neurocritical care society Neurocrit Care (2011) 15:447–453
DOI 10.1007/s12028-011-9547-2

ORIGINAL ARTICLE

Comparison of the Full Outline of UnResponsiveness and Glasgow Liege Scale/Glasgow Coma Scale in an Intensive Care Unit Population

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Published online: 28 April 2011

Abstract
Background The Full Outline of UnResponsiveness (FOUR) has been proposed as an alternative for the Glasgow Coma Scale (GCS)/Glasgow Liège Scale (GLS) in the evaluation of consciousness in severely brain-damaged patients. We compared the FOUR and GLS/GCS in intensive care unit patients who were admitted in a comatose state.
Methods FOUR and GLS evaluations were performed in randomized order in 176 acutely (<1 month) brain-damaged patients. GLS scores were transformed in GCS scores by removing the GLS brainstem component. Inter-rater agreement was assessed in 20% of the studied population ($N = 35$). A logistic regression analysis adjusted for age, and etiology was performed to assess the link between the studied scores and the outcome 3 months after injury ($N = 136$).
Results GLS/GCS verbal component was scored 1 in 146 patients, among these 131 were intubated. We found that the inter-rater reliability was good for the FOUR score, the GLS/GCS. FOUR, GLS/GCS total scores predicted functional outcome with and without adjustment for age and etiology. 71 patients were considered as being in a vegetative/unresponsive state based on the GLS/GCS. The FOUR score identified 8 of these 71 patients as being minimally conscious given that these patients showed visual pursuit.
Conclusions The FOUR score is a valid tool with good inter-rater reliability that is comparable to the GLS/GCS in predicting outcome. It offers the advantage to be performable in intubated patients and to identify non-verbal signs of consciousness by assessing visual pursuit, and hence minimal signs of consciousness (11% in this study), not assessed by GLS/GCS scales.

Keywords Coma · Full Outline of UnResponsiveness · Glasgow Coma Scale · Glasgow Liège Scale · Vegetative state · Minimally conscious state · Neurological assessment · Intensive care

Introduction

Following severe brain damage and coma, some patients may awaken (i.e., open the eyes) but remain unresponsive (i.e., only showing reflex movements). This clinical syndrome is called vegetative/unresponsive state [1, 2]. Patients who do recover, classically evolve to a minimally conscious state, defined by the presence of non-reflex voluntary movements such as orientation to pain, eye tracking, or reproducible albeit inconsistent command following. By definition, minimally conscious state patients cannot communicate their thoughts or wishes [3]. The clinical assessment of consciousness relies on

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disentangling automatic responses from non-reflex-oriented movements or command following. This can be very challenging in coma and related disorders. Misdiagnosis can have clinical and therapeutic consequences, especially with regard to treatment of pain [4, 5]. Contrary to patients in vegetative/unresponsive state, those in minimally conscious state retain some capacity for cognitive, emotional, and pain processing [6–8]. Neurological assessment of those comatose patients and their outcome prediction are complex due to the difficulty of capturing distinct details of the clinical examination. The complexity of such assessment can also be explained by the difficulty of finding usable terminology permitting to describe the neurological status of a single patient. In recognition of these problems, scales have been constructed in an attempt to bring uniformity to the neurological examination and to standardize communication about the level of consciousness. The most commonly used scale is the Glasgow Coma Scale (GCS) [9, 10]. The GCS initially intended to assess the level of consciousness after head injury in neurosurgical intensive care unit is widely used in neurological patients beyond the original intentions in the context of outcome prediction (e.g., [11].), neurosurgical prognostic indicator (e.g., [12].), cerebral dysfunction measurement (e.g., [13].), and consciousness evaluation [14]. Over the years, considerable limitations have been identified for this scale: the inconsistent inter-observer reliability [15], the impossibility to test the verbal component in intubated patients [16, 17], the exclusion of the brainstem reflexes [18], the incapacity to detect subtle changes in neurological examination, and the lack of correlation between outcome and GCS scores [19]. Attempts have been made to modify the GCS [20–22]. In 1982, Born et al. [18] suggested that adding measures of brainstem reflexes to the GCS could improve prognostic information, but this scale—the Glasgow Liège Scale (GLS)—never had a widespread international use. Wijdicks et al. [23] recently presented a new coma scale named the Full Outline of UnResponsiveness (FOUR) as an alternative to the GCS/GLS in the evaluation of consciousness in severely brain-damaged patients. The FOUR score, contrary to the GLS/GCS, avoids assessing verbal function. Indeed, in the acute care setting, most patients are intubated or tracheotomized which makes accurate assessment of verbal responses difficult. It consists of four components: eyes and motor responses, brainstem reflexes, and respiration.

