Renal Abnormalities among Sickle Cell Disease Patients in a Poor Management Setting: A Survey in the Democratic Republic of the Congo

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Abstract. Background and objective: Sickle cell disease (SCD) is now a well-established cause of renal damage. In the northeast of the Democratic Republic of Congo (DRC), SCD is common. However, sickle cell nephropathy remains unstudied in this region. Thus, this study aimed to assess renal abnormalities in SCD patients in Kisangani (northeastern DRC).

Methods: This cross-sectional study included 98 sickle cell patients selected from six health facilities in Kisangani and 89 healthy non-sickle cell subjects as the control group. Based on a survey form, a clinical examination and biological tests were performed to collect data related to the sex, age, weight, height, pressure, serum creatinine, serum uric acid, urinary albumin/creatinine ratio, and hemoglobin phenotype. We used a spectrophotometer to measure serum creatinine and uricemia, the sickle SCAN® device for hemoglobin phenotype, and an automatic multifunction analyzer for urine albumin/creatinine ratio. Data were entered into an Excel file and analyzed on SPSS 20.0.

Results: The mean urine albumin-to-creatinine ratio was 11.79±9.03 mg/mmol in SCD patients, significantly higher than in AA (1.69±1.89 mg/mmol) and AS (2.97±4.46 mg/mmol) subjects. The decrease in glomerular filtration rate was more observed in SCD patients with hyperuricemia compared to those with normal uric acid levels. A significantly elevated prevalence of chronic kidney disease was observed among SCD patients (87.8%) compared to 23.8% in AS and 7.7% in AA subjects.

Conclusions: This study highlighted that albuminuria and chronic kidney disease are common in SCD patients in Kisangani. More studies are needed to further document these complications.

Keywords: Sickle cell disease, Prevalence, Sickle cell nephropathy, Renal abnormalities, Democratic Republic of the Congo, Sub-Saharan Africa.

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**Introduction.** Sickle cell disease (SCD) is now a well-established cause of renal damage associated with high mortality in SCD patients. Renal involvement contributes to the diminished life expectancy of patients with SCD, accounting for 16–18% of mortality. In the study by Hamideh and Alvarez in the United States of America, nephropathy accounted for 16.4% of deaths in children and adults with SCD. Therefore, detecting renal abnormalities at an early stage when interventions may be more effective is essential to improve the lifespan of SCD patients.

Sickle cell disease patients may present with several types of renal dysfunction. Different pathophysiologic mechanisms have been proposed to explain the development of sickle cell nephropathy, where hemolysis-related vasculopathy and vaso-occlusive phenomena are the main contributors. Glomerular hyperfiltration and microalbuminuria/proteinuria are early manifestations of sickle cell nephropathy. Hyperfiltration starts as early as 9–19 months. Over time, hyperfiltration may lead to microalbuminuria and later to renal failure.

Aygun et al. demonstrated that hydroxyurea treatment, which is currently the only substantive treatment for SCD, was associated with improved renal function in SCD patients presenting hyperfiltration. However, few patients have access to hydroxyurea treatment in sub-Saharan Africa, including the Democratic Republic of the Congo (DRC). In general, there is still poor utilization of standard-care practices for SCD patients, and that exposes SCD patients living in this area to the risk of multi-organ damage. In Ghana, Anto et al. reported chronic renal disease related to sickle cell anemia in 73.5% of patients under 13 years of age. In Kinshasa (western part of the DRC), Aloni et al. reported a high prevalence of hyperfiltration among children with SCD, approximately one in three children. However, this study included only children younger than 14 years and moreover, in a center dedicated to the management of SCD and a teaching hospital. A study on adolescent and adult subjects with SCD has been made in Nigeria, where 204 HbSS patients were recruited. The prevalence of chronic kidney disease (CKD) was 38.9%. eGFR (Estimated Glomerular Filtration Rate) showed that 69 (26.8%) had hyperfiltration; 35 (13.6%) stage 1 CKD; 53 (20.6%) stage 2 CKD; 33 (12.8%) stage 3a CKD; 28 (10.9%) stage 3b CKD; 30 (11.7%) stage 4 CKD and 9 (3.5%) had end-stage renal disease; predictors of CKD using eGFR include age, Systolic Blood Pressure, number of units of blood transfusion, Packed red cell, urea, creatinine, and uric acid levels.

