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ORIGINAL RESEARCH ARTICLE

Utility of the 4C ISARIC mortality score in hospitalized COVID-19 patients at a large tertiary Saudi Arabian center

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ABSTRACT

Background: The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) 4C mortality score has been used before as a valuable tool for predicting mortality in COVID-19 patients. We aimed to address the utility of the 4C score in a well-defined Saudi population with COVID-19 admitted to a large tertiary referral hospital in Saudi Arabia.

Methods: A retrospective study was conducted that included all adults COVID-19 patients admitted to the Armed Forces Hospital Southern Region (AFHSR), between January 2021 and September 2022. The receiver operating characteristic (ROC) curve depicted the diagnostic performance of the 4C Score for mortality prediction.

Results: A total of 1,853 patients were enrolled. The ROC curve of the 4C score had an area under the curve of 0.73 (95% CI: 0.702-0.758), p<0.001. The sensitivity and specificity with scores >8 were 80% and 58%, respectively, the positive and negative predictive values were 28% and 93%, respectively. Three hundred and sixteen (17.1%), 638 (34.4%), 814 (43.9%), and 85 (4.6%) patients had low, intermediate, high, and very high values, respectively. There were significant differences between survivors and non-survivors with regard to all variables used in the calculation of the 4C score. Multivariable logistic regression analysis revealed that all components of the 4C score, except gender and O_2 saturation, were independent significant predictors of mortality.

Conclusions: Our data support previous international and Saudi studies that the 4C mortality score is a reliable tool with good sensitivity and specificity in the mortality prediction of COVID-19 patients. All components of the 4C score, except gender and O_2 saturation, were independent significant predictors of mortality. Within the 4C score, odds ratios increased proportionately with an increase in the score value. Future multi-center prospective studies are warranted.

Key words: ISARIC; 4C; mortality; predictor; COVID-19; Saudi Arabia, utility.

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Introduction

The COVID-19 pandemic spread rapidly worldwide, including in Saudi Arabia, leading to a severe health emergency [1]. The clinical presentation and progression of COVID-19 in patients are highly variable [2], making it difficult for physicians to triage patients and determine their risk of poor outcomes. While some patients may clearly present with severe disease, even patients presenting with mild symptoms may have rapid decompensation [3]. The variability in COVID-19 presentation necessitated the development of risk stratification tools that would allow early identification of COVID-19 patients at higher risk of mortality, using readily available objective criteria [3-5]. Accordingly, Knight *et al.* [6] utilized the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) World Health Organization Clinical Characterization Protocol to develop and validate such a tool, the ISARIC 4C mortality score. The ISARIC mortality score utilizes variables that are readily available upon hospitalization, thereby avoiding reliance on parameters such as radiological imaging or those that only become available after hospital/ICU admission [7]. The model has been demonstrated to have a high discriminatory ability for in-hospital mortality and prognostically categorizes COVID-19 patients into four categories of severity with a uniformly increasing mortality risk (Supplementary Table 1).

After its development and validation of the original 4C score for the population in the United Kingdom, and for generalizability, it has been externally validated in many countries [5,8,9], as well as in Saudi Arabia [10,11]. However, the later studies either focused only on ICU patients [10] or reported the validation of the 4C score among heterogenous populations (both in-patients and out-patients) after the early wave of COVID-19 [11].

Despite that the 4C score has been seen before as a valuable tool for predicting mortality in COVID-19 patients, still there is a need to clarify its utility among more populations. This would be of particular importance if large numbers of COVID-19 patients are admitted, at different timeframes and all through different COVID-19 waves, into large tertiary referral centers.

Therefore, in the current study, we aimed to address the utility of the 4C score in a well-defined Saudi population with COVID-19 admitted to The Armed Forces Southern Region (AFSR), Saudi Arabia, over a 21-month period.

Methods

Study setting, design and population

Armed Forces Hospital Southern Region (AFHSR) is a tertiary hospital. The current study is a retrospective study that included all adults (>14 years old) with COVID-19 admitted to AFHSR, Khamis Mushayt, Saudi Arabia, between January 1, 2021 and September 30, 2022.