We here aimed to compare the FOUR score with the GLS/GCS, assessing inter-observer variability of the FOUR and comparing outcome prediction and diagnostic accuracy of the different coma scales (i.e., identification of vegetative/unresponsive [2] vs. minimally conscious states [3]).

Method

We prospectively assessed the FOUR and the GLS scores, in a randomized order, in adults consecutively admitted to five subunits of the medical and general intensive care departments of the Liège University Hospital and in one unit of the Citadelle Regional Hospital in Liège, Belgium. GLS scores were transformed to the more widely used GCS scores (GLS equals to GCS scores except for the addition of brainstem reflex assessment) [18]. Hence, GCS and GLS were not independent measures. Inclusion criteria were GCS < 8 on admission and the absence of sedation or neuromuscular function blockers. Patients were assessed once within 1 month after the acute traumatic or non-traumatic brain injury. The assessments were performed by 1 ICU nurse (seen $N = 36$ patients), 4 neuropsychologists (seen $N = 115$ patients), 2 senior ICU specialists (seen $N = 32$ patients), and 1 senior registrar (seen $N = 28$ patients) who either had previous knowledge or had provided some type of care to these patients. Raters had established skill in scoring GLS/GLS, they were provided with a one-page written and visual instruction handout describing the FOUR score. These instructions were a French translation of the original instruction from the Mayo Clinic [23]. Raters were asked to grade a few patients using both GLS/GSC and FOUR scales prior the study. In intubated patients, the rating for the verbal domain of the GLS/GCS was defined to be 1.

First, we assessed the association between GLS/GCS and FOUR scales using Spearman correlation coefficient with Bonferroni correction for multiple comparisons. Second, to investigate the reliability between examiners, weighted Cohen's kappa (κ_w) values were used to determine the reproducibility of FOUR, GCS, and GLS total and sub-scale scores. κ_w values of 0.4 or less were considered as poor; 0.4–0.6 as fair to moderate; 0.6–0.8 as good; and >0.8 as excellent inter-observer agreement. We planned to assess inter-rater reliability in 20% of the patients' sample and hence randomly reassessed one patient in every five patients' block. For these patients, the ICU nurse or ICU physician evaluator in the pair blindly scored FOUR, GLS scores within an hour. Third, outcome was assessed at 3 months using the Glasgow Outcome Scale (GOS) [24]. Poor outcome was defined as a GOS of 3 or less. A logistic regression analysis adjusted for age and etiology of coma was performed to assess the link between the studied scales and the outcome. The area under the receiver operating characteristic (ROC) curve was calculated to assess each model discrimination capability. Data were analyzed using Stata 11.1 (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP). The study was approved by the University Medical Faculty Ethics

Committee, and written informed consent was obtained by the patients' legal representative.