In the northeast of the DRC, this issue remains unstudied. However, given the context of poor management of SCD as reported by Kambale et al. in this region, renal abnormalities may be of greater magnitude. Therefore, this study aimed to evaluate renal abnormalities in subjects with SCD in Kisangani (northeastern DRC), a city located about 1250 kilometers from Kinshasa and in one of three regions where approximately one-third of sickle cell births in the DRC occur.

**Methods.**

**Context and ethical considerations.** This study was carried out in Kisangani from January to May 2020 with the approval of the Ethical Committee of the University of Kisangani (Réf. UNIKIS/CER/007/2018). In addition, we obtained authorization from the Tshopo Provincial Health Division to survey the health facilities of the Tshopo province (N°701/DPS/TSHOPO/SEC/019/2019). Enrollment in the study was conditional on free and informed consent from participants. For individuals under 18 years of age, parental and/or guardian consent was required. The objectives and purpose of the study were explained, and subjects were informed of their right to refuse to participate or to withdraw from it at any time without this having any implication on their care. Confidentiality of results was guaranteed by ensuring anonymity in the data processing.

**Study design and settings.** This care facility-based survey was a cross-sectional study conducted in six health facilities in the city of Kisangani (Cliniques universitaires de Kisangani, Hôpital général de référence Makiso/Kisangani, Hôpital général de référence de Kabondo, Centre de santé ALABUL, Centre d’anémie SS «Gracia fondation», Cliniques Stanley), selected on the basis of their high attendance by SCD patients. Kisangani is one of the third largest cities in the DRC with an estimated population of 1.6 million inhabitants, the neonatal prevalence of homozygous form of SCD (SS) about 1%; and that of heterozygous form (AS) of 23.3%. In addition, it is an area where insufficient use of standard care practices for SCD patients has been recently reported (2021).

**Study population and sampling.** The study population consisted of homozygous SCD patients (HbSS) previously diagnosed by the sickle SCAN® rapid test and followed up from January to May 2020 in the health facilities mentioned above. They were included and surveyed during their follow-up appointment according to an exhaustive sampling. The control group consisted...
of healthy individuals with no SCD siblings of SCD patients, selected by non-probability convenience sampling. For their enrollment, sickle cell patients and/or their parents/guardians were sensitized and informed about the importance of screening for SCD and its renal complications during follow-up appointments. They, in turn, sensitized their family members. Family members who agreed to be screened came to the selected health facilities to be surveyed. The same inclusion and exclusion criteria were used for the study population (sickle cell disease patients and control group).

Inclusion criteria were: (1) being at least five years old, (2) having given consent to participate in the study or parental/guardian consent for subjects under 18 years of age, and (3) not having received a blood transfusion for at least three months. In addition, for sickle cell disease patients, (4) to be in inter critical stage, defined as the absence of acute complications of SCD or signs of other diseases for at least two weeks.

Exclusion criteria were: having a history of (1) hypertension, (2) diabetes mellitus, (3) frequent use of traditional therapy, (4) having signs of urinary tract infection on urinary sediment analysis or signs of other diseases at the time of the survey. In addition, for sickle cell disease patients, (5) being under hydroxyurea treatment.

Data collection. A survey form was used to collect data from the study participants. The following clinical and laboratory data were collected: (1) demographic and anthropometric characteristics [gender, age, weight, height], (2) Blood pressure, (3) serum creatinine, (4) serum uric acid, (5) urine albumin/creatinine ratio and (6) hemoglobin phenotype.

A physical examination collected the clinical data. Blood pressure was measured using standard procedure. Next, the weight and the height were measured using the weighing scale Seca® and stadiometer Seca®, respectively. Finally, the axillary temperature was measured by a mercury thermometer.

Sample collection and laboratory analysis. Blood collection. For each subject, 3 mL of whole blood was collected by vein puncture into a vacutainer tube with EDTA and 2 mL into a vacutainer tube without anticoagulant for the serum creatinine and uric acid.

