There was a strong linear correlation between the HOPPE score and PAOI, as calculated by the Qanadli method. (Figure 1)

In comparison to the previously validated PESI score, the HOPPE score had a higher accuracy (sensitivity 86.2% vs. 98.7%, p=0.036, specificity 37.2% vs. 48.3%, p=0.043) and discriminative power (AUC 0.74 vs 0.85, p=0.033). In addition, it also significantly improved both the discrimination (IDI, p=.002) and reclassification (NRI, p=.003) of the model for short term mortality.

DISCUSSION

In our analysis, we present a clinical prediction rule for identifying patients with a low risk of developing short-term complications following acute pulmonary embolism (PE). The

HOPPE score identified approximately one third of patients at low risk of short –term mortality, right ventricular dysfunction (RVD), non fatal medical outcomes across both the derivation and validation cohorts. In addition, the sensitivity (96-99%) and negative predictive value (95-96%) for predicting overall mortality among low-risk patients was excellent.

In the development of a clinical prediction rule, we sought to include variables that correlate independently with adverse outcomes in PE and are routinely available in busy emergency departments. Although we considered all the known main risk factors and clinical signs of PE for inclusion in the model, there are several differences between the clinical variables included in our study versus those of other similar clinical prediction rules (CPR).[4,5,19-21]In comparison to other previously validated PESI score, HOPPE score did not utilize demographic factors (age, sex) and the presence of comorbid illnesses (malignancy, heart failure, chronic lung disease). These comorbidities represent a spectrum of disease that is difficult to quantify using binary parameters. Nonetheless, our prediction rule performed well at identifying patients with low –risk of developing complications following pulmonary embolism. Not only did it have a higher accuracy than the PESI score, but the HOPPE score improved the discrimination and reclassification of the model for 30-day mortality.

It is worth noting that our prediction rule is the first to identify a group of PE patients with 30 day mortality <1% based on our cut off score to identify a low – risk group. Many previous studies have consistently identified PE patients with in hospital mortality <1% in low risk patients but not in terms of 30 day mortality.[21-27] However, our study did find a lower percentage of low-risk patients in comparison to the percentage of low risk and very low risk patients in the original study of Aujesky et al (40.9%) and Wicki et al. (67.2%). As noted in a recent meta-analysis, this wide range of proportion of patients classified at low risk

may be explained by different study populations across studies and by different parameters included in each CPR.[28]

The HOPPE score also effectively identified patients at a low risk of in-patient mortality, non- fatal cardiogenic shock, resuscitated cardiac arrest, and right ventricular dysfunction (RVD). Patients with RVD are known to be at risk of subsequent clinical worsening and PE-related death and may benefit from more aggressive therapeutic strategies.[29] To the best of our knowledge, this CPR is the first to identify patients with a low risk of echocardiographic RVD. The HOPPE score is successful in predicting RVD with a high sensitivity (95-96%) and negative predictive value (96-98%). It is of interest to note that nearly one fifth of the low risk patients had echocardiographic evidence of RVD. Although this finding may be influenced by lack of uniform criteria to diagnose RVD, future studies will need to determine whether this subset of patients are at short-term risk of PE-related mortality that may be independent of hemodynamic impairment.

Although based on prospective selection rather than formal CPRs, recent evidence suggests that many patients with low risk pulmonary embolism (PE) can be safely treated at home.[30] Utilization of the HOPPE score to identify and treat low-risk PE patients on outpatient basis can have substantial cost- savings. The potential economic benefit of outpatient treatment and early discharge of low risk PE patients has been highlighted in many studies.[3] Our prediction model has several distinctive strengths. It consists of clearly defined, routinely available clinical and ECG parameters, with an excellent interobserver agreement. The accuracy and reproducibility of the risk stratification score are supported by its external validation in an independent cohort. However as acknowledged by other authors, CPRs must be intended to supplement rather than supplant clinical judgment; physicians need to consider psychosocial contraindications to outpatient care and the availability of outpatient systems of health care.[19]

Our study has potential limitations. First, delayed echocardiography after the episode of PE may have lead to a missed diagnosis of right ventricular dysfunction (RVD) which resolved during the first hours of PE. Second, we could not estimate the potential impact of various treatment regimens as this data was not consistently available. Third, the categorization of continuous variables may oversimplify the way physicians interpret predictor variables. Finally, we could not asses the incidence of recurrent PE and major bleeding as these were not routinely documented in our database.