Results

176 acutely brain-damaged patients were included in our study (mean age 63 ± 15 years, range 18–87; 96 males; median time since ICU admission 8, range 46). Etiology was ischemic or hemorrhagic stroke ($n = 52$ patients), post anoxic-ischemic encephalopathy ($n = 33$), traumatic head injury ($n = 22$), central nervous system infection ($n = 13$), metabolic encephalopathy ($n = 9$), seizures and status epilepticus ($n = 8$), subarachnoid hemorrhage ($n = 7$), and miscellaneous acute neurological conditions ($n = 32$). Since the sample size was limited, we decided to categorize etiologies into traumatic and non-traumatic according to the Multi-Society Task Force on PVS [25]. Hundred and thirty-one patients were intubated at the time of assessment (74%) and hence were scored 1 for the GLS/GCS verbal sub-score (15 non-intubated patients showed a "genuine" score of 1 on this GLS/GCS sub-scale). The frequency distribution of the 176 FOUR score and GLS/GCS ratings are displayed in Fig. 1. FOUR total score correlated with GCS and GLS total scores ($r = 0.81$, $P < 0.001$ and $r = 0.82$, $P < 0.001$, respectively).

The inter-rater agreement for the FOUR total score was good ($\kappa_w = 0.75$). For the agreement of each sub-scale, kappa values were good for visual ($\kappa_w = 0.80$), fair to moderate for motor ($\kappa_w = 0.59$), good brainstem ($\kappa_w = 0.77$), and respiration sub-scales ($\kappa_w = 0.74$). Agreement for the GCS and GLS total scores was good ($\kappa_w = 0.68$ and 0.66, respectively). Kappa values were good for the eyes ($\kappa_w = 0.68$), motor ($\kappa_w = 0.69$), and brainstem sub-scales ($\kappa_w = 0.73$) but fair to moderate for the verbal ($\kappa_w = 0.56$) sub-scale.

Outcome 3 months after acute brain insult was obtained in 136 patients (23% missing data) (Table 1). Characteristics (age, etiology, GLS, GCS, and FOUR total scores) of patients with missing outcome were not different from those in whom outcome data were available (Table 2). Considering the FOUR score total score, 1-point increase in total score was associated with a 17% decrease of the odds ratio for poor outcome. This was also observed after adjusting for age and etiology (traumatic vs. non-traumatic). Similarly, for every 1-point increase in GCS total score, there was an odds ratio reduction of 19% of experiencing poor outcome under the unadjusted model. This relation remained after adjusting for age and etiology (traumatic vs. non-traumatic). For the GLS total score, there was an estimated odds ratio reduction of 19% of experiencing poor outcome under the unadjusted and the adjusted (age and etiology) model. Table 1 shows the relations between total scores and patients' outcome for each of the three scales.

Association between FOUR, GCS, GLS sub-scales, and outcome was assessed using stepwise backward logistic regressions. For the FOUR score, sub-scales associated with outcome were brainstem reflexes but not respiration. The only GCS sub-scales associated with outcome was the verbal sub-score even when adjusted for ventilation. The brainstem component of the GLS score was not associated with outcome; however, no patient with an absent pupillary reflex showed a good outcome in the present cohort. No patient with a FOUR score of 0 or 1 survived ($n = 6$), while 3 out of 15 patients with a GCS total score of 3 were alive after 3 months. However, no significant difference was found between the two scales ($P = 0.53$). ROC curves were estimated to compare prediction of poor outcome between the three scales. The area under the ROC curve (AUROC) were equivalent for the GCS versus the FOUR (AUROC = 0.68 and 0.70, respectively, for GCS and FOUR, $P = 0.67$) and for the GLS versus the FOUR (AUROC = 0.72 and 0.70, respectively, for GLS and FOUR, $P = 0.73$), but not for the GCS versus the GLS (AUROC = 0.68 and 0.72, respectively, for GCS and GLS, $P = 0.006$).

In terms of clinical diagnosis, 71 included patients were considered as being in a vegetative/unresponsive state based on GCS assessment (i.e., GCS sub-scores showing spontaneous or stimulation-induced eye opening $E > 1$; absence of verbalization $V < 3$; and absence of localization of pain $M < 5$). The FOUR score identified 8 of these 71 patients (11%) as being minimally conscious given that they showed visual pursuit (FOUR sub-score Eye = 4).