COVID-19 was confirmed by nasopharyngeal reverse transcription–polymerase chain reaction (RT-PCR). The criteria for admission were as per the COVID-19 management recommendations of the Saudi Ministry of Health [12]. After the completion of data collection, patients with missing variables that preclude the calculation of the ISARIC score were excluded.

Data collection

Demographic, clinical, laboratory, and outcome data were collected from electronic medical records. The demographic data included age, gender, and nationality. Clinical data included the main presenting symptoms, signs, admission data (ICU *versus* non-ICU), and comorbidities. Included comorbidities were chronic cardiac disease, chronic pulmonary disease, chronic kidney disease, chronic liver disease, diabetes mellitus (type 1 or 2), chronic neurological disease, connective tissue/rheumatological disease, malignant neoplasm, dementia, and HIV/AIDS. Laboratory data included basic investigations and inflammatory markers. Outcome data included mortality during hospitalization.

The 4C mortality score

For calculating the ISARIC score [6], the following variables were collected from the electronic database of the patients' medical records: age; gender; number of comorbidities; respiratory rate (RR), peripheral oxygen saturation (SpO_2) on room air, and Glasgow coma scale (GCS) at hospital admission; first available

Table 1. Demographic and clinical features of the study cohort.

Feature	n=1853
Age (years)	
Mean ± SD	57.20 ± 21.6
Median (range)	28.6 (15 - 109)
Gender	
Male	1045 (56.4%)
Female	808 (43.6%)
Nationality	
Saudi	1808 (97.6%)
Non-Saudi	45 (2.4%)
Respiratory rate	
0-20 cycles/min.	1040 (56.1%)
20-29 cycles/min.	783 (42.3%)
> 29 cycles/min.	30 (1.6%)
O_2 saturation	
> 92%	510 (27.5%)
< 92%	1343 (72.5%)
GCS	
= 15	1692 (91.3%)
< 15	161 (8.7%)
BUN	
< 7	1136 (61.3%)
7-14	494 (26.7%)
> 14	223 (12%)
CRP	
< 50	661 (35.7%)
50-100	573 (30.9%)
> 100	619 (33.4%)
No. of comorbidities	
0	735 (39.6%)
1	578 (31.2%)
≥2	540 (29.2%)
Clinical status	
Stable (non-ICU)	1505 (81.2%)
Critical (ICU)	348 (18.8%)
Outcome	
Alive	1541 (83.2%)
Dead	312 (16.8%)
4C score	
0-3	316 (17.1%)
4-8	638 (34.4%)
9-14	814 (43.9%)
>15	85 (4.6%)

blood urea level (mmol/L); and C-reactive protein (CRP) (mg/L).

The 4C Mortality Score ranges from 0 to ≥15 and it divides patients into four risk groups: low (0-3), intermediate (4-8), high (9-14), and very high-risk groups (≥15).

Study outcomes

The primary outcome of the study was the performance of ISARIC score in our settings by evaluating its discriminatory ability of survivors and deceased in all-cause hospital mortality outcome. The secondary outcome was the comparison between subjects with scores above and below the optimal cut-off value of ISARIC.

Ethical considerations

Ethical approval was obtained from the institutional review board of the AFHSR (approval no; AFHSRMREC/2022/PULMONOLOGY-INTERANL MEDICINE/603). The study participants were fully informed about the study procedures.

Statistical analysis

Data were verified, coded by the researcher, and analyzed using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA). Descriptive statistics: means, standard deviations (SD), medians, inter-quartile range (IQR) and percentages were calculated. Significance test: Chi-square/Fisher's exact test was used to compare the differences in frequency between groups. Test of normality, Shapiro-Wilk or Kolmogorov Smirnoff was used to test the normality of continuous variables. For continuous variables with two categories, independent sample *t*-test/Mann Whitney U test was used to compare the difference in means/median as appropriate. The clinical and demographic factors with proven statistical significance were included in the multivariable logistic regression models. Multivariable logistic regression analysis was calculated to investigate the independent significant predictors of mortality [odds ratio (OR) 95%, confidence interval (CI) 95%]. The receiver operating characteristic (ROC) curve depicted the diagnostic performance of the 4C Score for mortality prediction, analyzed as area under the curve (AUC), standard error (SE) and 95% CI. Validity statistics [sensitivity, specificity, positive and negative predictive value (PPV, NPV)] were calculated. A $p<0.05$ was considered significant.

