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Original Article:

The Barrow Neurological Institute (BNI) Grading Scale as a predictor for delayed cerebral ischemia and outcome after aneurysmal subarachnoid hemorrhage - Data from a nationwide patient registry (Swiss SOS)

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Running title: Multicenter validation of the BNI grading scale to predict DIND

ABSTRACT

Objective: To analyze the Barrow Neurological Institute (BNI) grading scale, a quantitative scale measuring maximal subarachnoid hemorrhage thickness on axial computed tomography, on delayed cerebral ischemia (DCI) and outcome (modified Rankin scale; mRS) at discharge and 1-year follow-up (1FU) in patients with aneurysmal subarachnoid hemorrhage (aSAH) from a nationwide SAH registry.

Methods All patient data was obtained from the Swiss nationwide multicentre registry database of aSAH (Swiss SOS). In 1321 patients demographic data, BNI scale, DCI and mRS up to the 1FU were available for descriptive and univariate statistics. Outcome was dichotomized in favorable (mRS 0-2) and unfavorable (mRS 3-6). Odds ratios (OR) for DCI of Fisher 3 patients (n=1115, 84%) compared to a control cohort of Fisher grade 1,2 and 4 patients (n=206, 16%) were calculated for each BNI grade separately.

Results Overall, 409 patients (31 %) developed DCI with a high DCI rate in the Fisher 3 cohort (34%). For what concerns the BNI scale, DCI rates went up progressively from 26% (BNI 2) to 38% (BNI 5) and corresponding OR for DCI increased from 1.9 [1.0 – 3.5, 95 % CI] to 3.4 [2.1 – 5.3], respectively. BNI grade 5 patients had high rates of unfavorable outcome with 75% at discharge and 58% at

1FU. The likelihood for unfavorable outcome was high in BNI grade 5 patients with OR 5.9 [3.9 – 8.9] at discharge and OR 6.6 [4.1 – 10.5] at 1FU.

Discussion This multicenter external validation analysis from a prospective nationwide patient registry confirms that patients with a higher BNI grade show a significantly higher risk for DCI. The BNI grade was also a predictor for unfavorable outcome at discharge and at 1FU.

INTRODUCTION

Previous data indicate that the amount of subarachnoid blood in aneurysmal subarachnoid hemorrhage (aSAH) correlates with the incidence of delayed cerebral ischemia (DCI).¹⁻⁶ The most commonly used grading scales to predict vasospasm or DCI in aSAH are the Fisher or the modified Fisher scales, which account for the blood extension in the subarachnoid space as well as for presence of intraventricular or –cerebral hemorrhage.^{1,4} Recently, a relatively simple grading scale – the so called Barrow Neurological Institute (BNI) grading scale – focusing on the prediction of symptomatic vasospasm based on the maximal clot thickness in any cistern or fissure was published.⁷ Despite being simpler to apply than the previously established (modified) Fisher scales, the BNI scale could predict symptomatic vasospasm more accurately in the initial single center analysis. The findings were recently confirmed by an external single-center validation.⁸

To confirm that the findings of the BNI grading scale are universally valid, a multicenter external validation is still needed and was performed in this study. With our prospectively collected Swiss nationwide aSAH registry (Swiss SOS) we have the unique opportunity to validate the BNI grading scale in a large, unselected and multi-cultural cohort.

PATIENTS AND METHODS

Patients and inclusion criteria

All anonymous patient data was obtained from the prospective Swiss nationwide multicenter registry for aSAH (Swiss SOS; <http://swiss-sos.ch>; IRB No 11-233R (NAC 11-085R)) and was approved by the local ethical committee from Zurich (54-2015).⁹ All patients with a complete dataset including a CT/CTA at admission to analyse the BNI grade (n=1321) were included for this analysis. Anonymous patient data from the following neurosurgical centers were analysed: Aarau, Basel, Bern, Geneva, Lausanne, Lugano, St. Gallen and Zurich.

