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Re-evaluation of the stroke prognostication using age and NIH Stroke Scale index (SPAN-100 index) in IVT patients — the-SPAN 100⁶⁵ index

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Abstract

Background: The SPAN-100 index adds patient age and baseline NIHSS-score and was introduced to predict clinical outcome after acute ischemic stroke (AIS). Even with high NIHSS-scores younger patients cannot reach a SPAN-100-positive status (index ≥ 100). We aimed to evaluate the SPAN-100 index among a large, contemporary cohort of i.v.-thrombolysed AIS-patients and exclusively among older patients who can at least theoretically achieve SPAN-100-positivity.

Methods: The SPAN-100 index was applied to AIS-patients receiving i.v.-thrombolysis (IVT) in our institution between 01/2006 and 01/2013. Clinical outcome and symptomatic intracerebral hemorrhage rates were compared between SPAN-100-positive and -negative patients. Furthermore we excluded patients < 65 years, without any theoretical chance to achieve SPAN-100-positivity, and re-evaluated the index (SPAN⁶⁵-100 index).

Results: SPAN-100-positive IVT-patients (124/1002) had a 9-fold increased risk for unfavorable outcome compared to SPAN-negative patients (OR 9.39; 95% CI 5.87–15.02; $p < 0.001$). The odds ratio for mortality was 7.48 (95% CI 4.90–11.43; $p < 0.001$). No association was found between SPAN-100-positivity and sICH-incidence (OR 0.88; 95% CI 0.31–2.53; $p = 0.810$).

SPAN⁶⁵-100-positivity (124/741) was associated with an 8-fold increased risk for unfavorable outcome (OR 7.6; 95% CI 4.71–12.22; $p < 0.001$) but not associated with higher sICH-rates (OR 0.86; 95% CI 0.29–2.53; $p < 0.001$).

Conclusions: Also for patients ≥ 65 years the SPAN-100 index can be a fast, easy method to predict clinical outcome of IVT-patients in everyday practice. However, it should not be used to determine the risk of sICH after IVT. Based on a SPAN-positive status IVT should not be withheld from AIS-patients merely because of feared sICH-complications.

Keywords: SPAN-100 index, SPAN-100⁶⁵ index, Acute ischemic stroke, I.V.-thrombolysis, Clinical outcome, Symptomatic intracerebral hemorrhage

Background

Age and stroke severity are known major risk factors and predictors for unfavorable outcome in acute ischemic stroke (AIS) patients [1–3]. However, impact of higher age and higher initial National Institutes of Health Stroke Scale (NIHSS)-scores on clinical outcome after AIS and the way how these two factors interact with each other

still remain not entirely clear. In particular data showing which individual patient will achieve favorable or unfavorable outcome is sparse. Different scores to predict clinical outcome after AIS have been introduced [4–8]. Most of them are rather complex and may therefore not be extensively used in daily routine. In order to create a fast and practical tool to predict clinical outcome of AIS patients the Stroke Prognostication using Age and NIH Stroke Scale index (SPAN-100 index) was introduced [9]. It simply combines patient age (years) and the NIHSS-Score at stroke onset. Patients with a score ≥ 100 are classified as

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SPAN-100-positive and those with a score < 100 are designated as SPAN-100-negative. The index was applied to the dataset of the National Institute of Neurological Disorders and Stroke (NINDS)-tPA trials [10] and found to be of good value to predict clinical outcome and risk of intracerebral hemorrhage [9]. Since its introduction the SPAN-100-index has been evaluated several times in different patient cohorts [11–15]. However, previous investigations have in common that they included patients who could not achieve a SPAN-100-positive status at all, e.g. the original SPAN-100-evaluation [9] with a considerable proportion of younger patients. Even with very high NIHSS-scores they were not able to reach a SPAN-Index of ≥ 100 . Including such patients might have increased selectivity of the score potentially leading to an overestimation of its benefit.

The first aim of our study was to re-evaluate reliability of the original SPAN-100 index in an independent, more recent cohort of 1002 i.v.-thrombolysed AIS-patients. The second objective was to exclude younger patients from our patient cohort to exclusively evaluate the SPAN-index among the subgroup of patients who could at least theoretically achieve SPAN-100-positivity.