Results

Demographic and clinical features

There were 2,148 confirmed COVID-19 admissions during the study period. Of these, 150 had insufficient data to calculate a score, 100 were discharged against medical advice, and 45 were transferred to other hospitals. Accordingly, the study finally included 1,853 patients (Figure 1). The vast majority of the patients were Saudis (97.6%), and 56.4% of patients were males. A total of 1,118 /1,853 (60.3 %) patients had one or more comorbidities. The most commonly encountered comorbidity was diabetes mellitus (DM), where 899/1853, 48.5% of patients suffered from it. Among the study cohorts, 18.8% needed ICU admission. During the study period, 1,541 (83.2%) survived, while 312 (16.8%) patients died. Table 1 depicts the demographic and clinical characteristics of the cohort.

The ISARIC 4C score

The average age of the study subjects was 57.2±21.6 years. With regards to comorbidities, 39.6%, 31.2%, and 29.2%, had 0, 1, and ≥2 comorbidities, respectively. With regards to ISARIC score, 316 (17.1%), 638 (34.4%), 814 (43.9%), and 85 (4.6%) of patients had low, intermediate, high, and very high values, respectively. Table 1 shows these results.

Comparison between survivors and non-survivors

Table 2 details the differences between survivors and non-survivors. For comorbidities, there were significant differences between the survivors and non-survivors between patients with all comorbidities, except those with chronic liver disease, connective tissue disease, and HIV. There were significant differences between survivors and non-survivors with regard to all variables used in the calculation of ISARIC 4C score. There were significant differences between survivors and non-survivors among patients within each category of the ISARIC score. Characteristically, high-risk and very high-risk patients were 64.4% and 15.4% among patients who died, respectively, while among patients who survived the categories high risk and very high risk were only 39.8% and 2.4%, $p<0.001$.

Predictors of mortality

Multivariable regression analysis revealed that clinical status, and all components of the ISARIC 4C score, except gender and O_2 saturation, were independent significant predictors of mortality. Thus, 6 out of 8 components of the 4C score were independent predictors of mortality. For the 4C score, characteristically odds ratios increased proportionately with the increase in the value of each score category. The odds ratio was 6.598 (95% CI 1.032-8.334), $p<0.001$ for the category 4-8, 15.480 (2.702-28.635), $p<0.001$ for the category 9-14, and 23.676 (4.541-72.582), $p<0.001$, for the category >15, respectively. Table 3 details these data.

Diagnostic criteria of the 4C score

The ROC curve of ISARIC score had AUC of 0.73 (95% CI: 0.702–0.758, $p<0.001$) (Figure 2). The sensitivity and specificity with scores >8 were 80% and 58%, respectively; the PPV and NPV were 28% and 93%, respectively (Table 4).

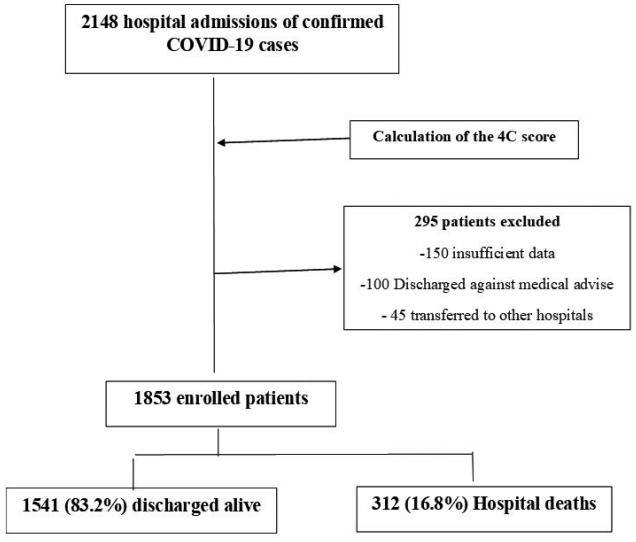

Figure 1. Flow chart of the studied patients.

