ABSTRACT

Objective To develop an NIH Stroke Scale (NIHSS)-compatible, all-in-one scale for rapid and comprehensive prehospital stroke assessment including stroke recognition, severity grading and progression monitoring as well as prediction of large vessel occlusion (LVO).

Methods Emergency medical services (EMS) personnel and stroke physicians (n=326) rated each item of the NIHSS regarding suitability for prehospital use; best rated items were included. Stroke recognition was evaluated retrospectively in 689 consecutive patients with acute stroke or stroke mimics, prediction of LVO in 741 consecutive patients with ischaemic stroke with acute vessel imaging independent of admission NIHSS score.

Results Nine of the NIHSS items were rated as ‘suitable for prehospital use.’ After excluding two items in order to increase specificity, the final scale (termed shortened NIHSS for EMS, sNIHSS-EMS) consists of ‘level of consciousness’, ‘facial palsy’, ‘motor arm/leg’, ‘sensory’, ‘language’ and ‘dysarthria’. Sensitivity for stroke recognition of the sNIHSS-EMS is 91% (95% CI 86 to 94), specificity 52% (95% CI 47 to 56). Receiver operating curve analysis revealed an optimal cut-off point for LVO prediction of ≥6 (sensitivity 70% (95% CI 65 to 76), specificity 81% (95% CI 76 to 84), positive predictive value 70 (95% CI 0.78 to 0.84)). Test characteristics were non-inferior to non-comprehensive scales.

Conclusions The sNIHSS-EMS may overcome the sequential use of multiple emergency stroke scales by permitting parallel stroke recognition, severity grading and LVO prediction. Full NIHSS-item compatibility allows for evaluation of stroke progression starting at the prehospital phase.

INTRODUCTION

A considerable number of stroke scales for prehospital use have been published over recent years.1 2 However, most of these scales only focus on single aspects of acute stroke care, that is, either stroke recognition,1 2 early prediction of outcome,3 prediction of thrombolysis,4 5 or severity grading and large vessel occlusion (LVO).6-15 Consequently, to provide a comprehensive prehospital stroke assessment, emergency medical services (EMS) personnel must apply at least two scales. Furthermore, the majority of existing scales lack compatibility with the NIH Stroke Scale.
Scale (NIHSS), the in-hospital ‘gold-standard’ for stroke severity grading. This impedes the seamless evaluation of stroke progression from pre to in-hospital care. In the era of endovascular treatment of LVO, decisions regarding direct emergency referrals to specialised comprehensive stroke centres will have a major impact on patients’ outcomes. As those are left entirely to EMS personnel, it is essential to equip them with an effective tool to guide prehospital triage.

We present the development and validation of a novel comprehensive stroke scale, specifically designed for prehospital use with input from EMS. Our aim was to allow for parallel stroke recognition, severity grading and—owing to full NIHSS compatibility—progression monitoring as well as LVO prediction.

**METHODS**

**International online survey**

We invited non-neurological EMS personnel (paramedics and emergency physicians) and stroke physicians from Austria, Germany and Switzerland to rate each individual NIHSS item regarding its applicability in a prehospital emergency setting. Invitations were sent out via the German Stroke Society, the German Society for Neuro-Intensive Care and Emergency Medicine as well as EMS providers. Participation was voluntary, no financial incentive was offered and participation was only allowed once. Non-neurological EMS personnel did not use the NIHSS routinely and did not receive specific NIHSS training before the survey. For each NIHSS item, we created and provided a short video demonstrating in-hospital bedside assessment according to the NIHSS training instructions (a screenshot is shown as figure 1A in the online supplementary appendix). Having watched the video, participants were asked to rate each NIHSS item regarding its suitability for prehospital use on a 6-item scale, ranging from 0 (most suitable) to 5 (most unsuitable). Ratings were automatically entered into a database together with name (optional), profession, professional experience and place of work. Participation was possible from 19 November 2015 until 15 April 2016, the prespecified closing date.

**Patient cohorts**

Test characteristics of the newly designed scale were calculated with regard to performance in stroke recognition and prediction of acute LVO using two distinct clinical cohorts described below.