Discussion

In order to overcome deficiencies of the GLS/GCS, the FOUR score has been designed to provide further neurological details in coma patients, recognize certain unconscious states, and predict outcome (e.g., [23, 26].). Our study shows a good concurrent validity between the FOUR score and validated behavioral scales as the GCS and the GLS, in line with previous findings [23, 27–29]. Including the GLS in our coma scale assessment could be regarded of limited interest since this scale is not frequently used in clinical practice outside of French-speaking countries. However, before the FOUR was launched GLS was one of the rare, if not the only, coma scale including brainstem assessment. Our results pertain to a sample of severely brain-damaged patients (GCS < 8 on admission) in contrast to other studies validating the FOUR in moderate or mild brain damage [23] [26, 29]. Even if it is a basic rule to assess patients free of any drug influence, the

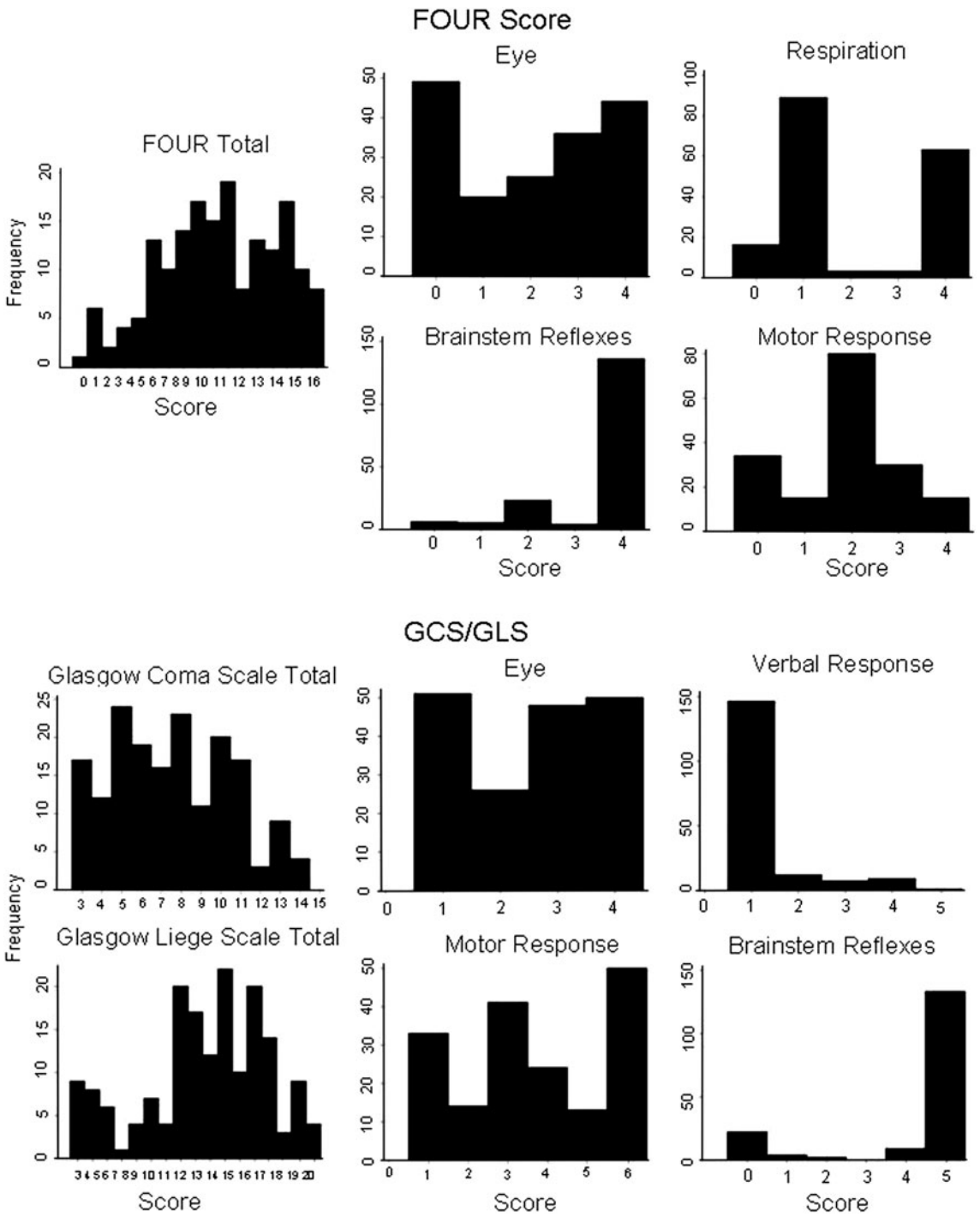

Fig. 1 Distribution of Full Outline of UnResponsiveness (FOUR), Glasgow Coma Scale (GCS), and Glasgow Liege Scale (GLS) sub-scores: eye, motor and verbal responses, brainstem reflexes, and respiration pattern

exclusion of patients receiving sedation or neuromuscular blocking agents could have introduced some bias and limit the generalizability of our conclusions. On the contrary including sedated patients would have led to overestimating patients' severity, bias their prognosis and hence negatively influence clinician attitudes. The reported results confirm good inter-rater reliability between ICU nurses and ICU physicians for the FOUR total