Following vein puncture, samples were stored at 4–8°C in an isothermal box containing cold packs and then transferred to the laboratory within two hours at most. The serum uric acid and serum creatinine levels were estimated enzymatically by a spectrophotometer using commercial Uric Acid and Creatinine Assay kits from Cypress Diagnostics (Cypress Diagnostics: Nijverheidsstraat 8.2235 Hulshout, Belgium) following the procedure outlined in the manuals supplied with the kits. According to the manufacturer's instructions, hemoglobin phenotyping was performed using the sickle SCAN® rapid test.15

Urine collection. The urine of each participant was collected into a clean, sterile, and leak-proof container. The urine albumin/creatinine ratio was determined using an automatic multifunction analyzer (Model: Icare-2100, Changsha Sinocare Inc.NO.265, Guyuan Road, Hi-tech Zone, Changsha, Hunan Province 410205, China). In addition, a drop of decanted urine deposit was observed under a microscope for urine cytobacteriological examination.

Outcomes criteria: Estimated glomerular filtration rate (eGFR) and chronic kidney disease.

For the subjects under 18 years of age, the updated Schwartz equation16 was used for calculating the eGFR. For subjects aged 18 years and older, we used the MDRD (Modification of Diet in Renal Disease)17 formula.

Chronic kidney disease (CKD) was classified according to the Kidney Disease Improving Global Outcome (KDIGO)18 as follow:

Stage 1: ≥ 90 ml/min/1.73 m² (kidney damage with normal or increased eGFR);
Stage 2: 60–89 ml/min/1.73 m² (kidney damage with mildly decreased eGFR);
Stage 3a: 45–59 ml/min/1.73 m² (mildly to moderately decreased eGFR);
Stage 3b: 30–44 ml/min/1.73 m² (moderate to severely decreased eGFR);
Stage 4: 15–29 ml/min/1.73 m² (severely decreased eGFR) and
Stage 5: <15 ml/min/1.73 m² (Kidney failure).

The urine albumin-to-creatinine ratio scored kidney damage≥ 3 mg/mmol; hyperfiltration was defined as an eGFR greater than 140 ml/min/1.73 m². Subjects were considered hyperuricemia if their total serum uric acid concentrations were greater than the upper limits of normal for age and sex.

Statistical Analysis. The data were entered into an electronic database (Microsoft Excel 2019), and all the analyzes were carried out on statistical software (SPSS 20.0). The quantitative variables were compared using the mean and its standard deviation. The qualitative variables were described with the numbers and proportions of each modality. An analysis of the variance(ANOVA) was used to compare a quantitative variable between hemoglobin phenotype subgroups. In the case of heterogeneity of data variances, we used Welch homogeneity correction. For the crossing between several qualitative variables, the Chi2 test was used if the application conditions allowed it. If not, Fisher's exact test was performed. The risk of species 1 alpha was set at 5% for all analyzes, and Significant levels were measured at 95% CI.
Results. The study was conducted on 98 SCD patients and 89 no sickle cell subjects as the control group (26 AA and 63 AS subjects). The procedure of participant recruitment is outlined in Figure 1. There were 51 (52%) females and 47 (48%) males in the SCD patients; 50 (56.2%) females and 39 (43.8) males in the control group without significant difference. The mean age of SCD patients was 12.82±7.5215 years, and that of AA and AS was 15.54±6.65 years and 12.71±7.68 years, respectively. Overall, hyperuricemia was observed in 39.8% of SCD patients versus 10.1% in the control group (Table 1). Furthermore, the mean uric acid level was significantly higher in SCD patients compared to AA (p<0.01) and AS (p<0.001) subjects (Figure 2). In addition, the decrease in eGFR was more observed in SCD patients with hyperuricemia than SCD patients with normal uric acid levels. However, there was no significant difference (Figure 3).

Microalbuminuria was more prevalent in SCD patients, 85 subjects (86.7%) versus 21 subjects (23.6%) in the control group. In addition, the mean urine albumin-to-creatinine ratio was 11.79±9.03 mg/mmol in SCD patients, significantly higher than in AA (1.69±1.89 mg/mmol) and AS (2.97±4.46 mg/mmol) subjects. Hyperfiltration was observed in 22.4% of the SCD patients, whereas no case was observed in the control group (Table 2). Compared to AA (66.6 µmol/L ± 8.52 µmol/L) and AS (70.71 µmol/L ± 17.12 µmol/L) subjects, SCD patients had significantly lower mean serum creatinine levels (52.59 µmol/L±18.59 µmol/L) (p

Figure 1. Participant recruitment.