For stroke recognition, we used a prospectively collected cohort of consecutive patients with acute ischaemic or haemorrhagic stroke and stroke mimics, which had already served as a validation cohort in a previous comparison of existing stroke scales. In summary, the database consists of pseudonymised data of consecutive patients (including comatose) with preclinical ‘suspected acute CNS disorder’ admitted to the Emergency Room of the Department of Neurology, Heidelberg University Hospital, Germany, by EMS between November 2007 and August 2010. For all patients, a full-length NIHSS score assessed by certified raters was available at admission. The diagnostic reference standard was the diagnosis at hospital discharge. Cases were dichotomised (by the authors AE and CH) in stroke and non-stroke, that is, stroke mimics. AE and CH were blinded for the admission NIHSS and sNIHSS-EMS scores.

Test characteristics regarding the prediction of LVO were calculated in a prospectively collected second cohort consisting of consecutive patients with acute ischaemic stroke, admitted to the Department of Neurology, Tuebingen University Hospital, Germany, between January 2013 and July 2015. In accordance with local standard operating procedures, all received acute vessel imaging on admission independent of stroke severity. Neuroradiological reports and original images were reviewed by the authors HR and SP for presence of acute LVO. HR and SP were blinded to patients’ NIHSS scores. Cases were considered as LVO positive if an acute symptomatic occlusion was present in one of the following arteries: common carotid artery, internal carotid artery, carotid T, middle cerebral artery (including M1/M2 segments), anterior cerebral artery, basilar artery or posterior cerebral artery.

**Statistics**

To determine suitable items for use in the prehospital phase, we analysed the online survey response data set; median and IQRs were calculated. NIHSS items receiving median scores of 0 and 1 were—as predefined—regarded eligible for further consideration. Rating differences between the professional groups (ie, non-neurological EMS personnel and stroke physicians) were determined using the Mann-Whitney U test. For the calculation of test performance regarding stroke recognition, the sNIHSS-EMS score was dichotomised as indicative of stroke (score ≥1), or not (score=0). Sensitivity (the proportion of patients with stroke who had a positive test, ie, indicative of stroke) and specificity (the proportion of non-stroke patients who had a negative test), positive predictive value (PPV) and negative predictive value (NPV) were calculated with 95% CIs. Details of the sample size calculation are described in the extended methods in the online supplementary appendix. To determine the predictive power for LVO detection, we calculated sensitivity, specificity, PPV and NPV, with 95% CI for each scale score ranging from 0 to 29 for the sNIHSS-EMS, and from 0 to 42 for the original NIHSS. Accuracy is reported additionally. Receiver operating curve (ROC) analysis was performed, area under the curve (AUC) and Youden index were calculated. For comparison of the sNIHSS-EMS with existing dedicated LVO prediction scales, we calculated the corresponding scores using the NIHSS equivalents and cut-offs as stated in the original publications. Statistical comparison of AUCs was performed according to DeLong et al. Calculation of the Los Angeles Motor Scale (LAMS) for our LVO cohort was not possible since the item ‘grip-strength’ was not routinely documented. p Values were
two sided with values less than .05 considered statistically significant. SPSS (V.23.0.0.2, IBM), MedCalc (V.16.8.4, Ostend, Belgium) and GraphPad Prism (V.6.0b, San Diego, California, USA) were used for data handling and analysis, and graphic presentation. This study was performed in accordance with the STARD guidelines for studies on diagnostic tests.

RESULTS
Scale development
Three hundred twenty-six (13%) of 2562 recipients responded to our international online survey (Austria, Germany and Switzerland), with the majority (57%) representing non-neurological EMS personnel (33% paramedics and 24% prehospital emergency physicians); 33% stroke physicians and 10% not specified. Participants reported a high level of professional experience (>10 years, 45%; <5 years, 20%).

Nine of the NIHSS items received a median score of 0 or 1 (equivalent to most suitable and suitable for prehospital use), whereas the items ‘best gaze’, ‘visual’, ‘limb ataxia’ and ‘extinction’ were rated as less suitable and thus removed from further analyses (table 1A in the online supplementary appendix). Although rating by stroke physicians was more rigorous, item selection based on median ratings of 0 or 1 was not shifted by the professional vote (table 1A).

We decided to exclude item 1b (level of consciousness (LOC) questions) and item 1c (LOC commands). Despite being easily assessable and thus rated suitable for prehospital use, these two items are either present in the absence of stroke as frequent features of non-stroke conditions (eg, dementia, infection or dehydration) or heavily influenced by aphasia and thus redundant for stroke recognition. The new 7-item scale was termed ‘shortened NIHSS for emergency medical services’ (sNIHSS-EMS; table 1).