Clinical and radiological patient data

Age, gender, WFNS grade, Fisher grade and outcome at discharge and 1-year follow-up (1FU) using the modified Rankin Scale (mRS) were used for analysis. Clinical outcome was dichotomized into favorable (mRS 0-2) and unfavorable (mRS 3-6). In addition, each center collected radiographic data to calculate the BNI grade based on CT scans at admission. The BNI grade according to the original publication was based on a single measurement of the maximal clot thickness in any cistern or fissure.⁷ The measurement was made perpendicular to the direction of the cistern/fissure and in case of multiple measurements, only the largest measurement was used. Clinical deterioration attributable to delayed cerebral ischemia (DCI) was defined according to Vergouwen et al. as a delayed decrease of consciousness by at least 2 points on the Glasgow Coma Scale (GCS) and/or a new focal neurological deficit, after ruling out other causes.¹⁰

Statistical testing

Statistical analysis was performed using SPSS 20 (IBM, Chicago, IL, USA) and figures were generated using Microsoft Excel (Microsoft Corporation, Redmont, WA, USA). Continuous variables are presented as mean with standard error of the mean. Comparisons between groups were performed using the Mann-Whitney-U test for continuous parameters and the Chi-square test or the Fisher's exact test for categorical parameters. Statistical significance was established at the alpha level of $p = 0.05$. The performance of the BNI scale, the WFNS score, a new combined score including BNI, WFNS and patient age was evaluated by comparing the areas under the receiver-operating characteristic curves (AUROCs). An AUROC of 0.5 indicates no discrimination, whereas an AUROC of 1 indicates perfect discrimination.

RESULTS

Overall, 1321 patients were included in this study (468 males, 853 females). Median age was 55 years (IQR, 47 – 65). The rate of high-grade aSAH (WFNS grades 4 and 5) was high with 37.9 % (500/1321). The majority of patients belonged to the Fisher 3 cohort (1115, 84.4 %). Details of the patient characteristics as well as the BNI grading, the WNFS and the Fisher grading are depicted in Figure 1 as well as in Table 1.

BNI grading and DCI rates

Overall, 402 (31.0 %) patients developed DCI. Specific DCI rates for WFNS grade, Fisher grade and BNI grade are depicted in Figure 2 and patient characteristics of patients that developed DCI and those without are shown in Table 1. Patients with a Fisher grade of 3 were by far the largest group with 1115 of 1321 patients (84.4 %). As expected, the DCI rate was high in the Fisher 3 cohort with

377/1115 (33.8 %). In order to sub-stratify DCI risks within this large cohort of Fisher 3 patients, the odds ratios (OR) for DCI of Fisher 3 patients (n=1115, 84.4 %) compared to a control cohort of Fisher grade 1, 2 and 4 patients (n=206, 15.6 %) were calculated for each BNI grade separately (Table 2). BNI grade 1 patients (no visible SAH) were by definition not part of the Fisher 3 cohort and were therefore not included in this comparison. DCI rates went up from 25.6 % (BNI 2) to 38.2 % (BNI 5) with corresponding OR of 1.9 [1.0 – 3.5, 95 % CI] and 3.4 [2.1 – 5.3, 95 % CI], respectively.

BNI grading and clinical outcome

Outcome was dichotomized in favorable (mRS 0-2) and unfavorable (mRS 3-6) and assessed at two time points: at discharge (data of 1298 patients available) and at 1FU (data of 1119 patients available). Again, clinical outcome of Fisher 3 patients were compared to Fisher grade 1, 2 and 4 and ORs were calculated for each BNI grade. Outcome data at discharge is depicted in Table 3 and outcome at 1FU is shown in Table 4. Non-aggregated mRS data is shown for both time points and each BNI grade in Figure 3. Of note, BNI grade 5 patients had high rates of unfavorable outcome with 74.9 % at discharge and 57.9 % at 1FU. Correspondingly, ORs were high with OR 5.9 [3.9 – 8.9, 95 % CI] at discharge and OR 6.6 [4.1 – 10.5, 95 % CI] at 1FU. The effect sizes of the influence of high grade BNI on unfavorable outcome were more pronounced than the effect sizes of the influence of high grade BNI on DCI.

