
Risk factors for death in adults with severe asthma

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Background: Mortality risk in adult asthma is poorly understood, especially the interplay among race, disease severity, and health care access.

Objective: To examine mortality risk factors in adult asthma.

Methods: In a prospective cohort study of 865 adults with severe asthma in a closed-panel managed care organization, we used structured interviews to evaluate baseline sociodemographics, asthma history, and health status. Patients were followed up until death or the end of the study (mean, 2 years). We used Cox proportional hazards regression to evaluate the impact of sociodemographics, cigarette smoking, and validated measures of perceived asthma control, physical health status, and severity of asthma on the risk of death.

Results: We confirmed 123 deaths (mortality rate, 6.7 per 100 person-years). In an analysis adjusted for sociodemographics and tobacco history, higher severity-of-asthma scores (hazard ratio [HR], 1.11 per 0.5-SD increase in severity-of-asthma score; 95% confidence interval [CI], 1.01–1.23) and lower perceived asthma control scores (HR, 0.91 per 0.5-SD increase in perceived asthma control score; 95% CI, 0.83–0.99) were each associated with risk of all-cause mortality. In the same adjusted analysis, African American race was not associated with increased mortality risk relative to white race (HR, 0.64; 95% CI, 0.36–1.14).

Conclusions: In a large managed care organization in which access to care is unlikely to vary widely, greater severity-of-asthma scores and poorer perceived asthma control scores are each associated with increased mortality risk in adults with severe asthma, but African American patients are not at increased risk for death relative to white patients.

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INTRODUCTION

Death caused by asthma is a devastating potential outcome. Asthma-specific mortality is considered to be preventable if high-risk patients are identified and appropriately treated.¹ Existing research on adult asthma mortality is incomplete. Most studies of asthma mortality have been retrospective, with limited information on asthma severity or other measures of health status.^{1–7} Furthermore, they have relied on cause-of-death information from death certificates to identify asthmatic cohorts,^{1–7} which introduces unavoidable inaccuracies in ascertainment.^{8–12} Prospective studies^{13–20} that have

examined risk factors for death in asthma have had little information on disease severity and virtually no information about race and have mostly studied populations outside the United States.

Within this context, retrospective studies^{2–7} have repeatedly observed racial and ethnic differences in asthma mortality, with mortality rates for African American individuals being approximately 4- to 5-fold higher than those for other racial groups. This apparent discrepancy has prompted the National Heart, Lung, and Blood Institute to make reducing racial disparities in asthma a research priority.²¹ However, it has not thus far been possible to confirm or refute this association prospectively, in particular taking into account correlated sociodemographic characteristics, disease severity and control, and access to care.

In a prospective cohort analysis, we examined risk factors for mortality in adults with asthma in a large, racially diverse cohort. By recruiting patients after hospitalization for asthma, we focused on patients with more severe asthma, which should have the effect of increasing statistical power to detect risk factors for mortality.^{22,23} It was, therefore, feasible in this modest-sized cohort to examine the impact of previously validated measures of asthma severity and health status on the risk of all-cause mortality. Furthermore, because the study patients were all members of a single closed-panel health care system, we could investigate whether racial disparities in mortality persist in asthmatic patients with established access

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to health care and after controlling for socioeconomic status and disease severity and control.

METHODS

Overview

This study obtained baseline survey information from Northern California Kaiser Permanente (KP) patients who had recently been hospitalized for asthma. After baseline survey, all the patients were treated according to the usual care practices for asthma at KP. Patients were followed up until death, termination of KP membership, or the end of the study period. KP is a closed-panel integrated health system and the nation's largest nonprofit managed care organization. The demographic characteristics of Northern California KP members are similar to the overall Northern California population, except for the extremes in income distribution.²⁴ This study was approved by the University of California, San Francisco, Committee on Human Research and the Kaiser Foundation Research Institute's institutional review board.