Stroke recognition and severity grading
In our stroke recognition validation cohort of 689 consecutive patients with ‘suspected acute CNS disorder,’ 29% received ‘stroke’ as discharge diagnosis. Patients with ischemic stroke (n=200) had an admission NIHSS of 9 (IQR 4–17), patients with hemorrhagic stroke (n=55) of 17 (IQR 5–35). Non-stroke patients (n=489) had a median admission NIHSS of 1 (IQR 0–6). The sNIHSS-EMS was found to have 90.5% (95% CI 85.6 to 94.2) sensitivity and 51.5% (95% CI 47.0 to 56.1) specificity for stroke recognition (PPV 43.3% (95% CI 38.5 to 48.2), NPV 93.0% (95% CI 89.3 to 95.6)). Cross tabulations are shown in table 2A in the online supplementary appendix. Excluding patients in a coma (n=49), sensitivity was 89.1% (95% CI 83.6 to 93.3) and specificity was 54.2% (95% CI 49.5 to 58.8).

LVO prediction
In the distinct LVO validation cohort of consecutive 741 patients with ischemic stroke with acute vessel imaging independent of their admission NIHSS score (86.9% CT-angiography (CT-A); see table 3A in the online supplementary appendix for patient characteristics), an ROC analysis of the sNIHSS-EMS regarding LVO prediction revealed a maximal Youden index at the cut-point of ≥9 (77.1–84.6)). For comparison, in the original NIHSS, the maximal Youden index was calculated for a cut-point of ≥9 (table 2). Combined inclusion of the NIHSS items ‘visual’, ‘gaze’ and ‘extinction’ improved test characteristics (AUC 0.826 vs 0.808, p<0.001). Reinclusion of singular items did not improve test characteristics. Exclusion of patients in a coma (n=5) did not change the optimal cut-off and test characteristics (sensitivity 70.0% (64.4–75.3), specificity 81.1% (77.1–84.6)).

We validated the sNIHSS-EMS against existing LVO prediction scales through applying them to our cohort and calculation of ROC and Youden indices (table 3, figure 1). No statistically significant differences compared with existing scales were found, except for the full-length NIHSS, and the sNIHSS-8. Notably, due to characteristics of our cohort, external validation based on maximal Youden indices led to cut-points different from those reported in the respective original publications (table 3).

DISCUSSION
The sNIHSS-EMS is the first comprehensive stroke scale assessed for parallel stroke recognition, severity grading and LVO prediction. Test characteristics regarding identification of patients with LVO are non-inferior to existing LVO prediction scales. Furthermore, compatibility with the item assessment in the full-length NIHSS allows for continuous evaluation of the clinical course from pre to
As previously shown by our work group, some of the available stroke severity scales may be used for stroke recognition with similar sensitivity and specificity when compared with scales developed for stroke recognition alone. Existing scales, however, either include items requiring complex assessment (such as extinction11 15) or exclude items highly relevant for evaluation of stroke progression (such as level of consciousness, arm or leg motor function17 11).

Sensitivity of the sNIHSS-EMS regarding stroke recognition (91%) was superior to previously published results for the simpler Cincinnati Prehospital Stroke Scale (CPSS; 85%) and Field Assessment Stroke Triage (FAST; 87%) evaluated in the same cohort of patients.2 In contrast, specificity (52%) was lower compared with the CPSS (65%) and FAST (64%).2 As the overall burden of a missed stroke outweighs the potentially increased workload of emergency departments, higher sensitivity may be considered more relevant. Simpler stroke scales may provide a slightly faster initial assessment, but subsequently require the use of at least one additional scale to determine stroke severity or predict LVO. The use of multiple scales, however, may be error prone and complicates communication with receiving hospitals.

According to recent European and American recommendations, clinical screening tools may be considered in order to facilitate direct transport of patients with suspected LVO to Comprehensive Stroke Centers (CSC) with endovascular facility.20 24 For LVO prediction, our analysis revealed a maximum Youden index for the cut-point of 6 for the sNIHSS-EMS and, in accordance with previous findings, 9 for the original NIHSS.25 Importantly, to adjust for hospital capacities and local stroke network requirements, this threshold can be adapted: higher cut-points result in an increased specificity (table 2) leading to reduced numbers of patients bypassing Acute Stroke Ready Hospitals (ASRH) or Primary Stroke Centers (PSC) without endovascular facility.