Figure 2. Serum uric acid level stratified by hemoglobin (Hb) phenotypes.

Figure 3. Average estimated glomerular filtration rate according to uricemia.
Table 1. Characteristics of study participants.

| Variable                  | Hb phenotypes | Total | p-value  |
|---------------------------|---------------|-------|----------|
|                           | AA (N=26)     | AS (N=63) | SS (N=98) | (N=187) |
| Gender, n(%)              |               |        |          | 0.689*  |
| Female                    | 16(61.5)      | 34(53.9) | 51(52)   | 101(54.1) |
| Male                      | 10(38.5)      | 29(46.1) | 47(48)   | 86(45.9)  |
| Age(years) (Mean ± SD)    | 15.54±6.65    | 12.71±7.68 | 12.82±7.52 | 13.16±7.48 | 0.219** |
| Age group (year), n (%)   |               |          |          | 0.735*  |
| 5-14                      | 15(75.7)      | 37(58.7) | 66(67.3) | 118(63.1) |
| 15-24                     | 7(26.9)       | 19(30.2) | 23(23.5) | 49(26.2)  |
| ≥25                       | 4(15.4)       | 7(11.1)  | 9(9.2)   | 20(10.7)  |
| Weight(Kg) (Mean ± SD)    | 46.93±13.38   | 42.52±21.82 | 29.63±14.14 | 36.38±18.42 | <0.001*** |
| Height(m) (Mean ± SD)     | 1.52±0.97     | 1.42±0.24 | 1.33±0.26 | 1.38±0.24  | <0.001*** |
| BMI (Kg/m²) (Mean ± SD)   | 19.87±3.61    | 19.08±4.79 | 15.8±7.39 | 17.51±4.54 | <0.001*** |
| Hyperuricemia, n(%)       |               |          |          | <0.001*  |
| Yes                       | 4(15.4)       | 5(7.9)   | 39(39.8) | 48(25.7)  |
| No                        | 22(84.6)      | 58(92.1) | 59(60.2) | 139(74.3) |
| Serum uric acid(mg/dL) (Mean ± SD) | 3.86±0.86   | 3.30±1.32 | 5.05±1.82 | 4.29±1.74  | <0.001*** |
| Blood pressure (mmHg) (Mean ± SD) | 112.55±5.68  | 114.83±15.06 | 106.30±17.12 | 109.71±15.92 | 0.003*** |

SD= Standard deviation, BMI= Body mass index, BP=Blood pressure, *Chi square test, **ANOVA test, ***ANOVA test with Welch homogeneity correction.

Table 2. Analysis of renal abnormality and hemoglobin phenotype.

| Variable                  | Hb phenotype | Total | p-value  |
|---------------------------|--------------|-------|----------|
|                           | AA (n=26)    | AS (n=63) | SS (n=98) | (n=187) |
| ACR≥3(mg/mmol), n(%)     |              |        |          |         |
| Yes                       | 6(23.1)      | 15(23.8) | 85(86.7) | 106(56.7) |
| No                        | 20(76.9)     | 48(76.2) | 13(13.3) | 81(43.3)  |
| ACR (mg/mmol) (Mean ± SD) | 1.69±1.89    | 2.97±4.46 | 11.79±9.03 | 0.195*  |
| Serum creatinine (μmol/L) (Mean ± SD) | 66.6±18.52  | 70.7±17.12 | 52.59±18.59 | 0.249*  |
| eGFR (mL/min/1.73 m²), n(%) |       |        |          |         |
| Hyperfiltration (≥140)    | 0(0)         | 0(0)   | 22(22.4) | 22(11.8)  | 1.00**  |
| ≥ 90 - 139                | 14(53.8)     | 16(25.4) | 38(38.8) | 68(36.4)  | 1      |
| 60-89                     | 12(46.2)     | 41(65.1) | 34(34.7) | 87(46.5)  | 0.02*  |
| < 60                      | 0(0)         | 6(9.5)  | 4(4.1)   | 10(5.3)   | 0.05** |
| Overall CKD, n(%)         | 2(7.7)       | 15(23.8) | 86(87.8) | 103(55.1) |
| CKD, eGFR(mL/min/1.73 m²), n(%) |       |        |          |         |
| Stage 1 : eGFR ≥ 90 + ACR  | 0(0)         | 3(4.8)  | 55(56.1) | 58(31)    | 0.55** |
| Stage 2 : eGFR 60-89 + ACR | 2(7.7)       | 6(9.5)  | 27(27.6) | 35(18.7)  | 1.00*  |
| Stage 3a : eGFR 45–59     | 0(0)         | 6(9.5)  | 4(4.1)   | 10(5.3)   | 0.17** |
| No CKD, n(%)              | 24(92.3)     | 48(76.2) | 12(12.2) | 84(44.9)  | 1      |