Patient Recruitment

Patient recruitment methods have been described in detail previously.^{25–27} Briefly, we identified all adult KP members, on a rolling monthly basis, hospitalized at any Northern California KP hospital with either (1) a primary discharge diagnosis of asthma or (2) a primary discharge diagnosis of an acute asthma-related respiratory condition and a secondary discharge diagnosis of asthma.²⁸ Persons with a primary or secondary discharge diagnosis of chronic bronchitis, emphysema, or chronic airway obstruction were excluded. The diagnosis of asthma was previously validated in a stratified random sample of 100 individuals.²⁶ The cohort included 865 patients with severe asthma who completed interviews (53% of all eligible patients). Patients who did and did not participate were similar in terms of age, sex, and race/ethnicity ($P > .20$ for all).²⁶

Measurements

Structured telephone interviews performed after hospital discharge ascertained age, sex, race/ethnicity, educational attainment, household income, marital status, and tobacco history, as previously described.^{25,27,29} We measured asthma severity using a 13-item disease-specific severity-of-asthma score, which is based on the frequency of current asthma symptoms (daytime or nocturnal), the use of systemic corticosteroids, the use of other asthma medications (other than systemic corticosteroids), and history of hospitalization and endotracheal intubation.^{30,31} Possible total scores range from 0 to 28, with higher scores reflecting more severe asthma. Previous works^{30–32} have established the reliability, concurrent validity, and predictive validity of the severity score, including its ability to predict future hospitalizations for asthma.

General physical health status was measured using the Physical Component Scale based on the 12-Item Short Form Health Survey,³³ which has been shown to be valid for adults

with asthma.³⁴ Higher scores reflect more favorable physical health status.

Perceived asthma control was measured using the validated 11-item Perceived Control of Asthma Questionnaire,^{27,35} which assesses individuals' perceptions of their ability to manage their asthma and its exacerbations. Higher scores reflect greater perceived asthma control.

Study Outcome: Mortality

The primary study outcome was all-cause mortality after patient enrollment (which required survival to discharge from the index hospitalization before recruitment) and before December 31, 2004, which corresponded to the last available mortality information. We used all-cause mortality for the primary outcome rather than death specifically attributed to asthma on death certificates for 2 reasons: death certificate information may underestimate death due to asthma^{8–12} and asthma may play an indirect but clinically important role in other causes of death, such as cardiovascular disease, chronic obstructive pulmonary disease (COPD), and pneumococcal disease.^{15,36–38} Note that all-cause mortality has been a major end point, and usually the primary end point, used in previous prospective studies of mortality in asthma.^{13–19}

However, to complement the analysis of all-cause mortality, we also performed 2 additional analyses in which we used deaths with respiratory causes as the outcomes. In the first model, the outcome was death in which a respiratory cause was listed on the death certificate as the underlying cause.³⁹ In a second model, the outcome was death in which a respiratory cause was either the underlying or a contributing cause.⁴⁰ We classified deaths as respiratory based on a priori categorization of a complete list of *International Classification of Disease, Tenth Revision*, codes that can be used as causes of death on death certificates.

To obtain vital status, we first used KP's computerized record system. For patients who had terminated their KP membership and for whom we did not, therefore, have vital status, we obtained this information by searching the National Death Index, a database that is abstracted from all death certificates from throughout the United States.⁴¹ We also obtained underlying and contributing causes of death for all deceased patients from the National Death Index listed according to the *International Classification of Disease, Tenth Revision*.⁴²

Statistical Analysis

We performed statistical analysis using a software program (Stata/SE version 9.2; StataCorp, College Station, Texas). To evaluate sociodemographic characteristics and health status measurements as single predictors of death, we used the t test to compare means for continuous variables and the χ^2 test to compare 2 or more percentages for categorical variables.

In Cox proportional hazards regression models that adjusted for multiple potentially explanatory variables, person-time was censored for patients who terminated KP membership or reached the end of the study period without mortality.

The proportional hazards assumption was verified by obtaining scaled Schoenfeld residuals ($P > .10$ for all variables in the model). We scaled the continuous health status measures by half of their SD, which generally corresponds to a minimally clinically significant score change.⁴³

To provide insight into the death rate of the cohort relative to a standardized population, we calculated a standardized mortality ratio (SMR) for the cohort relative to age- and sex-matched California mortality rates between 2000 and 2004, the years in which this study took place.⁴⁴ This was achieved by dividing the number of observed deaths by the expected number of deaths in each age decile and sex-specific California stratum (eg, males aged 45–55 years). This SMR calculation was not incorporated into other statistical analyses.