The NIHSS items ‘visual’, ‘gaze’ and ‘extinction’ are part of some dedicated LVO prediction scales, but

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**Figure 1** Receiver operating curves for prediction of acute large vessel occlusion. 3I-SS, 3-item Stroke Scale; CPSSS, Cincinnati Prehospital Stroke Severity Scale; FAST-ED, Field Assessment Stroke Triage for Emergency Destination; NIHSS, NIH Stroke Scale; PASS, Prehospital Acute Stroke Severity Scale; RACE, Rapid Arterial Occlusion Evaluation scale; ref, reference; sNIHSS-EMS, shortened NIHSS for emergency medical services.

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**Table 2** Cut-off points for prediction of acute large vessel occlusion

| Cut-off point | Sensitivity | Specificity | Positive predictive value | Negative predictive value | Accuracy | J |
|--------------|-------------|-------------|---------------------------|---------------------------|----------|---|
| sNIHSS-EMS   |             |             |                           |                           |          |   |
| 5            | 74.8 (69.4–79.7) | 73.4 (69.1–77.4) | 66.4 (59.0–69.5) | 81.9 (77.8–85.6) | 74.0 | 0.482 |
| 6*           | 70.3 (64.7–75.5) | 80.7 (76.8–84.3) | 70.1 (64.5–75.3) | 80.9 (76.9–84.4) | 76.7 | 0.511 |
| 7            | 65.2 (59.4–70.6) | 85.8 (82.2–88.9) | 74.7 (68.9–79.9) | 79.3 (75.4–82.8) | 77.7 | 0.510 |
| NIHSS        |             |             |                           |                           |          |   |
| 8            | 72.4 (66.9–77.5) | 80.7 (76.8–84.3) | 70.7 (65.2–75.8) | 82.0 (78.1–85.4) | 77.5 | 0.531 |
| 9*           | 69.3 (63.7–74.6) | 85.4 (81.8–88.5) | 75.3 (69.7–80.3) | 81.2 (77.4–84.6) | 79.1 | 0.547 |
| 10           | 65.9 (60.1–71.3) | 88.0 (84.7–90.9) | 78.0 (72.2–83.0) | 80.0 (76.2–83.5) | 79.4 | 0.539 |

Data are % (95% CI). J indicates Youden index.
*Indicates the optimal cut-off according to the Youden index.
NIHSS, NIH Stroke Scale; sNIHSS-EMS, shortened NIHSS for emergency medical services.
Table 3  Comparison of clinical scales for prehospital prediction of LVO

|                        | sNIHSS-8 | sNIHSS-5 | 3I-SS | LAMS | RACE | CPSSS | FAST-ED | PASS | sNIHSS-EMS |
|------------------------|----------|----------|-------|------|------|-------|---------|------|------------|
| **Reference**          | 3        | 3        | 10    | 16   | 11   | 12    | 15      | 14   | 10         |
| **Scale characteristics** |          |          |       |      |      |       |         |      |            |
| No. of items assessed* | 7        | 4        | 3     | 3    | 5±   | 3     | 5       | 3    | 3          |
| Score range            | 0–24     | 0–16     | 0–6   | 0–5  | 0–9  | 0–4   | 0–9     | 0–3  | 0–29       |
| NIHSS compatible item assessment | ●       | ●       | –     | –    | –    | –     | –       | –    | ●          |
| Stroke recognition     | ●        | ●        | –     | –    | –    | –     | –       | –    | –          |
| Stroke severity grading | ●      | ●       | –     | (●)  | (●)  | –     | –       | –    | ●          |
| LVO prediction         | ●        | ●        | ●     | ●    | ●    | ●     | ●       | ●    | ●          |
| **LVO prediction, test characteristics, own cohort (n=741, 44% LVO)** |          |          |       |      |      |       |         |      |            |
| Cut-point used†        | ≥6       | ≥3       | ≥4    | ≥4   | ≥5   | ≥2   | ≥4      | ≥2  | ≥6         |
| Sensitivity            | 64%      | 69%      | 40%   | –§   | 59%  | 59%   | –       | 60%  | 68%        |
| Specificity            | 88%      | 81%      | 95%   | –§   | 91%  | 89%   | 90%     | 84%  | 81%        |
| PPV                    | 78%      | 70%      | 85%   | –§   | 81%  | 77%   | 80%     | 74%  | 70%        |
| NPV                    | 79%      | 80%      | 71%   | –§   | 78%  | 77%   | 78%     | 81%  | 81%        |
| **LVO prediction, test characteristics, original cohorts¶** |          |          |       |      |      |       |         |      |            |
| Cohort (N (% LVO))     | –        | –        | 83 (35%) | 119 (62%) | 357 (21%)** | 303 (73%) | 727 (33%) | 3127 (35%) †† | – |
| Sensitivity            | –        | –        | 67%   | 81%  | 85%  | 83%   | 61%     | 66%  | –          |
| Specificity            | –        | –        | 92%   | 89%  | 68%  | 40%   | 89%     | 83%  | –          |
| PPV                    | –        | –        | 74%   | ND   | 42%  | ND    | 72%     | 68%  | –          |
| NPV                    | –        | –        | 89%   | ND   | 94%  | ND    | 82%     | 81%  | –          |