In summary, we derived and validated a prediction rule that identifies patients with acute PE who are at a low risk for short term mortality, RVD and other non-fatal outcomes. Prospective validation of our prediction rule is necessary before its implantation in clinical practice to select the patients eligible for ambulatory treatment or shortened hospitalization.

CONFLICT OF INTEREST: None Declared

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FIGURE LEGENDS

Figure 1: Scatter diagram shows strong positive correlation ($r=0.903$, $p<0.001$) between HOPPE score and CT Pulmonary Artery Obstruction Index.

Table 1: Demographic and Clinical Characteristics of the Patients in the Derivation and Validation Cohorts

Variables	Derivation Sample (N=300)	Internal Validation Sample (N=100)	External Validation Sample (N=82)	P value
Age (years)	54.2 ± 12.2	53.8 + 11.9	55.1 + 9.7	0.53
Men	162 (54%)	56(56%)	45 (55%)	0.46
Deep Vein Thrombosis	85 (28.3%)	26 (26%)	21 (27%)	0.32
Surgery (<3months)	50 (16.7%)	14 (14%)	12 (15%)	0.21
Bone Fracture (<3months)	46 (15.3%)	14 (14%)	9 (11%)	0.33
Chronic Airway Disease	40 (13.3%)	15 (15%)	16 (20%)	0.26
Heart Failure	50 (16.7%)	18 (18%)	13 (16%)	0.43
Malignancy	45 (15.0%)	16 (16%)	12 (15%)	0.46
Systolic Blood Pressure (mmHg)	109.7± 13.4	111.1±12.4	107.9 ± 10.9	0.44
Diastolic Blood Pressure (mmHg)	73.5±9.5	72.3±8.6	75.2 ± 10.4	0.42
Heart Rate (beats/minute)	97.6±9.9	101.5±11.3	100.4 ± 93.4	0.18
Respiratory Rate (breaths/ minute)	27.8±4.1	26.6±3.8	26.0 ± 4.0	0.63
Pa_{O_2} (mmHg)	70.5±8.2	72.2±9.6	69.9± 8.9	0.45
Pa_{CO_2} (mmHg)	30.2±6.1	29.6±5.2	31.5±5.9	0.23
P_{AO_2}-Pa_{O_2} (mmHg)	35.7±4.6	39.8±5.1	38.7±6.1	0.20
Modified ECG Score	3.4±0.8	3.2±0.7	3.5± 0.8	0.39

Continuous variables are represented as mean ± standard deviation. Pa_{O2} =arterial partial pressure of oxygen, Pa_{CO2} = arterial partial pressure of carbon dioxide, P_{AO2}-Pa_{O2}=alveolar-arterial difference in partial pressure of oxygen.

Table 2: Independent Predictors of 30-day mortality in the Derivation Sample and Point Scoring System of the Prediction Model (HOPPE Score)

Variable	B coefficients	95% confidence interval	Points
Systolic Blood Pressure (mmHg)			
>120	0.23	0.16-0.31	+1
100-120	0.57	0.40-0.75	+2
<100	0.88	0.64-1.13	+3
Diastolic Blood Pressure (mmHg)			
>80	0.29	0.20-0.38	+1
65-80	0.48	0.34-0.62	+2
<65	0.8	0.61-1.01	+3
Heart Rate (beats/min)			
<80	0.31	0.23-0.40	+1
80-100	0.55	0.41-0.70	+2
>100	0.68	0.48-0.89	+3
PaO_2 (mmHg)			
>80	0.30	0.18-0.42	+1
60-80	0.46	0.31-0.61	+2
<60	0.61	0.52-0.70	+3
ECG Score			
<2	0.27	0.19-0.35	+1
2-4	0.41	0.22-0.60	+2
>4	0.77	0.59-0.95	+3