Although the diagnosis of asthma was confirmed via medical record review, we performed a sensitivity analysis in which we attempted to strictly ensure that all the patients had asthma rather than COPD as their primary underlying diagnosis. We restricted this sensitivity analysis to patients who were highly likely to have asthma because they either never smoked cigarettes during their lifetime or had onset of asthma symptoms during childhood (<10 years old) before COPD can develop ($n = 426$). We a priori chose this cutoff age of 10 years because most childhood asthma begins in early childhood.⁴⁵

RESULTS

During the study, 123 deaths occurred in 865 adults hospitalized for asthma. The mean (SD) age of the cohort at baseline was 60.3 (16.3) years. Patients were followed up for a mean (SD) of 781 (356) days, corresponding to a mortality rate of 6.7 per 100 person-years (95% confidence interval [CI], 5.6–7.8 deaths per 100 person-years). The mortality rate per 100 person-years ranged from a low of 1.9 for patients aged 30 to 40 years to a high of 17.8 for those older than 80 years. The age- and sex-standardized mortality ratio for the study cohort relative to the general California population was 367% (95% CI, 307%–438%).

Baseline characteristics as single predictors of mortality are summarized in Table 1. Age, cigarette smoking history, and marital status were statistically significantly associated with mortality risk. Education ($P = .06$) and household income ($P = .053$) were not associated with mortality at the conventional level of statistical significance. Race/ethnicity was not associated with all-cause mortality risk. Because of the a priori study interest in African American–associated risk,²¹ we reanalyzed these data comparing African American patients ($n = 154$) with all others ($n = 711$). In that analysis, African American race was significantly associated with decreased risk ($P = .04$).

Greater asthma severity, poorer health status, and poorer perceived asthma control were each predictive of death when analyzed without other explanatory variables (Table 2). The frequency of all deaths grouped by broad category of underlying cause is given in Table 3. Respiratory causes were the

Table 1. Baseline Sociodemographic Characteristics and Smoking Status in Relation to Mortality Risk in 865 Patients With Asthma^a

Baseline characteristic	Died (n = 123)	Survived (n = 742)	P value ^b
Age, mean (SD), y	69 (14)	59 (16)	<.001
Sex			.17
Female	80 (13)	528 (87)	
Male	43 (16)	214 (94)	
Marital status			.047
Married/cohabitating	65 (12)	462 (88)	
Single	58 (17)	280 (83)	
Education			.06
College graduate or higher	20 (10)	179 (90)	
Some college or lower	103 (15)	563 (85)	
Race/ethnicity			.34
Non-Latino white	79 (15)	445 (85)	
African American	14 (9)	140 (91)	
Asian	9 (16)	47 (84)	
Latino	10 (14)	60 (86)	
Other	11 (18)	50 (82)	
Annual household income ^c			.053
>\$60,000	8 (8)	97 (92)	
≤\$60,000	103 (15)	603 (85)	
Smoking history			.005
Current or former smoker	94 (17)	470 (83)	
Never smoker	29 (10)	272 (90)	

^a Data are given as number (row percentage) except where indicated otherwise.

^b The t test was used for age and the likelihood ratio χ^2 test was used for all other characteristics.

^c The number of patients for annual household income does not sum to 865 because 54 patients declined to state their income.

Table 2. Baseline Asthma Severity and Health Status and the Risk of Death in Asthma^a

Score	Died (n = 123)	Survived (n = 742)	P value
Severity-of-asthma score, mean (SD)	12.8 (4.0)	11.8 (3.4)	.005
SF-12 Physical score, mean (SD)	31.7 (10.7)	35.5 (11.6)	.001
Perceived asthma control score, mean (SD)	37.2 (3.5)	38.2 (4.3)	.01

Abbreviation: SF-12, 12-Item Short Form Health Survey.

^a Higher severity-of-asthma scores reflect more severe asthma. Higher SF-12 physical scores and higher perceived control of asthma scores reflect more favorable health status.

single largest category of underlying cause of death. Underlying cause of death was attributed to asthma in only 2 patients, although asthma, including status asthmaticus, was listed as a contributing cause of death in an additional 7 patients. When underlying and contributing causes of death are considered, 78 of 123 deaths (63%) were respiratory related.