*Motor arm (or leg) scored for each side (left or right) is counted as one item.
†If right-sided hemiparesis, aphasia is assessed; if left-sided hemiparesis, agnosia.
‡Cut-points according to original publications, with exception of the sNIHSS-8 and sNIHSS-5. Based on the Youden indices calculated from our data, optimal cut-points are different: 3I-SS ≥2, RACE ≥3, CPSSS ≥1, FAST-ED ≥3.
§Grip strength was not routinely documented, therefore external validation of the LAMS was not possible.
¶Definition of LVO according to original publications (3I-SS: carotid T or M1; LAMS: ICA, M1, M2, M3/4, ACA; RACE: terminal ICA, M1, tandem CCA/ICA+M1, BA; CPSSS: ICA, M1, tandem ICA+M2, BA; FAST-ED: ICA, M1, M2, BA; PASS: ‘visible clot in the anterior or posterior circulation on CTA or MRA’; abbreviations within the main text).
**Including cases assessed by transcranial duplex only (n=197).
††Only patients who received intravenous tissue plasminogen activator; two-thirds of entire cohort was taken as a random sample for derivation. In the remaining one-third, sensitivity was 61%, specificity 83%.
ACA, anterior cerebral artery; BA, basilar artery; CCA, common carotid artery; 3I-SS, 3-item Stroke Scale; CPSSS, Cincinnati Prehospital Stroke Severity Scale; FAST-ED, Field Assessment Stroke Triage for Emergency Destination; ICA, internal carotid artery; LAMS, Los Angeles Motor Scale; LVO, large vessel occlusion; ND, no data; NIHSS, NIH Stroke Scale; NPV, negative predictive value; PASS, Prehospital Acute Stroke Severity Scale; PPV, positive predictive value; RACE, Rapid Arterial Occlusion Evaluation scale; sNIHSS-EMS, shortened NIHSS for emergency medical services.
were not included in the sNIHSS-EMS due to unfavourable ratings regarding prehospital assessability. Reinclu-
sion of each separate item did not result in the presumed higher predictive value for LVO detection. Only combined
reinclusion of all three rejected items led to marginally enhanced test characteristics, but would result in a signifi-
cantly increased number of complex-to-assess items and thus an inconvenient scale.

For comparison with existing scales, we externally vali-
dated dedicated LVO prediction scales in our cohort by
using the cut-points as provided in the original publica-
tions and found the sNIHSS-EMS to offer comparable
sensitivity and specificity (table 3). Better test character-
istics reported in the original publications for some scales
may be due to differences in the definition of LVO (eg, the 3I-SS (3-item stroke scale) focused on carotid T and
M1 occlusions only,10 while the LAMS also included M3/4
occlusions16). The sNIHSS-8, which had a higher AUC in
the ROC analysis than the sNIHSS-EMS, was not devel-
oped for LVO prediction and includes items rejected by
EMS personnel in our survey due to the complexity of
correct assessment.

LVO prediction by clinical scales has recently been crit-
icised due to the high false-negative rate compared with
vessel imaging17 20. The sNIHSS-EMS is not intended to
substitute in-hospital acute vessel imaging17, and prehos-
pital acute vessel imaging is still an exception.27 Currently,
mainly due to the narrow time window for effective inra-
venous thrombolysis, patients are transferred to the
closest stroke centre regardless of LVO suspicion. In the
era of interventional thrombectomy however, ASRH or
PSC may have to be bypassed in favour of CSC with endo-
vascular facility in sensibly selected cases.