Methods

The Erlangen Stroke and Thrombolysis Database is a prospective database of all AIS-patients at the University Hospital Erlangen, Germany. It contains baseline demographic and stroke related data as well as treatment specifics, imaging information and outcome parameters for each stroke patient. Outcome at day 90 was assessed using the mRS (modified Rankin Scale) evaluated by a neurologist as part of the general database independently from the present study using a semi-structured interview either in person or by telephone. Favorable clinical outcome was defined as mRS: 0–2 and/or clinical recovery to the pre-stroke mRS. Unfavorable outcome was defined as a mRS of 4–6. The study was approved by the local ethics committee. 17/1002 patients were lost to follow-up at day 90. Symptomatic intracerebral hemorrhage (sICH) was defined according to the European Cooperative Acute Stroke Study (ECASS) III criteria (sICH-definition 1) [16]. To assure comparability to the derivation cohort we additionally applied the sICH-definition (any documented decline in the neurologic status) used in the original publication [9] (sICH-definition 2). Our institutional guidelines are less restrictive than the European Medicines Agency -licence for tPA, therefore more than half of our patients receive off-label IVT. Besides that all patients were treated and monitored on our stroke unit in accordance with European guidelines [17]. Standard CT-based treatment was performed within the 4.5-h-window. For patients within an extended or unknown time window our institution uses an MRI mismatch-based algorithm as described

elsewhere [18]. Follow-up imaging was performed after 24 to 36 h to evaluate for intracerebral hemorrhage and infarct distribution. NIHSS-scores were documented by NIHSS-certified stroke neurologists.

Study population

For this study we extracted all AIS-patients from the database who consecutively received IVT between 01/2006 and 01/2013. We applied the SPAN-100 index to this cohort to create two groups by adding age (years) to the NIHSS-score on admission. Patients with a score ≥ 100 were classified as SPAN-100-positive, whereas all patients with a score < 100 were designated as SPAN-100-negative. We compared clinical outcomes and sICH-rates of SPAN-100-negative and SPAN-100-positive patients. To identify patients who were eligible for the second part of our study, we subtracted the highest NIHSS-score documented in our patient cohort from the SPAN-100 cut off score of ≥ 100 . Referring to the NIHSS-Coma Scoring Rules (as stated in the original scoring manual developed for the NINDS Trial of tPA for Acute Stroke) this was a NIHSS-score of 35 resulting in a second patient-cohort aged ≥ 65 years. We again compared clinical outcomes at day 90 and sICH-rates in both groups (SPAN⁶⁵-100-positive and SPAN⁶⁵-100-negative patients).

Statistical analysis

Statistical analysis was performed using PASW Statistics 19 (SPSS Inc., Chicago, Ill., USA). All data were tested for normality. Categorical variables are presented as frequencies and percentages, whereas continuous data are expressed as mean and standard deviation or as median and interquartile range as appropriate. Intergroup differences were assessed using analysis of variance for normally distributed items, the Kruskal-Wallis test for non-normal data, and the χ^2 -test for dichotomous variables. Binary logistic regression was performed with SPAN-100-status as independent variable. *p*-values ≤ 0.05 were considered significant.

Results

1002 AIS-patients received IVT at our institution between 01/2006 and 01/2013. After applying the SPAN-100 index 124 (12.4%) were classified as SPAN-100-positive.

Baseline characteristics

Mean age was 87 years for SPAN-100-positive and 72 years in SPAN-100-negative patients. Median NIHSS-scores on admission were 19 for SPAN-100-positive and 8 for SPAN-100-negative patients respectively. Door-to-needle-time did not differ in both groups. Compared to SPAN-100-negative patients, those in the SPAN-100-positive group were more likely to be women and to suffer from coronary artery disease and atrial fibrillation. SPAN-100-positive patients had

worse pre-stroke-mRS scores than SPAN-100-negative patients. Baseline characteristics are summarized in Table 1.