Based on AUROC (Figure 4 A) the BNI scale showed a significantly lower area under the curve (AUC) (0.663) and therefore a lower prediction of favorable patient outcome (mRS 0-2) at discharge compared to the WFNS score (0.734). A new score based on the BNI scale, WFNS score and patient age (Figure 4 B)

showed a higher AUC (0.768; $p < 0.0001$). There was hence a better discrimination of clinical outcome possible when adding information of the BNI score to the WFNS-score based outcome prediction model.

DISCUSSION

In this external validation analysis from a prospective multicenter patient registry in Switzerland (Swiss SOS) we were able to confirm that patients with a higher BNI grade showed a significantly higher risk for DCI. In addition, we demonstrated that the BNI grading system is useful to predict unfavorable outcome at discharge and at 1FU.

This is an important finding, since previously published results were only based on single institution data sets with small patient numbers, less accurate point estimates and relatively large confidence intervals. In this respect, it must be pointed out that previous results were not universally valid.^{7,8} The Swiss SOS data spans over eight neurovascular centers, combines four linguistic areas in Switzerland (German, French, Italian, Romansh language) and the multi-cultural character of registered patient data allows to generalize the here-presented results to other populations. At present, the Fisher score is still used in clinical routine to estimate the risk for DCI. Our results clearly demonstrate that the BNI grading system shows advantages as it provides a precise gradual, almost linear prediction of DCI. According to the Fisher scale, however, most patients are graded as “Fisher 3”, and further sub-stratification of the risk for DCI is not possible. Moreover, the Fisher scale, despite its value for the management of aSAH patients over decades, is known for weaknesses inherent to interobserver reliability issues.¹¹

Compared to the initial publication, our patient cohort included more high-grade aSAH patients similar to the patient cohort from Dengler et al.⁸ This explains our high overall DCI rate of approximately 30%. The higher amount of patients with high-grade aSAH can be explained by the unique setting in Switzerland, where tertiary neurovascular centers specialized in aSAH can be reached within a short time frame. Therefore, severe aSAH patients will more likely reach specialized neurovascular centers for resuscitation, compared to regions with longer time delay before hospital admission or interhospital transfer. For this validation study it was useful to have this high-grade aSAH patient cohort due to the higher incidence of DCI, which further strengthens our results.

The effect sizes of our validation results were generally lower than the initial results from Wilson et al.: Our DCI rates were 25.6 % in BNI grade 2 patients, and 38.2 % in BNI grade 5 patients with corresponding ORs of 1.9 [1.0 – 3.5, 95 % CI] and 3.4 [2.1 – 5.3, 95 % CI], respectively. The original paper from the Barrow Neurological Institute reports BNI-grade dependend rates of symptomatic vasospasm in the range between 12.5 – 50 %, and corresponding ORs of 1.57 [0.40 – 6.20, 95 % CI] up to 11.0 [2.27 – 53.37, 95 % CI], respectively.⁷ The relatively wide CIs of the original study indicate that point estimates might have been less accurate. Our 95% CIs were much narrower, representing robust estimates of the real effect. For example, a patient graded “BNI grade 5” will be 3.4 times as likely as a patient graded Fisher 1, 2 or 4 to experience DCI. Based on the large sample size, we are 95% confident that the real risk lies between 2.1 – 5.3. Dengler et al. also confirmed significant prediction of the BNI scale for radiological vasospasm, but showed that the effect size is also dependent on the presence of intracranial and intraventricular hemorrhage.⁸ These results summarize that the BNI score is valid to predict DCI, but the effect size is not as high as initially reported by Wilson et al..⁷