Based on clinical criteria alone, the sNIHSS-EMS identi-
fies the majority of patients with acute LVO, that is, those patients who might benefit from a direct transfer to
CSC with endovascular facility. In addition, the minority
of patients with LVO not bypassed to endovascular ready
CSC (ie, total score <6 despite LVO) are not lost to endo-
vascular therapy since secondary transportation to an
endovascular ready CSC is still possible.

The sNIHSS-EMS is designed to permit the moni-
toring of stroke progression from pre to in-hospital care
on the item level, a feature that has been neglected in
other scales. Clinical implications include the earlier
recognition of symptom fluctuation with consequences,
for example, for blood pressure management or selec-
tion of imaging modality. In practice, if a ‘2’ is scored for
‘Motor Leg left’ on the sNIHSS-EMS, a ‘4’ on the same
item during routine NIHSS examination in the Emergency
Room points to early clinical deterioration. Clinical scores
using merged items (eg, ‘hemiparesis’10 or ‘language/
dysarthria’)4 or modified item scoring (eg, motor func-
tion scoring from 0 to 2 instead of 0 to 4)11 12 14–16 impede
seamless monitoring of symptom progression.

Despite the positive aspects of the sNIHSS-EMS, some
limitations of the present study require further discus-
sion. Test characteristics regarding LVO prediction were
calculated in a cohort of patients with confirmed ischaemic
stroke because determination of the ‘true’ LVO prediction
threshold is only possible in a cohort without stroke mimics
or haemorrhagic stroke. However, although this approach
is in concordance with methods used in the past in the
design of dedicated LVO prediction scales,12 14 16 future
prospective validation in the prehospital target population
will be necessary to determine prevalence-dependent test
characteristics. We were not able to assess LVO prediction
of the LAMS because the item ‘grip strength’ is not part of
the NIHSS, and thus was not routinely documented in
our cohort. According to a retrospective validation study in
anterior circulation stroke, the sensitivity of the LAMS for
LVO prediction was reported as 81% (at a threshold of 4).16
As patients with stroke mimics (and thus no LVO) exhibit
low NIHSS scores, inclusion of these cases into the analyses
would lead to an increased specificity of our cut-points.
The sNIHSS-EMS is not able to differentiate between
ischaemic and haemorrhagic strokes. This might not be
a disadvantage as patients severely affected with haemor-
hagic stroke benefit from direct admission to a CSC with
neurological intensive care capacity.29 Despite involvement
of EMS systems from three European countries, general-
siability to further EMS systems around the world cannot
be concluded. The low response rate of our online survey
makes a non-response bias likely. Due to the participants’
high professional experience, one might have expected a
shift of the suitability assessment towards more complex
items. However, this was not observed. As a strength of
this study, LVO was evaluated by CT-A or MR-angiography,
and not with less accurate duplex sonography as done in
previous studies evaluating LVO prediction scales.11 16 The
sNIHSS-EMS was primarily designed to fulfil requirements
for prehospital use. Although kept simple, additional
training on the new scale is recommended. Moreover, the
sNIHSS-EMS may also serve in telemedicine with usually
non-neurological physicians performing the initial patient
examination.

CONCLUSION
The sNIHSS-EMS may overcome the need for sequen-
tial use of multiple emergency stroke scales by enabling
parallel stroke recognition, severity grading and LVO
prediction. Full NIHSS-item compatibility permits evalua-
tion of stroke progression starting from the prehospital
phase. Offering comparable test characteristics as dedi-
cated scales, the sNIHSS-EMS may be a promising tool for
rapid and comprehensive prehospital stroke assessment
and triage.

Author affiliations
1Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany
2Department of Neurology and Stroke, Hertie Institute for Clinical Brain Research,
Tuebingen University Hospital, Tuebingen, Germany
3Department of Medical Informatics, University of Tuebingen, Tuebingen, Germany
4Department of Computer Science and Software Engineering, University of Stuttgart,
Stuttgart, Germany
5Department of Anesthesiology, University of Heidelberg, Heidelberg, Germany
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SP and JCP conceived and designed the study. EP provided the EMS data. HR and SP created and validated the LVO prediction database. SP, JCP, AE and CH collected and analysed the data. JH and JA developed and maintained the online survey. JCP, FH and SP drafted the article. JCP, HR, FH, CH, PAR, SN and SP revised the manuscript.

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