Discussion

The current study was conducted to address the utility of the ISARIC 4C mortality score among COVID-19 inpatients admitted to a large Saudi Arabian tertiary referral hospital between January 1, 2021 and September 30, 2022. Our data showed that the 4C mortality score is a valid tool to prognosticate mortality among hospitalized COVID-19 patients. We observed an overall AUC of 0.73 (95% CI: 0.702-0.758, p<0.001) which is identical to the initial derivation research of Knight and coworkers [6].

The 4C score has been validated outside of the United Kingdom in many countries, including Canada [8,13], Italy [5], Japan [9], as well as in Saudi Arabia [10,11]. Characteristically, the 4C score has shown utility all over the study period (21 months), during which many changes occurred with regard to the COVID-19 timeline [14,15]. Changes over time in the dominant strain of

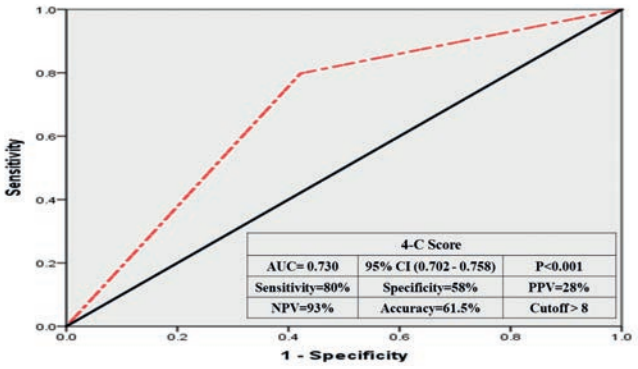

Figure 2. Receiver operating characteristic of the ISARIC 4C score.

Table 2. Determinants of mortality among the studied Cohort (n=1,853).

	Alive (n=1541, 83%)	Dead (n=312, 17%)	p
Age/years (median - IQR)	55 (30)	73.5 (19)	<0.001*
Age groups			<0.001**
<50	622 (40.3%)	23 (7.3%)	
50-59	250 (16.2%)	42 (13.5%)	
60-69	255 (16.5%)	64 (20.5%)	
70-79	239 (15.5%)	79 (25.3%)	
≥80	175 (11.4%)	104 (33.3%)	
Gender (M/F)	849/692	196/116	0.012**
Nationality (Saudi/Non)	1499/42	309/3	0.065**
No. of comorbidities			<0.001**
0	671(43.5%)	64 (20.5%)	
1	482 (31.3%)	96 (30.7%)	
≥2	388 (25.2 %)	152 (48.7%)	
Respiratory rate			<0.001**
0-20 cycle/min	913 (59.2%)	127 (40.7%)	
20-29 cycle/min	612 (39.7%)	171 (54.8%)	
>29 cycle/min	16 (1%)	14 (4.5)	
O_2 saturation (<92%)	1071 (69.5%)	272 (87.2%)	< 0.001**
Glasgow coma scale (<15)	76 (4.9%)	85 (27.2%)	< 0.001**
Blood urea nitrogen			
<7	1034 (67.1%)	102 (32.7%)	
7-14	367 (23.8%)	127 (40.7%)	<0.001**
>14	140 (9.1%)	83 (26.6%)	
C-reactive protein			
< 50	603 (39.1%)	58 (18.6%)	
50-100	494 (32.1%)	79 (25.3%)	< 0.001**
> 100	444 (28.8%)	175 (56.1%)	
Clinical status (critical)	87 (5.6%)	261 (83.9%)	< 0.001**
4 C score			<0.001**
0-3	314 (20.4%)	2 (0.6%)	
4-8	577 (37.4%)	61 (19.6%)	
9-14	613 (39.8%)	201 (64.4%)	
>15	37 (2.4%)	48 (15.4%)	

*Mann Whitney U-test was used to compare the differences in median between groups; **Chi-square test was used to compare the differences in frequency between groups; ***Fisher's exact test was used to compare the differences in frequency between groups.

SARS-CoV-2, vaccine distribution, and treatment practices (*e.g.*, use of steroids) could all potentially impact the predictive ability of a mortality risk score [8].