In the initial manuscript the BNI score was not correlated with clinical outcome.⁷ In our patient cohort we were able to show that the BNI grading system may also be used as a predictor for unfavorable clinical outcome (mRS >2). The ORs for poor outcome in BNI 5 patients were high with 5.9 [3.9 – 8.9, 95 % CI] at discharge and 6.6 [4.1 – 10.5, 95 % CI] at 1FU. These findings are expected, since patients with DCI have also a higher risk for unfavorable clinical outcome.¹² Similar results were presented by Dengler et al. with increasingly unfavorable patient outcomes and higher rates of new cerebral infarctions for each increase in BNI grade.⁸ In their analysis, the BNI grade was less relevant for outcome prediction in a multivariate analysis compared to patient age and clinical aSAH scores.⁸ Our AUROC analysis confirmed the lower outcome prediction of the BNI score compared to the WFNS score (Figure 4), but indicates that discriminative ability for outcome is increased if the BNI score is added to the WFNS score.

Strengths and limitations

This was an external validation study using prospective, multicenter data from various linguistic and cultural areas in Switzerland. The relatively high number of cases allowed us to generate robust estimates. However, our study was limited to parameters available for analysis based on the Swiss SOS database. The definition of vasospasm, symptomatic vasospasm (as used in the original paper), delayed ischemic neurological deficit (DIND) and DCI is diverse, but we here used the consensus-definition of DCI, representing the current gold standard.¹⁰ Unfortunately, information on new cerebral infarction attributable to DCI were not available for analysis from all centers. The slightly different definition of the primary end-point is likely to explain the differences in the effect sizes. Other explanations factoring into

this are differences in study population, proportion of high-grade aSAH patients, amongst others.

Overall the BNI grading scale outperforms the Fisher scale in predicting DCI and may find its role in predicting clinical outcome together with clinical aSAH scores. The advantages of the BNI grading score are its simplicity, the better distribution of aSAH patients over BNI grades and its linear increase in risk for DCI with higher score. The BNI scale appears to be useful for clinical practice, as well as for risk-stratification in prospective studies testing new therapies to prevent DCI.

CONCLUSION

In this multicenter, external validation analysis from a prospective nationwide patient registry we confirmed that patients with higher BNI grades showed gradually higher risks for DCI. Besides predicting DCI, the BNI grade was also a predictor for unfavorable outcome at discharge and at 1FU.

TABLES AND FIGURE LENGENDS

Table 1. Basic patient characteristics and group differences

	all patients (n = 1321)	DCI (n = 409)	no DCI (n = 912)	p-value
Age (years), median (IQR)	55 (47 - 65)	53 (47 - 62)	55 (47 - 66)	0.046 [*]
Sex m/f (m/f ratio)	468/853 (0.55)	128/281 (0.46)	340/572 (0.59)	0.040 ⁺
WFNS grade (%)				
1	451 (34.1)	113 (27.6)	338 (37.1)	0.023 [‡]
2	258 (19.5)	83 (20.3)	175 (19.2)	
3	108 (8.2)	38 (9.3)	70 (7.7)	
4	141 (10.7)	52 (12.7)	89 (9.8)	
5	359 (27.2)	122 (29.8)	237 (26.0)	
n/a	4 (0.3)	1 (0.2)	3 (0.3)	
Fisher grade (%)				
1	40 (3.0)	1 (0.2)	39 (4.3)	<0.001 [‡]
2	87 (6.7)	16 (3.9)	71 (7.8)	
3	1115 (84.4)	377 (92.2)	738 (80.9)	
4	79 (6.0)	15 (3.7)	64 (7.0)	
BNI grade (%)				
1	57 (4.3)	3 (0.7)	54 (5.9)	<0.001 [‡]
2	231 (17.5)	50 (12.2)	181 (19.8)	
3	377 (28.5)	111 (27.1)	266 (29.2)	
4	402 (30.4)	148 (36.2)	251 (27.9)	
5	254 (19.2)	97 (23.7)	157 (17.2)	

abbreviations: DCI: delayed cerebral ischemia; IQR: interquartile range; WFNS: World Federation of Neurosurgical Societies; BNI: Barrow Neurological Institute

* Mann-Whitney-U test; + Chi-Square test; ‡ Fisher`s exact test

Table 2. Risk of delayed cerebral ischemia (DCI) by BNI Grade and Fisher Grade. Fisher grade 3 patients (n=1115) are compared to Fisher grades 1,2 and 4 (n=206).