Outcome comparison of SPAN-100-positive and SPAN-100-negative patients

SPAN-100-positive patients were more likely to have unfavorable outcomes (80.1% vs. 30.1%; $p < 0.001$), and only 13 of them achieved favorable outcome at day 90 (10.7% vs. 36.9% in the SPAN-100-negative group; $p < 0.001$) (Fig. 1). Mortality during hospital stay (29.8% vs. 6.4%; $p < 0.001$) and after three months (44.6% vs. 9.7%; $p < 0.001$) was significantly higher in SPAN-100-positive patients. Unadjusted binary regression analysis showed a 9-fold increase in the odds of unfavorable outcome for SPAN-100-positive patients and

a 7.5-fold increase for mortality after three months (Table 2).

Area under the curve (AUC) for the SPAN-100 concerning mRS 4–6 was 0.74; 95%; $p < 0.0001$; 95% CI (0.71–0.77). Sensitivity and specificity for the cut-off of 100 was 0.27 and 0.96 respectively.

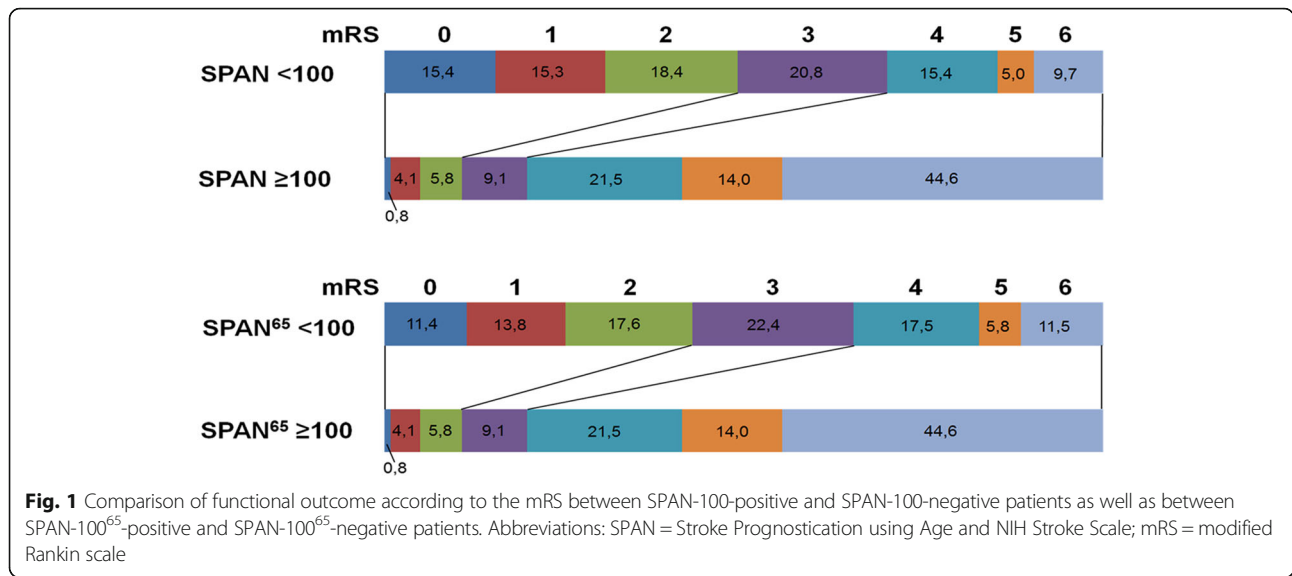
sICH comparison between SPAN-100-positive and SPAN-100-negative patients

Of 36 sICH (sICH-definition 1) 4 (3.2%) occurred in SPAN-100-positive and 32 (3.7%) in SPAN-100-negative patients, respectively ($p = 1.000$). The binary logistic regression analysis showed that SPAN-100-positive status was not predictive for sICH-incidence regardless if sICH-definition 1 or 2 were applied (Table 2).