score, corroborating previous studies showing a good to excellent inter-rater reliability between ICU physicians raters pairs [23, 30], trained and not trained ICU or neuroscience nurses [26, 29–31], non-neurology staff [32], medical intensivists, fellows and consultants pairs [29], and expert or novice clinicians and nurses pairs [27, 28]. It should

Table 1 Comparison of outcome predictions (Glasgow Outcome Scale (GOS) poor outcome at 3 months) by the Full Outline of UnResponsiveness score (FOUR), the Glasgow Coma Scale (GCS), and the Glasgow Liege Scale (GLS)

	GOS poor outcome at 3 months		Adjusted for age and etiology	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
FOUR score	0.83 (0.74–0.93)	0.002	0.83 (0.73–0.95)	0.002
Eye	0.75 (0.57–0.97)	0.029	0.75 (0.58–0.99)	0.041
Motor	0.62 (0.43–0.90)	0.011	0.63 (0.44–0.92)	0.016
Brainstem	0.51 (0.27–0.98)	0.043	0.46 (0.22–0.95)	0.037
Respiration	0.71(0.54–0.92)	0.011	0.71 (0.54–0.93)	0.013
GCS score	0.81 (0.71–0.93)	0.003	0.82 (0.71–0.95)	0.007
GLS score	0.81 (0.72–0.91)	0.001	0.81 (0.71–0.92)	0.001
Eye	0.86 (0.61–1.20)	0.360	0.86 (0.60–1.22)	0.386
Motor	0.75 (0.6–0.94)	0.014	0.77 (0.61–0.98)	0.032
Verbal	0.44 (0.29–0.69)	<0.001	0.45 (0.29–0.71)	0.001
Brainstem	0.25 (0.04–1.53)	0.135	0.18 (0.02–1.59)	0.122

Table 2 The patients' characteristics (age, etiology, interval, GCS total score, and FOUR total score) with missing outcome were not different from those where outcome data were available

	Non missing	Missing	*P* value
Age	63.3 ± 15.2	63.9 ± 14.2	0.81
Etiology (Traumatic)	39/138 (28%)	10/29 (26%)	0.145
FOUR	9 (6;12)	10 (8;14)	0.10
GLS	12 (9;15)	13 (11;15)	0.08
GCS	7 (5;10)	8 (6;10)	0.10