In the current study, the AUC was almost identical to those by Knight *et al.* [6] and Jones *et al.* [8], but lower than in others: van Dam *et a.* [4] and Wellbelove *et al.* [16]. Despite that the current study was conducted among the Saudi population, our AUC was lower than those observed among other studies that addressed the 4C score among Saudi patients [10,11]. This variation among studies – although minimal – utilizing the same prediction model may reflect the variations in the studied populations, with regard to their demographic characteristics, hospitalized or out-patients, clinical severity, and sample size. For example, in our study, the age range was so wide (from 15 to 109 years). On the other hand, other studies from Saudi Arabia had reported data for patients only admitted to the ICU [10] or data of both hospitalized and home-isolated patients [11].

An important finding was highlighted in the current study. There were rising mortality rates across groups of severity, that is, a directly proportional relationship between mortality risk and increase in score. This is in agreement with those observed by the original study [6] and Aletreby *et al*. [10]. This reflects that the model performs optimally, especially when taking into consideration that the higher mortality rates were higher within all groups in our study compared with the original study. Our finding was not in concordance with those observed by Mohamed and coworkers [11], who found that the 4C Score underestimated mortality risk among the very high-risk group with overestimation in other risk groups.

The diagnostic parameters of 4C scores >8 were the sensitivity, specificity, PPV, and NPV of 80%, 58%, 28%, and 93%, respectively. Compared with our study, an Italian study [5] reported almost identical sensitivity (88.1%) and specificity (55.9%). The same study considered this score as the most accurate mortality predictor compared with other scores like COVID-19-Gram Critical Illness Risk Score [17], Quick COVID-19 Severity Index [18], and the National Early Warning Score [19].

On the other hand, different cut-off values and diagnostic parameters were found among the original British study [6] Saudi [10,11] and international studies [8,9,20]. One of the most important diagnostic parameters is NPV, which indicates the probability of survival in patients with scores ≤8. In our model, NPV was 93%, which provides a reasonable risk probability to guide clinical decision-making.

Our results have shown significant differences between survivors and non-survivors among patients within each category of the 4C score. Moreover, multivariable regression analysis revealed that all components of the ISARIC 4C score, except gender and O_2 saturation, were independent significant predictors of mortality. In another ward, 6 out of 8 components of the 4C score were independent predictors of mortality. Hypoxemia, being a non-significant independent predictor of mortality, might be explained by the phenomenon of "happy hypoxemia" observed in patients with COVID-19. In patients with COVID-19, arterial hypoxemia is induced by intrapulmonary shunting, dysregulated hypoxic pulmonary vasoconstriction, impaired lung diffusion, and formation of intravascular microthrombi [21]. At the stage that COVID-19 patients are admitted to the hospital with hypoxemia (and the 4C score is calculated), viral replication is well underway. Furthermore, as in the first days of the disease, the lung mechanics are well-preserved and there is no increased airway resistance or dead space ventilation. Thus, the respiratory center does not sense an uncomfortable sensation of breathing. However, sudden and rapid respiratory decompensation may occur, and tachypnea and

Table 3. Independent predictors of mortality: multivariable logistic regression.

Predictor	Odds ratio (95% Confidence interval)	p
Age groups		
<50	1 (Reference)	0.001
50-59	2.892 (1.242-3.881)	0.004
60-69	3.324 (1.335-5.022)	0.006
70-79	4.676 (1.615-6.433)	<0.001
≥80	5.805 (1.743-7.574)	<0.001
Gender (male)	0.906 (0.692-1.186)	0.471
Clinical status (critical)	7.009 (1.882-11.987)	<0.001
No. of comorbidities		
0	1 (Reference)	<0.001
1	1.792 (1.042-2.481)	<0.001
≥2	2.020 (1.729-2.361)	<0.001
0-20 cycle/min	1 (Reference)	0.001
-29 cycle/min.	1.892 (1.242-2.881)	0.003
>29 cycle/min.	6.805 (1.743-9.574)	0.006
Glasgow coma scale (< 15)	3.324 (1.835-6.022)	<0.001
O_2 saturation (< 92%)	1.272 (0.870-1.860)	0.214
Blood urea nitrogen		
<7	1 (Reference)	0.009
7-14	1.419 (0.896-2.246)	0.136
>14	2.414 (1.372-4.247)	0.002
C-reactive protein		
<50	1 (Reference)	<0.001
50-100	1.484 (0.848-2.597)	0.167
>100	2.676 (1.615-4.433)	<0.001
4C score		
0-3	1 (Reference)	<0.001
4-8	6.598 (1.032-8.334)	<0.001
9-14	15.480 (2.702-28.635)	<0.001
>15	23.676 (4.541-72.582)	<0.001

Table 4. Diagnostic criteria of 4C score for mortality prediction.

