External Validation of the Prestroke Independence, Sex, Age, National Institutes of Health Stroke Scale (ISAN) Score for Predicting Stroke-Associated Pneumonia in the Athens Stroke Registry

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Background and purpose: The Prestroke Independence, Sex, Age, National Institutes of Health Stroke Scale (ISAN) score was developed recently for predicting stroke-associated pneumonia (SAP), one of the most common complications after stroke. The aim of the present study was to externally validate the ISAN score. *Methods:* Data included in the Athens Stroke Registry between June 1992 and December 2011 were used for this analysis. Inclusion criteria were the availability of all ISAN score variables (prestroke independence, sex, age, National Institutes of Health Stroke Scale score). Receiver operating characteristic curves and linear regression analyses were used to determine the discriminatory power of the score and to assess the correlation between actual and predicted pneumonia in the study population. Separate analyses were performed for patients with acute ischemic stroke (AIS) and intracerebral hemorrhage (ICH). *Results:* The analysis included 3204 patients (AIS: 2732, ICH: 472). The ISAN score demonstrated excellent discrimination in patients with AIS (area under the curve [AUC]: .83 [95% confidence

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interval {CI}: .81-.85]). In the ICH group, the score was less effective (AUC: .69 [95% CI: .63-.74]). Higher-risk groups of ISAN score were associated with an increased relative risk of SAP; risk increase was more prominent in the AIS population. Predicted pneumonia correlated very well with actual pneumonia (AIS group: $R^2 = .885$; β-coefficient = .941, $P < .001$; ICH group: $R^2 = .880$, β-coefficient = .938, $P < .001$). *Conclusions:* In our external validation in the Athens Stroke Registry cohort, the ISAN score predicted SAP very accurately in AIS patients and demonstrated good discriminatory power in the ICH group. Further validation and assessment of clinical usefulness would strengthen the score's utility further. **Key Words:** ISAN score—pneumonia—stroke—intracerebral hemorrhage—prediction—outcome.

Introduction

The incidence of pneumonia after stroke ranges between 1% and 44%.[1,2] Regardless of the exact percent, which depends highly on the heterogeneity of the performed studies, pneumonia is widely recognized as one of the most frequent medical complications of stroke.[3] Stroke-associated pneumonia (SAP) has a detrimental impact on survival (threefold increased risk of 30-day mortality after adjusting for admission severity and propensity for pneumonia),[4] healthcare costs (3.5-fold increase in hospitalization cost and 70% more likely to require extended care post discharge),[5] and, in most studies, functional outcome.[6-9] Therefore, the ability to predict the risk of SAP could aid in targeting interventions to reduce SAP risk to the patients at highest risk (improved patient outcomes in daily clinical practice and stroke logistics) and to facilitate more appropriate patient selection for clinical trials of preventative or therapeutic interventions.

Despite the high significance of SAP, attempts to build and widely validate a rapidly calculated and accurate prognostic score are quite limited,[10-16] in comparison to scores related to other stroke outcomes.[17-19] Prestroke Independence, Sex, Age, National Institutes of Health Stroke Scale (ISAN), the most recently introduced score in this category, was developed and internally validated in a national UK cohort of patients with stroke.[13] The score had a similar accuracy in the 2 cohorts, but its discriminatory power was higher in the acute ischemic stroke (AIS) group than in the intracerebral hemorrhage (ICH) group.

The aim of the present study was to externally validate the ISAN score in the Athens Stroke Registry, a prospectively collected stroke population of AIS and ICH patients recorded under different geographical, temporal, and socioeconomic circumstances.

Materials and Methods

Study Population and Definitions

All consecutive patients with a first-ever stroke (AIS or ICH) registered in the Athens Stroke Registry (ASR) between June 1992 and December 2011 were included in the present study. The ASR is the prospective registry of all patients with first-ever strokes admitted in Alexandra University Hospital (Athens, Greece). By definition, transient ischemic attacks, subarachnoid hemorrhages, and recurrent strokes are not included in the ASR. All patients have been treated according to current international guidelines at the time of admission. The clinical settings, the definition of variables, the diagnostic algorithms applied, and the way data were collected and recorded have been previously described.[20,21]