In the adjusted Cox proportional hazards regression model of all-cause mortality, higher baseline severity-of-asthma

Table 3. Underlying Cause of Death in 123 Adults With Asthma

Underlying cause of death	Patients, No. (%)
Respiratory ^a	44 (36)
Cardiovascular	34 (28)
Cancer	21 (17)
Other	24 (20)

^a The respiratory group is composed of 2 patients with asthma (*International Classification of Disease, Tenth Revision* [ICD-10], code J45.9), 3 with emphysema (ICD-10 code J43.9), 4 with “other specified chronic obstructive pulmonary disease” (ICD-10 code J44.8), 27 with “chronic obstructive pulmonary disease, unspecified” (ICD-10 code J44.9), 5 with pneumonia, 1 with aspiration pneumonitis, 1 with secondary pulmonary hypertension, and 1 with bronchiectasis. Contributing respiratory causes were listed on 34 of the nonprimary respiratory cases.

scores (HR, 1.11 per 0.5-SD increment in score; 95% CI, 1.01–1.23) and lower perceived asthma control scores (HR, 0.91 per 0.5-SD increment in score; 95% CI, 0.83–0.99) were each associated with a greater prospective risk of death (Table 4). A history of former or current tobacco use was associated with increased risk of death (HR, 1.81; 95% CI, 1.18–2.79). African American race was not associated with a higher risk of death relative to non-Latino white race (HR, 0.64; 95% CI, 0.36–1.14). In contrast, Latino, Asian, and “other race/ethnicity” were each associated with an increased point estimate of mortality relative to white patients. The CIs for these relatively small groups, however, were wide and included unity.

In the sensitivity analysis, in which we attempted to more strictly ensure that all the patients had asthma rather than COPD as their primary underlying diagnosis, the point estimates for the HRs of the severity-of-asthma score (HR, 1.12; 95% CI, 0.96–1.31) and perceived asthma control score (HR, 0.91; 95% CI, 0.79–1.06) were virtually unchanged, although the 95% CIs using this smaller subset of data were larger and included unity.

We also performed another set of analyses in which we used 2 alternative mortality outcomes in adjusted models: (1) underlying respiratory cause of death ($n = 44$) and (2) underlying or contributing respiratory cause of death ($n = 78$) (Table 5). In both analyses, the severity-of-asthma score was even more strongly associated with mortality (HR, 1.54; 95% CI, 1.30–1.81 for respiratory as underlying cause of death and HR, 1.40; 95% CI, 1.24–1.58 for respiratory as underlying or contributing cause of death). African American race was still related to a decreased point estimate of risk of death (HR, 0.68; 95% CI, 0.26–1.79 for respiratory as underlying cause of death and HR, 0.75; 95% CI, 0.38–1.49 for respiratory as underlying or contributing cause of death). Asian race became a stronger predictor of death in which a respiratory cause was underlying (HR, 3.94; CI, 1.47–10.6) and death in which a respiratory cause was underlying or contributing (HR, 2.72; 95% CI, 1.20–6.13).

Table 4. Risk Factors for All-Cause Mortality ($n = 123$) in 865 Adults With Severe Asthma^a

Factor	HR (95% CI)	
	Unadjusted	Adjusted
Demographic characteristic		
Age ^b	1.23 (1.16–1.32)	1.28 (1.19–1.37)
Female sex	0.81 (0.56–1.18)	0.84 (0.55–1.26)
Married/cohabitating	0.68 (0.48–0.97)	0.72 (0.49–1.05)
College graduate	0.60 (0.37–0.96)	0.61 (0.37–1.00)
High income (>\$60,000)	0.50 (0.24–1.02)	0.74 (0.35–1.56)
Race/ethnicity		
White non-Latino	1 [Reference]	1 [Reference]
African American	0.59 (0.34–1.05)	0.64 (0.36–1.14)
Latino	0.93 (0.48–1.79)	1.16 (0.60–2.26)
Asian	0.96 (0.48–1.92)	1.77 (0.88–3.57)
Other	1.21 (0.64–2.27)	1.68 (0.88–3.19)
Current or former smoker ^c	1.78 (1.17–2.7)	1.81 (1.18–2.79)
Health status and severity ^d		
Severity-of-asthma score	1.09 (1.00–1.18)	1.11 (1.01–1.23)
SF-12 Physical score	0.83 (0.76–0.92)	0.91 (0.82–1.02)
Perceived asthma control	0.89 (0.82–0.96)	0.91 (0.83–0.99)

Abbreviations: CI, confidence interval; HR, hazard ratio; SF-12, 12-Item Short Form Health Survey.