Reference: 1, Hb = Hemoglobin, ACR= Albumin-to-creatinine ratio, eGFR = estimated glomerular filtration rate, CKD=Chronic kidney disease, * Chi square test, **Fisher exact test, ¥Elevate ACR: ≥ 3 mg/mmol.
Discussion. This study reported the abnormalities of uricemia and renal function observed in SCD patients in Kisangani, where SCD is still undermanaged. Overall, the results showed that hyperuricemia was observed in 39.8% of SCD patients versus 10.1% in the control group. The decrease in eGFR was more in SCD patients with hyperuricemia than in those with normal uric acid levels. Microalbuminuria was more prevalent in SCD patients (86.7%) compared to the control group (23.6%). The mean albumin-to-creatinine ratio was 11.79±9.03 mg/mmol in SCD patients, significantly higher than in AA and AS subjects. CKD prevalence in SCD patients was 87.8%, considerably higher than the 23.8% and 7.7% observed in AS and AA subjects, respectively.

Sickle cell patients have an increased risk of developing chronic kidney disease, primarily because of the renal pathophysiology associated with chronic heme exposure and sickling of red blood cells. However, other factors such as hyperuricemia and hypertension, which are established modifiable risk factors associated with the development of CKD in no SCD populations, could play a role in the occurrence of this complication. This study observed hyperuricemia in 39.8% of SCD patients versus 10.1% of controls. The mechanism of the development of hyperuricemia is either uric acid overproduction or inefficient renal excretion. In SCD, the mechanism often suggested is overproduction from an increased marrow activity and turnover of nucleic acids secondary to hemolysis. Several studies have reported elevated uric acid levels in SCD patients: 26.9%, 30%, 28%, 9.2%. Compared to these studies, the higher prevalence of hyperuricemia observed in this study could be explained, on the one hand, by the hemolytic phenomena related to the endemicity of infectious and parasitic diseases in our environment. On the other hand, it could be explained by the poor management of SCD in Kisangani, as reported by Kambule et al., which exposes patients to chronic hemolysis. Preventive measures, effective management of infections, and hydroxyurea could reduce the frequency of hyperuricemia. Normalization of serum uric acid levels in SCD patients is of great importance since, in this study, the decrease in eGFR was more observed in SCD patients with hyperuricemia (average eGFR = 106.91± 34.81 mL/min/1.73m²) compared to SCD patients with normal uric acid levels (average eGFR = 119.90 ± 53.78 mL/min/1.73m²) (p=0.512) (p>0.05). Although the difference was not statistically significant, these results suggest a possible link between hyperuricemia and eGFR decrease in patients with SCD. Thus, our observation is in agreement with that of Kaspar et al., who reported a decrease in mean eGFR in SCD patients with hyperuricemia compared to those with normal uric acid levels. Similarly, in Lebensburger et al., SCD patients with hyperuricemia showed a significant decrease in mean eGFR compared to those without hyperuricemia. In addition, hyperuricemia would be involved in certain painful crises observed in sickle cell patients. Although there is still little evidence supporting this hypothesis, Gupta et al. reported that in SCD patients, not all pain is sickle cell pain. Therefore, these findings further buttress the need to improve the management of SCD in the DRC. Nevertheless, further studies are strongly needed because if there is evidence for a link between hyperuricemia and renal dysfunction on the one hand and hyperuricemia and painful crises in SCD patients on the other, hyperuricemia will be a potential therapeutic target.