Table 1 Baseline characteristics of SPAN-100-positive and SPAN-100-negative patients

Variable	Total (n = 1002)	SPAN pos. (n = 124)	SPAN neg. (n = 878)	p-value
Age (years), median (IQR)	73 (18)	87 (8)	72 (17)	< 0.001
Sex (female), n (%)	473 (47.2%)	81 (65.3%)	392 (44.6%)	< 0.001
Risk factors, n (%)				
Hypertension	872 (87.0%)	111 (89.5%)	761 (86.7%)	0.475
Hypercholesterolemia	571 (57.3%)	47 (37.9%)	524 (60.0%)	< 0.001
Nicotine	145 (14.5%)	7 (5.6%)	138 (15.7%)	0.002
Diabetes	330 (32.9%)	40 (32.3%)	290 (33.0%)	0.919
Coronary artery disease	283 (28.2%)	46 (37.1%)	237 (27.0%)	0.025
Previous myocardial infarction	112 (11.2%)	19 (15.3%)	93 (10.6%)	0.128
Previous stroke/TIA	241 (24.1%)	33 (26.6%)	208 (23.7%)	0.501
Atrial fibrillation	412 (41.1%)	86 (69.4%)	326 (37.1%)	< 0.001
door-to-needle time [min.] Median (IQR)	32 (26)	34,5 (24)	32 (26)	0.543
NIHSS-score on admission Median (IQR)	10 (10)	19 (6)	8 (8)	< 0.001
Pre-stroke mRS: 0–1, n (%)	753 (75.1%)	57 (46.0%)	696 (79.3%)	< 0.001
Vital signs/laboratory findings				
Temperature on admission [°C] median (IQR)	36.6 (1.0)	36.4 (1.0)	36.7 (0.9)	0.004
Blood glucose on admission [mg/dl] median (IQR)	117 (41)	118 (34)	116 (43)	0.509
Systolic blood pressure on admission [mmHg], median (IQR)	160 (36)	160 (37)	160 (35)	0.748
Diastolic blood pressure on admission [mmHg], median (IQR)	88.5 (23)	85 (19)	89 (23)	0.028
Leucocytes on admission [$\times 10^3/\mu\text{l}$] median (IQR)	8.40 (3.73)	8.63 (3.61)	8.31 (3.79)	0.073
CRP on admission [mg/l], median (IQR)	4.3 (8.1)	6.85 (13.2)	4.0 (7.8)	0.001
Platelet count on admission [$\times 10^3$] median (IQR)	234 (98)	243.5 (102)	232 (97)	0.205
Triglycerides [mg/dl] median (IQR)	115 (71)	106 (49)	118 (78)	0.055
Stroke subtype				0.001
Large artery disease	92 (9.3%)	8 (6.5%)	84 (9.7%)	
Cardioembolic	440 (44.3%)	88 (71%)	352 (40.5%)	
Small-vessel disease	36 (3.6%)	3 (2.4%)	33 (3.8%)	
Other	36 (3.6%)	0	36 (4.1%)	
Unknown	389 (39.2%)	25 (20.2%)	364 (41.9%)	

Abbreviations SPAN = Stroke Prognostication using Age and NIH Stroke Scale, NIHSS = NIH Stroke Scale, TIA = transient ischemic attack, CRP = C-reactive protein



Evaluation of the SPAN-100 index in patients ≥65 years (SPAN-100⁶⁵ index)

741/1002 (74%) patients were ≥ 65 years old. After applying the SPAN⁶⁵-100 index, we identified 617 (83.3%) SPAN⁶⁵-100-negative and 124 (16.7%) SPAN⁶⁵-100-positive patients. Selected baseline characteristics for both subgroups are shown in Table 3.

Outcome results of the SPAN⁶⁵-cohort did not substantially differ from the findings of the total cohort. Mortality during hospital stay (29.8% vs. 7.1%; *p* < 0.001) and after three months (44.6% vs. 11.5%; *p* < 0.001) was higher for SPAN⁶⁵-100-positive patients. Patients in the SPAN⁶⁵-100-positive group were more likely to achieve unfavorable outcomes (80.1% vs. 34.8%; *p* < 0.001) and only 13 patients in the SPAN-100-positive group achieved a favorable outcome at 90 days (10.7% vs. 42.8% in the SPAN 100 negative group; *p* < 0.001) (Fig. 1). sICH (sICH-definition 1) occurred in 4 (3.2%) and 23 (2.7%) of the SPAN⁶⁵-100-positive and SPAN⁶⁵-100-negative patients, respectively (*p* = 1.000). Binary regression analysis revealed patients with SPAN⁶⁵-100-positive status to have an 8-fold increased risk in the odds for unfavorable outcome. AUC for the SPAN⁶⁵-100 was 0.73; 95%; *p* < 0.0001; 95% CI (0.69–0.76). Sensitivity and specificity for the cut-off of 100 was 0.32 and 0.94 respectively. No significant

association was found between SPAN⁶⁵-100-status and sICH-incidence regardless which sICH-definition was used. (Table 4).