however be pointed that our study is limited by the small patient's sample in which inter-rater reliability was assessed. Of all the FOUR's sub-scales, the motor sub-scale inter-rater agreement was shown to be lowest (i.e., κ_w of 0.59 reflecting fair to moderate raters' agreement) whereas some studies on the GGS have shown that its motor component is the most reliable [33]. Similar observations were reported by previous studies using the FOUR score assessing agreement between novice clinicians ($\kappa_w = 0.54$) and experienced nurses ($\kappa_w = 0.55$) in neurosurgical patients [27]. It could be proposed that the presence of variable motor apraxia in some patients could influence the scoring of hand-coded command following. The possible bias of apraxia in the assessment of consciousness remains very challenging and requires further study. In addition, the different scoring of stereotyped motor responses to noxious stimulation in the FOUR as compared to the GLS/GCS (i.e., M2 is scored for stereotyped bilateral flexion posturing and unilateral (pathological or normal) flexion) might also explain the observed between-rater variability. As said, the FOUR score unlike the GLS/GLS does not require a verbal response, and thus may be more valuable in intensive care departments practices that typically have a large number of critically ill patients who have undergone intubation and cannot manifest a verbal response. Indeed, 74% of our study sample was intubated, implying that the verbal sub-scale of the GLS/GCS could not be scored. Similar to previous studies [23, 29] on FOUR respiration assessment, very few 2 and 3 scores (i.e., Cheyne Stokes and irregular breathing, respectively) were observed in the present cohort. It remains to be shown if this finding truly reflects the uncommonness of these respiratory patterns or if these could be related to suboptimal knowledge and scoring of patients' respiration.

In line with previous studies, FOUR and GLS/GCS total scores were comparable in predicting outcome [23, 26, 29–32, 34]. In addition, no patient with a FOUR score of 0 or 1 survived, while 20% of patients with a GCS total score of 3 were alive at 3 month follow-up. Although this finding does not reach statistical significance, it corroborates previous studies [30, 35]. The GLS was shown to herald superior outcome prediction as compared to the GCS [36, 37], but the GLS was here not shown to be superior to the prognostic capacity of the FOUR.

It is important to stress that the FOUR, unlike the GLS/GCS, assesses eye tracking, one of the first signs heralding recovery of consciousness after coma and the vegetative/unresponsive state [3]. The vegetative/unresponsive state is a clinical diagnosis that does not require temporal criteria [38, 39]. The condition is called persistent when it persists for over 1 month (and permanent if over 3 months for non-traumatic and 12 months for traumatic etiology) [40]. Patients who fail to show signs of consciousness (i.e., command following or non-reflex movements) but do show eye opening (spontaneous or induced) are no longer in coma but are in vegetative/unresponsive state. Once voluntary movements or command following is observed but no functional communication can be established patients are now defined as being in a minimally conscious state [3]. Based on GLS/GCS and FOUR assessments, vegetative/unresponsive state was defined by GLS/GCS score of $E>1$, $V<3$, $M<5$, and FOUR score showing $E<4$, $M<3$. The diagnosis of minimally conscious [41] and

locked-in states [42] may be very challenging, especially in the acute setting. In the studied sample 40% ($N = 71$) of patients were "vegetative" (i.e., showed wakeful unawareness) based on GLS/GCS assessment. However, by identifying the presence of visual pursuit, the FOUR score showed that this diagnosis was erroneous in 11% (8 out of 71 patients) of these patients. Disentangling vegetative/unresponsive from minimally conscious state is of key medical and ethical importance [43] as functional neuroimaging [6] and behavioral [44] data have shown evidence for residual pain perception and emotional processing in the latter condition. The possible consequence of considering patients as unconscious (while they actually show (minimal) signs of consciousness) could have clinical consequences, for example, in terms of pain and symptom management. In our sample, the use of the FOUR could have permitted to treat for pain in about 1 in 10 of ICU patients (8/71) otherwise possibly considered as insensate and vegetative/unresponsive. Hence, the routine clinical use of the FOUR score may permit to identify as soon as possible minimal (non-verbal) signs of consciousness, permitting to assure early and appropriate pain and symptom management in these challenging non-communicative ICU patients [45, 46].

In conclusion, our prospective study comparing the FOUR, GLS/GCS scores in patients who are severely brain damaged shows that the FOUR is a valid tool with prognostic value comparable to GCS and GLS as here demonstrated by the AUC data from ROC analyses. The FOUR score may offer the additional advantage to be performable in intubated patients and to identify non-verbal signs of consciousness by assessing visual pursuit.

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