The ISAN score was calculated on the basis of prestroke **I**ndependency (0 points for modified Rankin Scale [mRS] score = 0-1, 2 points for mRS score = 2-5), **S**ex (1 point for males, 0 points for females), **A**ge (0 points if <60 years, 3 points if 60-69 years, 4 points if 70-79 years, 6 points if 80-89 years, and 8 points if ≥90 years) and **N**ational Institutes of Health Stroke Scale (NIHSS) score on admission (0 points if 0-4, 4 points if 5-15, 8 points if 16-20, and 10 points if ≥21).[13] The patients were stratified for their risk of pneumonia into low risk (ISAN score: 0-5), medium risk (6-10), high risk (11-14), and very high risk (≥15).[13]

Pneumonia was diagnosed according to the individual judgment of the treating physician, based on the presence of respiratory tract infection symptoms or signs (fever, cough, crackles in lung auscultation, or/and changes in expectoration), laboratory test results (increase of inflammatory markers, reduced oxygen saturation, or/and pathogen detection in sputum cultures), and typical radiological evidence. Pneumonia was considered as SAP if it presented during the patients' hospitalization for the stroke. Time delay to SAP onset was arbitrarily defined as the time window from the patient's admission to the first recording (temporally related to SAP) of body temperature less than 37.5°C.

Inclusion criteria were the availability of the prerequisite variables for the calculation of ISAN score and assessment of the patient for the development of pneumonia during hospitalization. No specific exclusion criteria were applied.

The Institutional Ethics Committee has approved the scientific use of the data collected in the ASR.

Statistical Analysis

Data were analyzed separately for AIS and ICH patients. Continuous covariates are summarized as median

value and interquartile range, and categorical ones as absolute number and percentage.

We used 2 methods to validate the ISAN score: discrimination (i.e., the degree to which the score enables the discrimination between patients with SAP and without SAP) and calibration (i.e., agreement between actual and predicted occurrences of SAP). The discriminatory power of the ISAN score for the prediction of SAP during hospitalization was assessed by calculating the area under the receiver operating characteristics curve (AUC) and the 95% confidence interval (CI). A subgroup analysis for patients with SAP onset within the first 7 days of admission was performed in pursuance of the protocol that was used in the development of the ISAN score. To avoid interference of early mortality in patients with ICH with the score's predictive power, sensitivity analysis excluding patients who died within 3 days of admission was carried out in this group.

Calibration was assessed by the Hosmer–Lemeshow goodness-of-fit test for logistic regression. Linear regression analysis was used to calculate the predicted pneumonia percent according to the ISAN score. Actual pneumonia (%) versus adjusted predicted pneumonia (%) plots in the AIS and ICH groups were drawn and R^2 (R-square) was used to assess correlation.

Logistic regression analysis was performed to identify the relative risk of SAP in different risk-stratification groups according to the ISAN score.

Statistical analyses were performed with the PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL) software.

Results

The population used in the present study consisted of 3204 patients (median age: 71 years, 38.3% females), of which 2732 were patients with AIS (median age: 71 years, 38.9% females) and 472 with ICH (median age: 71 years, 35.0% females). All recorded patients fulfilled the inclusion criteria and thus were eligible for this analysis. The patients' characteristics are summarized in Table 1.

Table 1. *Baseline characteristics and outcomes of the AIS and ICH populations in the Athens Stroke Registry*

	AIS n = 2732	ICH n = 472
Age (years)	71 (63-79)	71 (61-80)
Female gender	1063 (38.9%)	165 (35.0%)
Prestroke dependency (mRS score > 1)	70 (2.6%)	14 (3.0%)
GCS on admission	15 (13-15)	12 (6-15)
NIHSS on admission	5 (2-16)	17 (7-25)
Days of hospitalization	10 (6-15)	10 (5-16)
Cardiovascular comorbidities		
Smoking	875 (32.0%)	126 (26.7%)
Atrial fibrillation	933 (34.2%)	45 (9.5%)
Hypertension	2023 (74.0%)	390 (82.6%)
Dyslipidemia	1303 (47.7%)	179 (37.9%)
Diabetes Mellitus	734 (26.9%)	70 (14.8%)
Past TIA	299 (10.9%)	15 (3.2%)
Congestive Heart Failure	240 (8.8%)	14 (3.0%)
Coronary Artery Disease	553 (20.2%)	58 (12.3%)
Peripheral Artery Disease	121 (4.4%)	7 (1.5%)
TOAST classification		
Large artery atherosclerosis	649 (23.8%)	Not applicable
Cardioembolism	497 (18.2%)	
Small vessel occlusion	993 (36.3%)	
Undetermined etiology	532 (19.5%)	
Other determined etiology	60 (2.2%)	
Pneumonia	322 (11.8%)	88 (18.6%)
Mortality		
7-day	127 (4.6%)	109 (23.1%)
30-day	289 (10.6%)	177 (37.5%)
90-day	377 (13.8%)	191 (40.5%)

Abbreviations: AIS, acute ischemic stroke; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, Transient Ischemic Attack.