Discussion

The SPAN-100 index was introduced by Saposnik et al. to facilitate treatment decisions in stroke patients [9]. With age and stroke severity it combines two main predictors for unfavorable stroke outcome. After applying the index to the patients in the NINDS-tPA trials [10] SPAN-100-positivity was found to be associated with worse outcomes. Besides that higher ICH-rates were seen in SPAN-100-positive compared to SPAN-negative patients whether they had received IVT before or not. An IVT-benefit was described for SPAN-100-negative, but not for SPAN-100-positive patients [9]. However, several conditions may have influenced these results. First, the number of SPAN-positive patients who received IVT was rather small (*n* = 36). Second, the population of the NINDS-trials does not reflect current treatment standards, e.g. patients were randomized to tPA or placebo within 3-h after symptom onset [10].

Several additional studies evaluated the SPAN-100 index after its first introduction [11–15, 19]. Overall they confirmed that SPAN-100-positive patients are less likely to achieve favorable outcome compared to SPAN-negative patients. Only one Chinese study found a low prediction power of the SPAN-100 index for 3- and 12-month outcome [19].

However, data concerning the predictive power of the SPAN-100 index for sICH are inconsistent. Krishnan et al. found higher intracerebral hemorrhage-rates in SPAN-100-positive patients compared to the SPAN-negative patients [9, 13] while Abilleira et al. observed similar sICH-rates [11]. In contrast two other studies

Table 2 Association between SPAN-100-positivity and outcome

variable	OR	95% CI	<i>p</i> -value
mRS 4–6	9.39	5.869–15.021	< 0.001
mortality at 3 months	7.48	4.901–11.427	< 0.001
sICH-Def. 1	0.88	0.305–2.527	0.810
sICH-Def. 2	1.01	0.389–2.638	0.978

Abbreviations SPAN = Stroke Prognostication using Age and NIH Stroke Scale, mRS = modified Rankin scale, sICH = symptomatic intracranial hemorrhage, OR = odds ratio, CI = confidence interval

Table 3 Baseline characteristics of SPAN⁶⁵-100-positive and SPAN⁶⁵-100-negative patients

Variable	Total (n = 741)	SPAN ⁶⁵ pos. (n = 124)	SPAN ⁶⁵ neg. (n = 617)	p-value
Age (years), median (IQR)	78 (12)	87 (8)	76 (10)	< 0.001
Sex (female), n (%)	385 (52%)	81 (65.3%)	304 (49.3%)	< 0.001
NIHSS-score on admission, median (IQR)	10 (11)	19 (6)	8 (8)	< 0.001

Abbreviations SPAN = Stroke Prognostication using Age and NIH Stroke Scale, NIHSS = NIH Stroke Scale, IQR inter quartile Range

comparing performance of different sICH-scores found a poor predictive power of the SPAN-100 index [14, 20].

In our study, we initially re-evaluated the original SPAN-100 index among a larger, more contemporary cohort of 1002 IVT-patients, including off-label treated patients. In terms of outcome our results are in line with previous studies. Patients with SPAN-100-positive status had a 9-fold increased risk of unfavorable outcome at three months.

Irrespective of the used sICH-definition SPAN-100-positive status was not associated with a higher risk of sICH.

Therefore our data do not support the hypothesis by Saposnik et al. who suggested that the SPAN-100 index might help to evaluate the risk of ICH after IVT [9]. This discrepancy might possibly be explained by the fact that advances concerning diagnostic and treatment infrastructure were achieved since the NINDS trials [10]. Continued development of imaging techniques might account for lower sICH-rates despite inclusion of off-label treated patients, e.g. patients with prolonged or unknown time window.