Risk Classification	Total Score
Low	0-6
Intermediate	7-10
High	11-15

Table 3: Risk Class Distributions in the Derivation and Validation Cohorts

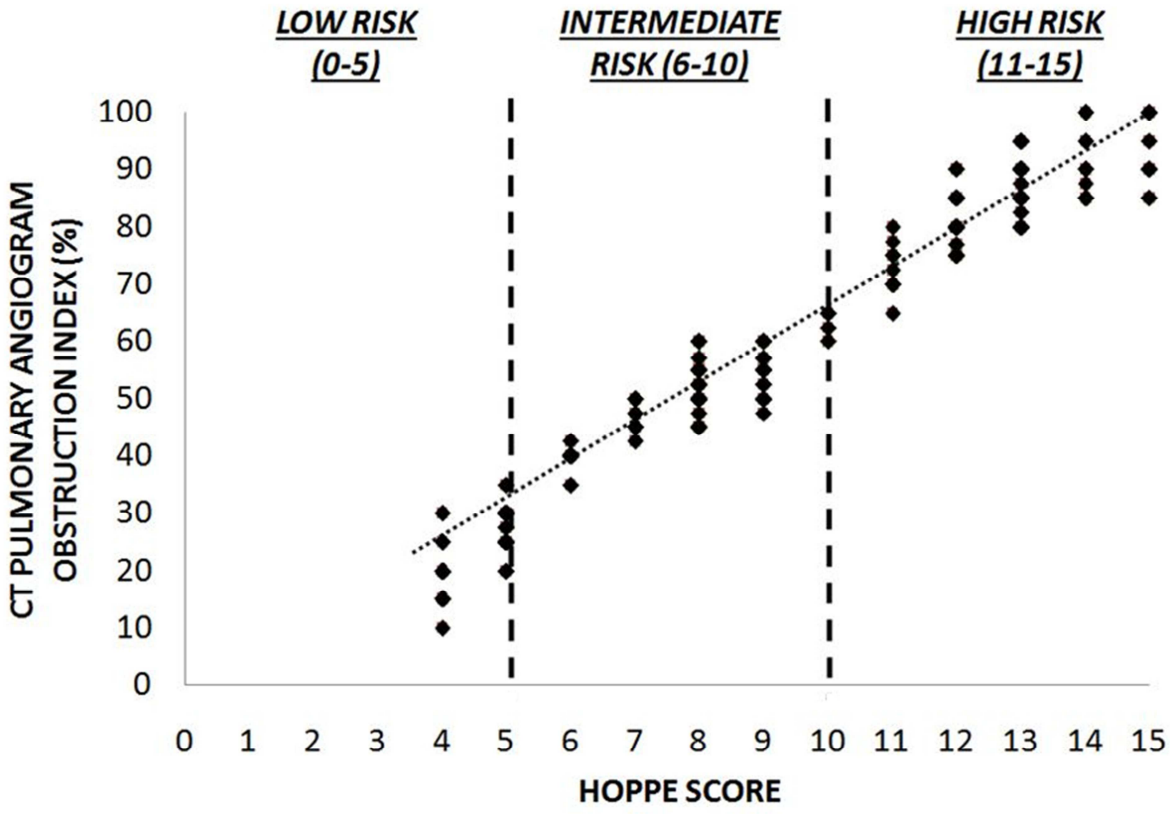
Risk Class	Derivation Cohort(n=300) (N, %)	Internal Validation Cohort (n=100) (N, %)	External Validation Cohort (n=82) (N, %)
Low	93 (31.0)	32 (32)	27 (33)
Intermediate	106 (35.3)	35 (35)	27 (33)
High	101 (33.7)	33 (33)	28 (34)