Continues variables are presented as median (interquartile range), Categorical variables are presented as number (% percentage of recorded values).

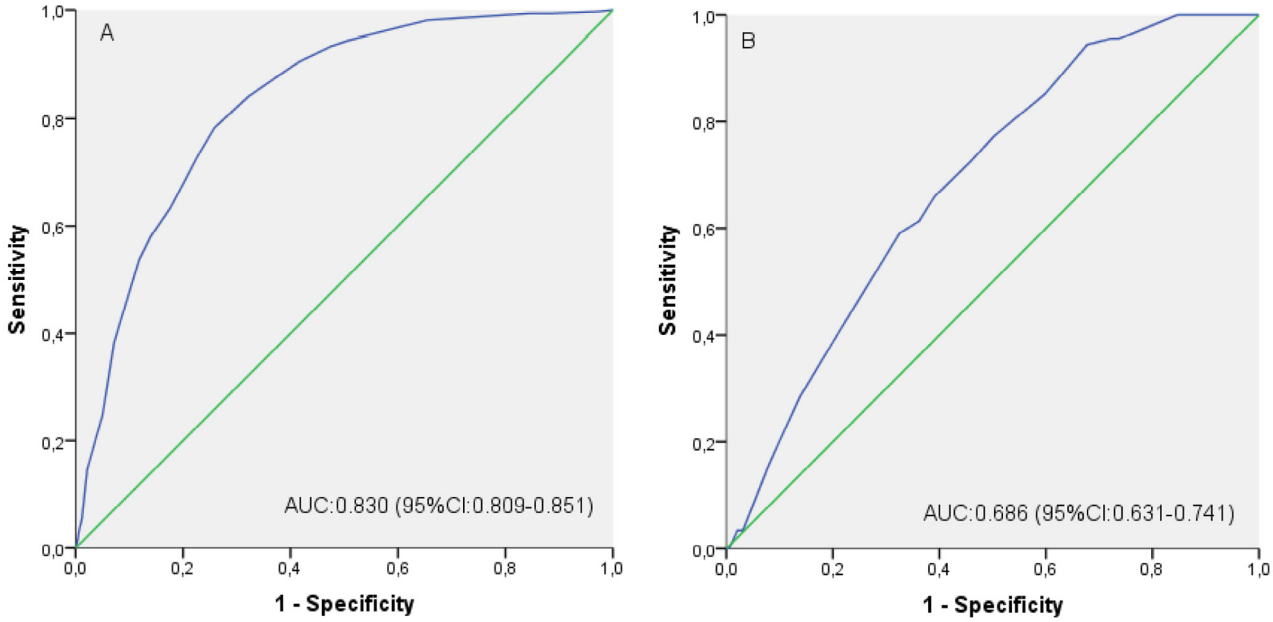

Figure 1. *ROC curves of ISAN score in the Athens Stroke Registry cohort for the prediction of stroke-associated pneumonia. (A) Acute ischemic stroke. (B) Intracerebral hemorrhage. Abbreviations: ISAN, Prestroke Independence, Sex, Age, National Institutes of Health Stroke Scale; ROC, receiver operating characteristic.*

SAP was diagnosed in 410 (12.8%) patients. The median time interval between stroke onset and SAP presentation was 15 hours (interquartile range: 3-36 hours). Only 8 patients developed SAP after the first 7 days of admission. In 59 patients the exact onset time of SAP was not available.

The AUC of ISAN score in patients with AIS was .83 (95% CI: .81-.85). In the ICH group, the score had a reduced discriminatory power of SAP, with an AUC of .69 (95% CI: .63-.74); the exclusion of patients who died in the first 3 days slightly improved the AUC: .72 (95% CI: .67-.78). The receiver operating characteristic curves for the prediction of SAP during hospitalization in patients with AIS and ICH are shown in Figure 1 (A and B, correspondingly). Of note, a similar discriminatory power was observed for patients with AIS (AUC: .84 [95% CI: .81-.86]) and ICH (AUC: .70 [95% CI: .64-.75]), when analysis was limited to the 343 patients with a recorded admission-to-SAP diagnosis time of 7 days or less.