Grade	No. of patients (%)	DCI (%)	OR for DCI (95% CI)
BNI 1	n/a	n/a	n/a
BNI 2	82 (7.4)	21 (25.6)	1.9 (1.0 – 3.5)
BNI 3	377 (33.8)	111 (29.4)	2.3 (1.5 – 3.5)
BNI 4	402 (36.1)	148 (36.8)	3.2 (2.1 – 4.9)
BNI 5	254 (22.8)	97 (38.22)	3.4 (2.1 – 5.3)
Fisher 3	1115 (84.4)	377 (34)	2.8 (1.9 – 4.1)
Fisher 1,2 and 4	206 (15.6)	32 (16)	-

Table 3. Risk of poor outcome at discharge (mRS 3-6) by BNI Grade. Outcome data was available for 1298 patients. Fisher grade 3 patients (n=1096) are compared to Fisher grades 1,2 and 4 (n=202).

Grade	No. of patients (%)	Poor outcome (%)	OR (95% CI)
BNI 1	n/a	n/a	n/a
BNI 2	82 (7.5)	24 (29.3)	0.8 (0.5 – 1.4)
BNI 3	374 (34.1)	132 (35.3)	1.1 (0.7 – 1.5)
BNI 4	393 (35.9)	201 (51.1)	2.1 (1.5 – 2.9)
BNI 5	247 (22.5)	185 (74.9)	5.9 (3.9 – 8.9)

Table 4. Risk of poor outcome at 1 year follow-up (mRS 3-6) by BNI Grade. Outcome data was available for 1119 patients. Fisher grade 3 patients (n=940) are compared to Fisher grades 1,2 and 4 (n=179).

Grade	No. of patients (%)	Poor outcome (%)	OR (95% CI)
BNI 1	n/a	n/a	n/a
BNI 2	72 (7.7)	16 (22.2)	1.4 (0.7 – 2.7)
BNI 3	334 (35.5)	76 (22.8)	1.4 (0.9 – 2.2)
BNI 4	318 (33.8)	116 (36.5)	2.7 (1.7 – 4.3)
BNI 5	216 (23.0)	125 (57.9)	6.6 (4.1 – 10.5)