Table 4: Comparison of Risk-Class-Specific Outcomes in the Derivation and Validation Cohorts

Risk Class	Derivation Cohort (N=300)	Internal Validation Cohort (N=100)	External Validation Cohort (N=82)	P Value
	(N, %, 95%CI)	(N, %, 95%CI)	(N, %, 95%CI)	
30-day mortality				
Low	0, 0 (0-0.5)	0, 0 (0-0.8)	0, 0 (0-0.6)	0.72
Intermediate	8, 7.5 (6.1-9.1)	3, 9 (7.0-9.2)	2, 7 (6.0 – 8.8)	0.35
High	19, 18.8(16.1-21.8)	6, 18(15.8-20.8)	5, 18 (15.2 – 20.6)	0.51
In Hospital Mortality				
Low	0, 0 (0-0.5)	0, 0 (0-0.4)	0,0 (0-0.6)	0.87
Intermediate	3, 2.8 (1.8-4.0)	1, 3 (2.0-3.9)	1, 4 (1.9-5.5)	0.65
High	9, 8.9 (7.5-10.4)	3, 9 (7.8-10.5)	2, 7 (5.8-8.6)	0.53
Nonfatal outcomes: Cardiogenic shock, Cardiorespiratory arrest				
Low	0, 0(0-0.5)	0, 0 (0-0.8)	0,0 (0-0.6)	0.62
Intermediate	2, 1.9 (1.1-2.9)	1, 3 (1.4-4.3)	1,4 (2.7-4.7)	0.06
High	6, 5.9 (4.2-7.7)	2, 6 (4.0-8.3)	2,7 (5.9-8.9)	0.33
Right Ventricular Dysfunction				
Low	20, 21.5(19.8-23.3)	7, 22 (19.5-24.5)	6,21 (18.4- 24.5)	0.71
Intermediate	79, 74.5(72.8-76.3)	26, 74 (70.2-78.7)	21,78 (74.4-81.2)	0.62
High	98, 98.0 (96.9-99.4)	32, 97 (95.0-98.9)	27,96 (94.1-98.7)	0.58

Table 5: Accuracy of the Prediction Rule to Predict 30-day Mortality and RV Dysfunction in the Derivation and Validation Cohorts

	30-day Mortality			Right Ventricular Dysfunction		
	Derivation	Internal Validation	External Validation	Derivation	Internal Validation	External Validation
Sensitivity(%)	99 (98-99)	96(94-98)	97 (95-99)	95 (93-98)	96(93-99)	96 (94-98)
Specificity(%)	48(36-60)	46 (32-69)	45 (31-59)	34 (25-43)	33(27-39)	35 (28-42)
Positive Predictive Value (%)	21(13-29)	23(15-31)	23 (15-31)	18(11-25)	18(10-26)	16 (9-24)
Negative Predictive Value (%)	95(90-99)	96 (92-99)	95 (91-99)	97(94-99)	98(97-99)	96 (93-99)
Positive Likelihood Ratio	1.31(1.15-1.48)	1.26(1.18-1.33)	1.20 (1.1-1.29)	1.43(1.31-1.56)	1.47(1.25-1.70)	1.39 (1.28-1.50)
Negative Likelihood Ratio	0.11(0.07-0.16)	0.14 (0.08-0.23)	0.10 (0.06-0.14)	0.13(0.10-0.16)	0.14(0.09-0.20)	0.11 (0.07-0.15)


LOW RISK
(0-5)
INTERMEDIATE
RISK (6-10)
HIGH RISK
(11-15)
CT PULMONARY ANGIOGRAM
OBSTRUCTION INDEX (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
HOPPE SCORE