ISAN score was well calibrated in both the AIS group ($P = .135$, chi-square: 12.375) and the ICH group ($P = .703$, chi-square: 5.503), as the Hosmer–Lemeshow test was not significant. The regression-adjusted, predicted pneumonia (%) for each ISAN score value correlated very well with the actual pneumonia (%) in both the AIS group ($R^2 = .885$, β-coefficient = .941, $P < .001$) and the ICH group ($R^2 = .880$, β-coefficient = .938, $P < .001$) (Fig 2).

Higher-risk groups of ISAN score were associated with an increased relative risk of SAP in comparison to the low-risk (ISAN score: 0-5) group. This observation was more prominent in the AIS population where the medium, high, and very-high-risk groups had a 6.6% (95% CI: 4.0%-11.6%), 19.7% (95% CI: 11.8%-32.9%), and 47.2% (95% CI: 28.1%-79.3%) relative risk of SAP respectively. Detailed results for both AIS and ICH populations are shown in Figure 3.

Discussion

The present study is the first to externally validate the recently introduced ISAN score. In the ASR, the ISAN score had a high discriminatory power for the prediction of SAP in the AIS group but did not perform equally well in the ICH group; calibration was good in both groups. To the best of our knowledge, ISAN score's AUC (.83) in AIS patients is comparable to the highest AUC observed among scores developed for the prediction of SAP,[10-13,15,16] that is, A^2DS^2 score's AUC in the development and external validation cohorts.[12,16]

Apart from ISAN, only the score by Kwon et al.[10] has been developed in a mixed population of patients with AIS and ICH for the prediction of SAP. Kwon et al.'s score has been externally validated in the AIS populations of the China National Stroke Registry and the Chinese Intracranial Atherosclerosis Study, but its accuracy was far below ISAN's (AUC ranging from .676 to .713).[11] Moreover, the accuracy of Kwon et al.'s score in patients with ICH has never been tested.

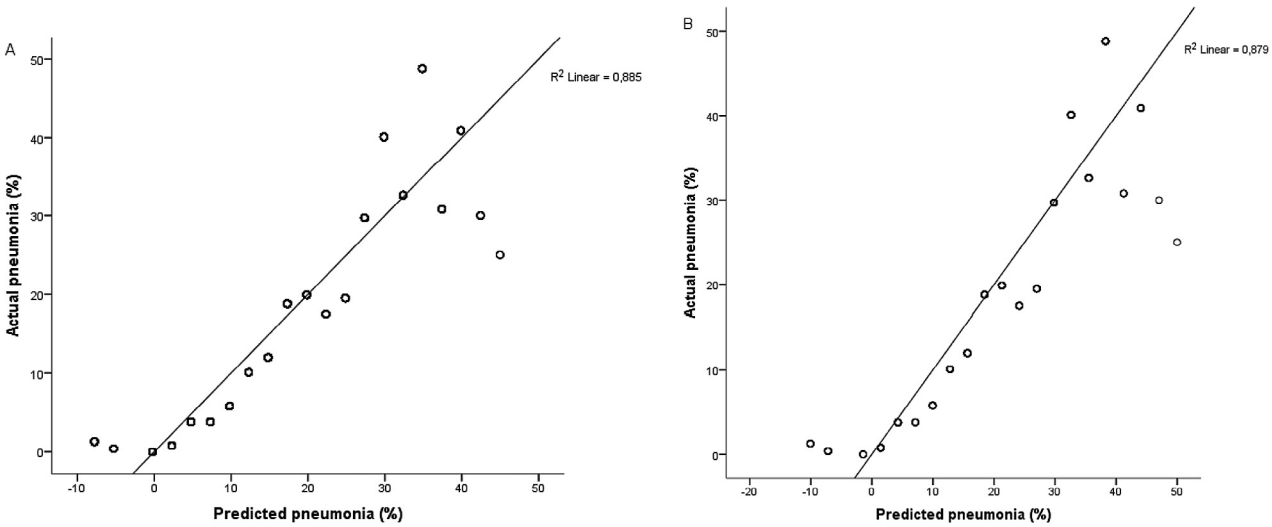

Figure 2. *Actual pneumonia (%) versus regression-adjusted predicted pneumonia (%) plots in Athens Stroke Registry. (A) Acute ischemic stroke. (B) Intracerebral hemorrhage.*

SAP prediction scores that were developed exclusively in AIS cohorts include A^2DS^2 score, acute ischemic stroke–associated pneumonia score (AIS-APS) score, and Chumbler et al.'s score.[11,12,15,16] Among them, A^2DS^2 is the best externally validated one (China National Stroke Registry, Chinese Intracranial Atherosclerosis Study, Henan Province Stroke Registry, and Sentinel Stroke National Audit Programme)[11,13,16] and the score with the highest observed AUC so far. However, ISAN achieved a similar AUC (.83) for the prediction of SAP in AIS patients.