Figure 1

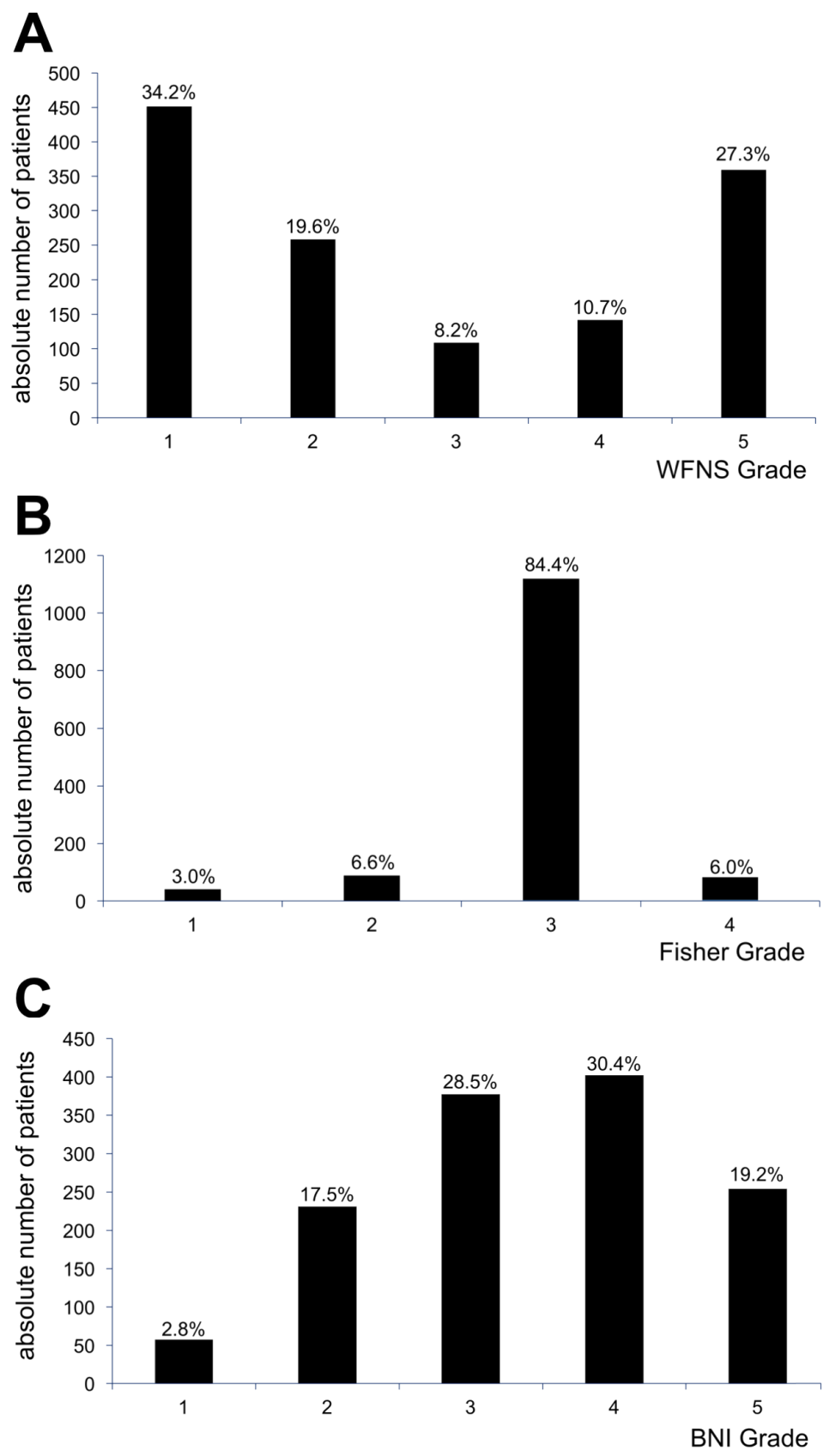


Figure 2

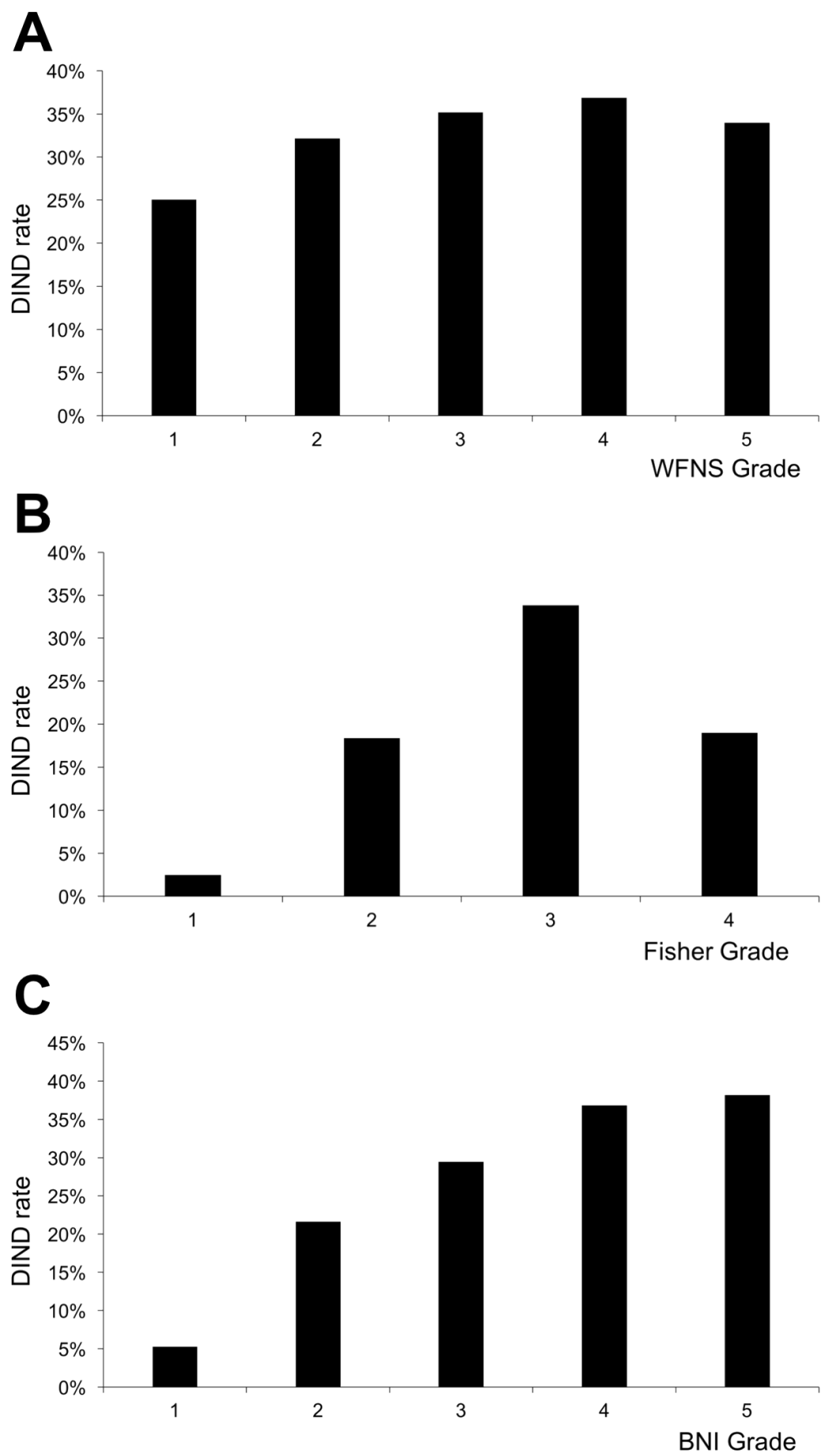


Figure 3

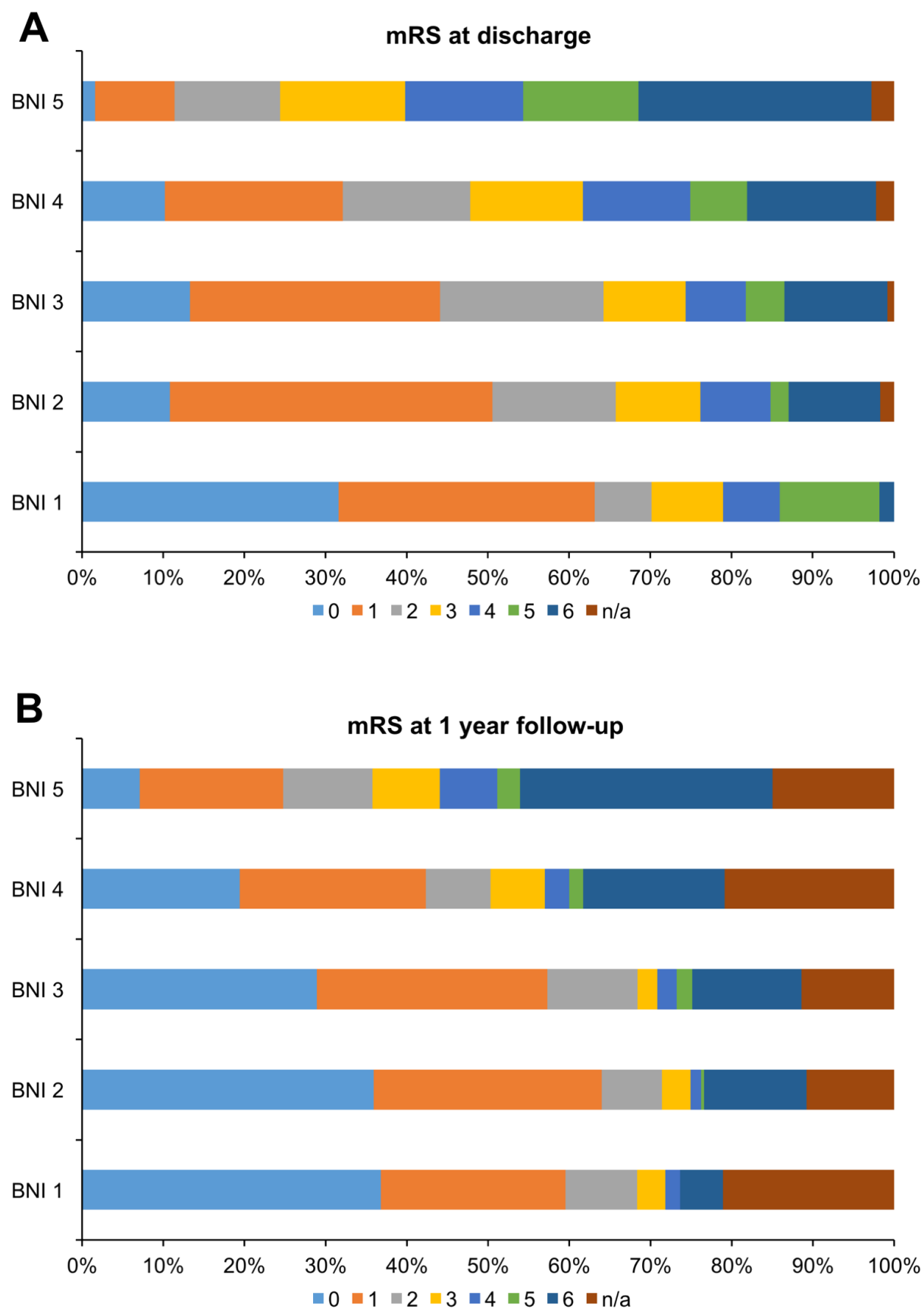
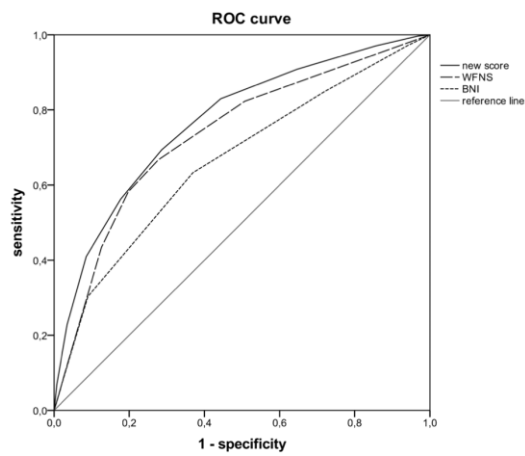


Figure 4

A



B

new score =
WFNS + BNI + 1 point if age > 60y

C

positiv if >	sensitivity	specificity
1	1	0
2	0.997	0.032
3	0.97	0.144
4	0.908	0.353
5	0.83	0.557
6	0.693	0.714
7	0.562	0.823
8	0.41	0.914
9	0.228	0.965
10	0.069	0.993

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