^a Unadjusted HRs include each factor, with appropriate reference group, analyzed by itself in a Cox proportional hazards model for death. Adjusted HRs include simultaneously all factors listed in the table.

^b Hazard ratio per 5-year increment in age.

^c When tobacco history is defined as current smoker, former smoker, or never smoker, the adjusted HRs, with never smoker as the referent, were as follows: current smoker, HR, 2.52; 95% CI, 1.25–5.08; and former smoker, HR, 1.74; 95% CI, 1.12–2.70.

^d Higher severity-of-asthma scores reflect greater severity; higher SF-12 Physical and perceived asthma control scores reflect better status. Hazard ratios are expressed per 0.5-SD change in score.

DISCUSSION

In this prospective cohort study of adults with severe asthma and comparable access to care, asthma severity and perceived asthma control were risk factors for death. Thus, gradations of asthma severity, even in a cohort characterized by disease severe enough to have led to recent hospitalization, confers substantive all-cause mortality risk. Furthermore, in examining death from a respiratory cause, asthma severity exhibits even more predictive power. This demonstrates internal consistency for this measure because we would expect that a respiratory-specific measure would be a stronger predictor of a respiratory-related outcome.

Even taking asthma severity into account, the subjective perception of disease control independently conferred mortality risk. Improved perceived asthma control has previously been demonstrated to be associated with decreased prospective risk of severe asthma attacks and health care utilization.^{27,35} Perceived asthma control, which is closely related to self-efficacy, is a patient’s self-perception of his or her ability to manage asthma and its exacerbations.³⁵ Higher perceived

Table 5. Sensitivity Analysis: Respiratory Causes of Death

Factor	Adjusted HR (95% CI) ^a	
	Respiratory underlying cause of death (n = 44)	Respiratory underlying or contributing cause of death (n = 78)
Demographic characteristics		
Age ^b	1.48 (1.28–1.72)	1.42 (1.29–1.58)
Female sex	0.83 (0.41–1.69)	0.77 (0.45–1.30)
Married/cohabitating	0.51 (0.27–0.99)	0.65 (0.39–1.06)
College graduate	0.79 (0.35–1.76)	0.62 (0.34–1.17)
High income (>\$60,000)	NA ^c	1.01 (0.44–2.33)
Race/ethnicity		
White non-Latino	1 [Reference]	1 [Reference]
African American	0.68 (0.26–1.79)	0.75 (0.38–1.49)
Latino	1.10 (0.37–3.25)	1.08 (0.45–2.55)
Asian	3.94 (1.47–10.6)	2.72 (1.20–6.13)
Other	NA ^c	0.23 (0.03–1.67)
Tobacco history		
Current or former smoker	2.67 (1.17–6.10)	2.10 (1.16–3.80)
Health status and severity		
Severity-of-asthma score ^d	1.54 (1.30–1.81)	1.40 (1.24–1.58)
SF-12 Physical score ^d	0.90 (0.74–1.10)	0.86 (0.75–1.00)
Perceived asthma control ^d	0.91 (0.78–1.06)	0.91 (0.82–1.02)

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not available; SF-12, 12-Item Short Form Health Survey.

^a Underlying cause of death is the disease that initiated the sequence of events leading to death. Contributing causes of death are significant conditions contributing to death but not resulting in the underlying cause.

^b Hazard ratio per 5-year increment in age.

^c Unable to calculate an HR because there were no deaths with underlying respiratory cause in the “other race” group or in the high income group.

^d Higher asthma severity scores reflect greater severity; higher SF-12 physical and perceived asthma control scores reflect better status. Hazard ratio expressed per 0.5-SD change in score.

control may result in improved disease control through improved self-management behaviors, improved medication adherence, or unknown mechanisms.²⁷ These data showing that higher perceived asthma control predicts lower mortality even after adjustment for asthma severity suggest that perceived control is playing an independent and important role. Previous research in other chronic disease models has shown that clinical outcomes can be improved by intervention programs focused on improving self-efficacy,^{46,47} which is confidence in one’s ability to perform a behavior necessary to reach a desired goal.⁴⁷ Further studies should investigate whether improving perceived asthma control can also reduce mortality risk.