The assessment of renal function in SCD patients has been the subject of numerous studies. However, these studies have been conducted with different exploration methods, on diverse populations, and under different management settings. These different methods have led to widely varying results, with a prevalence of sickle cell nephropathy ranging from less than 10% to values as high as 73.5%, depending on the above factors and the criteria retained in the definition of renal dysfunction.

The most commonly considered markers of sickle cell nephropathy are albuminuria, hyperfiltration, and CKD. In this study, the albuminuria, evaluated by the urine albumin-to-creatinine ratio, was more prevalent in SCD patients [85 of 98 subjects (86.7%) vs. 21 of 89 issues (23.6%) in controls]. In addition, CKD was present in...
87.8% of SCD patients vs. 19.1% of controls. The prevalence of albuminuria resulting from sickle cell nephropathy is high, varying between 26 and 68% in adult patients.26 However, consistent with our results, a higher prevalence of CKD has been reported by Anto et al. (73.5%),10 Isaza-López et al. (70%),27 and Ephraim et al. (68.4 %).28 Nevertheless, the prevalence observed in our study is higher than that reported elsewhere, and various factors, including the age of the respondents, the quality of SCD management, the infectious context, the haplotype found in the Democratic Republic of the Congo, and the method of assessing proteinuria may account for this. Indeed, the studies that reported lower prevalences of sickle cell nephropathy were mostly conducted in children.29,32,33 According to Gosmanova et al. and Adebayo et al.,34,35 the Clinical presentation of sickle cell nephropathy is age-dependent, with kidney dysfunction slowly beginning to develop from childhood, progressing to CKD and kidney failure during the third and fourth decades of life.11 In SCD patients, Ranque et al. observed sickle cell nephropathy in 27% of children younger than 10 years, and its frequency increased with age (48% in SCD patients aged >40 years).30 Therefore, our result could also be explained because our study included both children and adults.

The beneficial effect of hydroxyurea on sickle cell nephropathy has been demonstrated by Laurin et al., who observed proteinuria in 34.7% of SCD patients receiving hydroxyurea versus 55.4% among those not receiving this medication.36 However, in the Democratic Republic of the Congo, one of the major challenges in managing SCD is the accessibility of hydroxyurea to patients. The study by Kamble et al. showed that in the northeastern part of this country, only 5.1% of SCD patients have ever been treated with hydroxyurea,7 and this is a condition that can promote sickle cell nephropathy.

Different pathophysiological mechanisms have been proposed to explain the development of sickle cell nephropathy, where hemolysis and vascular occlusion are the main contributors.5 In the Kisangani setting, characterized by the endemicity of infectious and parasitic diseases and the poor management of SCD as documented in the milieu,7 hemolysis and vaso occlusion could be frequent and account for the high prevalence reported in this study. We also speculate that the Bantu haplotype, the most common in the Democratic Republic of the Congo and associated with severe disease manifestations, may be an additional factor in the development of sickle cell nephropathy in the Democratic Republic of the Congo.

Finally, due to the COVID-19 pandemic, the albumin-to-creatinine ratio was used for proteinuria evaluation without a second confirmation test. Thus, the possibility of false-positive results is a limitation for this study since high transient albuminuria has been reported by Kim et al.37

Limitations. As mentioned above, the urine albumin/creatinine ratio was performed to assess sickle cell nephropathy in the resource-limited setting of Kisangani (DRC), and the occurrence of the Covid-19 pandemic. Therefore, the urine albumin/creatinine ratio was performed once without repetition of tests to confirm the abnormalities. This limitation of the study implies that the high prevalence of albuminuria and CKD observed may be overestimated. Hence, we have interpreted the findings with caution. Nevertheless, despite this limitation, the results of this study globally indicate that sickle cell nephropathy is very common in northeastern DRC.

Conclusions. This study highlighted a high prevalence of hyperuricemia, albuminuria, and chronic kidney disease in SCD patients in northeastern DRC. Therefore, current management should routinely screen for and address renal complications, which could likely contribute to decreased morbidity and mortality of this disease. In addition, studies evaluating the benefit of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in the management of sickle cell nephropathy are strongly required in the DRC. Similarly, the link between hyperuricemia and sickle cell nephropathy should be further studied. Finally, there is an urgent need to implement dedicated centers offering comprehensive care to SCD patients in the DRC.

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