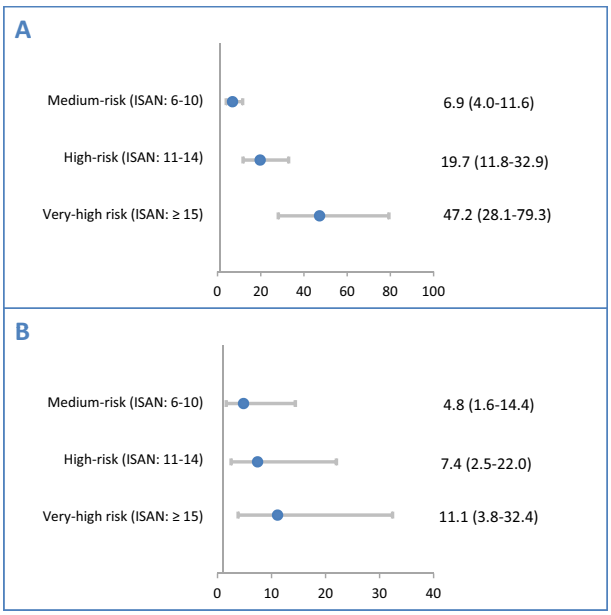

Figure 3. *Relative risk of SAP according to ISAN strata (as compared with ISAN score: 0-5). (A) Acute ischemic stroke. (B) Intracerebral hemorrhage. Abbreviations: ISAN, Prestroke Independence, Sex, Age, National Institutes of Health Stroke Scale; SAP, stroke-associated pneumonia.*

The accuracy of ISAN score in the ICH cohort of ASR was not as high as in the AIS population. Moreover, prediction of SAP in the ICH population (crude and sensitivity analyses) did not manage to reach the accuracy observed, either with ISAN or A^2DS^2, in ISAN's internal validation cohort.[13] As expected according to the above discussion, ISAN's accuracy was also below the discriminatory power of intracerebral hemorrhage–associated pneumonia score (ICH-APS), the only SAP prediction score developed in a pure ICH population.[14] However, it is worth mentioning that ICH-APS is a significantly more complicated score that includes 11 different variables in total and therefore might be more difficult to implement in clinical practice; 3 among them are imaging-based ones (infratentorial extension, ventricular extension, and hematoma volume).

Unfortunately, we did not have the opportunity to compare ISAN score in ASR, with any of the other SAP prediction scores. The main reason was that dysphagia, a variable included in all these scores, was not routinely recorded in ASR. On top of this, some scores such as AIS-APS had more than one missing variable in the ASR dataset (chronic obstructive pulmonary disease and dysphasia).

Among the strengths of the present study is the large sample size of prospectively recorded stroke patients. Secondly, the temporal (from the early 1990s up to 2011 versus the second decade of the 21st century) variability of the ASR cohort as compared to the development and internal validation cohorts of the score, along with the differences in prestroke dependency status (ASR includes first-ever strokes only), age, gender, and NIHSS score on admission, further strengthen the above presented results. Moreover, the use of a longer time window for the diagnosis of SAP extends ISAN score's applicability. Last but not least, the supervision of data collection

and recording by a single physician (K.V.) has limited any registration bias and diversity of pneumonia definition and data collection in ASR.

One of the limitations of the present study is the fact that the criteria applied for the diagnosis of SAP might not be fully consistent in all cases (physician's judgment might have interfered with the recorded outcomes), because there was no prospective study protocol for the diagnosis of pneumonia and validated criteria for diagnosing SAP are not available. On top of the above mentioned limitations and specifically for patients where pneumonia was identified in the very early hours poststroke, community-acquired pneumonia preceding stroke cannot be safely excluded. Finally, there are many difficulties in accurately determining time delay to SAP onset, and the selection of body temperature higher than 37.5°C (although it was temporally related to SAP) as a criterion for the subgroup analysis has several limitations.

In conclusion, on top of the simplicity in calculation, the ISAN score proves to be a very accurate score in the prediction of SAP in patients with AIS. Further validation of the score in non-European populations resulting in suchlike discriminatory accuracy could lead to the wide establishment of the score.

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