Diagnostic criteria	4C score
Area under the curve	0.730
95% CI	0.702-0.758
Standard error	0.014
p-value*	<0.001
Cut-off	8
Accuracy	61.5%
Sensitivity	80%
Specificity	58%
PPV	28%
NPV	93%
False discovery rate	20%
False omission rate	6%

*Null hypothesis: true area=0.5; sensitivity, true positives/all diseased; specificity, true negatives/all non-diseased; PPV, positive predictive value (true positives/all test positives); NPV, negative predictive value (true negatives/all test negatives).

hyperpnea might be the most important clinical warning signs of impending respiratory failure in COVID-19 patients [21].

With this regard, our results are in agreement with those by Mohamed and coworkers [11], who observed that among the eight components of the 4C score, only hypoxia, tachypnea, high BUN, and CRP were the significant independent predictors of mortality. The proliferation of COVID-19 risk models is evidence of the need for an accurate, accessible, and generalizable tool [22] and our data add to the body of evidence supporting the use of the 4C score. Despite that we did not compare between 4C score and other mortality prediction scores in the current study, our data might support the findings of studies [5,16-18, 22] which showed that the 4C mortality score outperformed existing scores in COVID-19 patients.

The current study has many implications for daily clinical practice, as shown in the recent literature [22-27]. In their analysis, Sellers *et al*. [23] questioned if the 4C mortality score may be used to predict which patients with moderate to severe COVID-19 would benefit the most from remdesivir at the time of hospital admission. Their results have shown that driven by patients who were categorized into the intermediate-risk and high-risk mortality groups using the 4C mortality score, patients in the remdesivir group had a longer time to recover compared to patients in the standard of care group (6 days vs 4 days) [23]. Automated calculation of the 4C score in electronic medical records could be used to guide resource management and support clinical decision-making such as early admission, treatment initiation [11, 23], and admission to the ICU [10]. This is of crucial importance in large tertiary hospitals where large numbers of COVID-19 patients could represent a burden on those healthcare centers.

Similar to the COVID-19 situation, the potential for application of the 4C score in other common, but potentially fatal respiratory infections, exists. A larger prospective validation study of the 4C mortality score versus established scoring systems is needed to confirm its utility in undifferentiated respiratory infection, focusing on the potential for the ongoing utility of the 4C mortality score, even after the pandemic has ended and the incidence of COVID-19 is much lower. A recent meta-analysis [25] was conducted to externally validate various prognostic models and scoring rules for predicting short-term mortality in patients admitted to hospitals for COVID-19, among 46,914 patients across 18 countries. While the prognostic value of the included models varied greatly between the data sources, the Knight 4C Mortality Score and Wang clinical model appeared most promising [25].

This study has some potential limitations to be considered while interpreting the results. First, the inherent limitations of the retrospective study design are applicable. Second, our study was performed in a single medical center, limiting the generalizability of the results. However, our cohort of patients with COVID-19 was relatively large and has been recruited in one of the tertiary referral hospitals in Saudi Arabia.

Further multicenter studies with a larger sample size and including those with varied severities are required to validate the score in the larger Saudi population and possibly explore predictors of mortality in COVID-19 patients. Recently, the 4C score was prospectively validated to predict clinical deterioration and mortality in a large prospective second-wave validation cohort of adult hospitalized patients with COVID-19, in the UK [27].

Conclusions

In conclusion, our data support previous international and Saudi studies that the 4C mortality score is a reliable tool with good sensitivity and specificity in mortality prediction of COVID-19 patients. All components of the 4C score, except gender and O_2 saturation, were independent significant predictors of mortality. Within the 4C score, odds ratios increased proportionately with an increase in the score value. Future multi-center prospective studies with larger sample sizes are warranted to support our results and to address the validity of the scoring system on different COVID-19 strains.

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