Previous evaluations of the SPAN-100-Index did not differentiate between patients who could a priori reach a SPAN-positive status and those who could not. Even with very high NIHSS-scores, younger patients are unable to reach the SPAN-100 index cut off score of 100. In the analysis by Saposnik et al. 219/624 (35.1%) patients in the SPAN-negative group were younger than 65 years [9]. This might have biased the SPAN-negative group towards a better outcome potentially increasing selectivity of the index and leading to an overestimation of its benefit. In the second part of our study we addressed this issue by removing patients younger than 65 years from our data set and applying the SPAN-100⁶⁵ index to the resulting new patient-cohort aged ≥65 years.

Table 4 Association between SPAN-100⁶⁵-positivity and outcome

variable	OR	95% CI	p-value
mRS 4–6	7.58	4.708–12.222	< 0.001
mortality at 3 months	6.18	3.996–3.996	< 0.001
sICH-Def. 1	0.86	0.291–2.526	0.781
sICH-Def. 2	1.22	0.488–3.031	0.674

Abbreviations SPAN = Stroke Prognostication using Age and NIH Stroke Scale, mRS = modified Rankin scale, sICH = symptomatic intracranial hemorrhage, OR = odds ratio, CI = confidence interval

Similar to the results of the total cohort, SPAN⁶⁵-100-positive patients had an 8-fold higher risk to reach unfavorable outcome. But even in IVT-patients ≥65 years sICH-rates did not differ between SPAN⁶⁵-100-positive and SPAN⁶⁵-100-negative patients. Hence, unfavorable outcome in our SPAN-100-positive patients was not related to hemorrhagic complications of thrombolytic therapy suggesting that IVT should not be withheld from older stroke patients with high NIHSS-scores merely because of safety reasons. This is in line with results from the SITS-ISTR Registry which show no excess risk of cerebral hemorrhage in patients with NIHSS-score > 25 [21]. Besides that several observational studies indicate safety and efficacy of tPA-treatment in stroke patients > 80 years [22–25] and the results of the third international stroke trial (IST-3) suggest that age should not be a barrier to IVT [26].

Our study has several limitations, primarily the single-center approach and the use of our institutional diagnostic and treatment guidelines as well as the retrospective design. However, including off-label patients might increasingly reflect common daily routine.

Conclusions

Our findings confirm the value of the SPAN-100 index. Also after excluding younger patients who a priori cannot reach a SPAN-positive status the SPAN-100 index can be an easy to use, readily available calculator in everyday clinical practice to predict clinical outcome in IVT patients. However, in our cohort SPAN-100-positive status was not predictive for the risk of sICH after IVT. Based on a positive SPAN-100 status IVT should not be withheld from patients merely because of feared sICH complications.

Abbreviations

AIS: Acute ischemic stroke; AUC: Area under the curve; CI: Confidence interval; CRP: C-reactive protein; i.v.: Intravenous; IVT: Intravenous thrombolysis; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; NINDS: National Institute of Neurological Disorders and Stroke; OR: Odds ratio; sICH: Symptomatic intracerebral hemorrhage; SPAN-100 index: Stroke Prognostication using Age and NIH Stroke Scale-100 index; SPAN-100⁶⁵ index: SPAN-100 index evaluated in patients ≥65 years; TIA: Transient ischemic attack; tPA: Tissue type plasminogen activator

Availability of data and materials

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CM Data acquisition, literature search, manuscript preparation. CB Data analysis, manuscript editing and review. SS Data analysis, manuscript editing and review. MK Study concept, manuscript editing and review. LB Study concept, data acquisition, data analysis, literature search manuscript editing and review. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Approval for data-collection for this non-interventional trial is provided within the institutional treatment agreement and is approved by the local ethics committee of the Medical Faculty Erlangen. Written consent was therefore obtained as part of the routine admission procedure. Decision-making capacity of patients was assessed by the stroke neurologist in charge based on a face to face interview and the patient's neurological status. In case patients were not able to consent approval was obtained from their legal representatives.

Consent for publication

Not applicable.

Competing interests

CM and CB reported no conflict of interest. SS reported having received speaker honoraria from Bayer, BMS Pfizer and Boehringer Ingelheim. MK reported having received advisory board and speaker honoraria and travel grants from Boehringer Ingelheim, BMS/Pfizer, Bayer and Novartis. LB reported having received speaker honoraria and travel grants from Bayer and travel grants from Boehringer Ingelheim.

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