The observation that African American race was not a risk factor for mortality is all the more striking in this context given that multiple previous studies^{2–7} have demonstrated a markedly higher risk of death attributed to asthma in African Americans. There are several possible explanations for these findings. First, this study prospectively identified patients with asthma rather than relying on potentially less accurate cause-of-death information to define the cohort.^{8–12} Second, in the closed-panel managed care organization in which the cohort was studied, asthmatic patients likely had equivalent access to care, thus controlling for this potential confounding variable. One key aspect to such health care access may be asthma-specific disease management programs. During the

past decade, Northern California KP has made a major effort to standardize and improve asthma care through disease management programs, including clinical guidelines, patient self-management education, disease registries, risk stratification, proactive outreach, reminders, multidisciplinary care teams, and performance feedback to providers.⁴⁸

We found that adults with severe asthma had a markedly higher mortality rate than the age- and sex-matched California population (SMR, 367%). However, cause of death was specifically attributed to asthma in relatively few patients. There are several explanations for these contrasting findings. Asthma may play an indirect role in death due to other causes, such as cardiovascular disease, either via inflammatory pathways or as a result of the treatment of the asthma with medications such as bronchodilators.^{37,38} Alternatively, cause-of-death information on death certificates may be inaccurate, as numerous studies have concluded generally.^{49,50} Some researchers^{49,50} have suggested that physicians may not consider cause-of-death accuracy to be a priority and that declining autopsy rates have exacerbated death certificate unreliability. Other studies have shown that deaths from asthma specifically are often mistakenly attributed to COPD.^{8–11} It is, therefore, possible that some deaths attributed to COPD in this study were in fact due to asthma. Finally, although we cannot say whether asthma was responsible for the entire increase in mortality suggested by the

SMR, the fact that the severity-of-asthma score was related to increased mortality suggests that patients' asthma did play a role.

Many more deaths were attributed to COPD than to asthma, which raises the question of whether some patients may have had COPD rather than asthma on enrollment. However, the diagnosis of asthma was previously validated at baseline by an in-depth medical record review of a stratified random sample of 100 patients.²⁶ In addition, all the patients reported a physician diagnosis of asthma during the survey. Finally, in a sensitivity analysis in which we attempted to more strictly ensure that included patients had asthma rather than COPD as their primary underlying diagnosis, the relationships of the severity-of-asthma score and perceived asthma control score to mortality were virtually unchanged. Although the 95% CIs were slightly wider, this is expected when an analysis is performed on a smaller subset of a study population. Consequently, misclassification of COPD as asthma on enrollment does not seem to explain the results.

Despite its strengths, this study has limitations. Although we recruited a cohort with severe asthma, follow-up was relatively brief, and death still remained an uncommon event. It is possible that the lack of associations, as seen with sex, were due to a lack of statistical power. In particular, the small number of Asian and Latino participants makes it difficult to draw clear conclusions about their risk. This is unfortunate because little has been published about the risk of death in asthmatic Asian patients, and our estimate of risk for Asians was the highest of any group. Despite the limitations of study size for the other groups, African Americans composed nearly 1 in 5 of this cohort and, given the observed point estimate and 95% CIs, African American race seems very unlikely to confer a higher risk of death. We also recruited a cohort with relatively severe asthma after hospitalization for this condition. Consequently, these results will likely not apply to populations with mild asthma.

Overall, these results demonstrate an elevated risk of death in adults with severe asthma and show that the potentially modifiable factors of asthma severity and perceived asthma control are prospectively associated with death. This provides justification for interventional research to investigate whether reducing asthma severity and improving perceived control can improve asthma outcomes. The severity score's application in a clinical context requires further validation, but ultimately it may help to identify patients at highest risk for death. Finally, this study did not find higher rates of death for African American asthmatic patients. Establishing access to care, as all patients in our cohort had done, stands out as one factor that may improve racial disparities in asthma mortality.

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