

Mortality Among Men Bearing Prostate Cancer and its Association With Sociodemographic and Clinical Variables

Mortalidade em Homens com Câncer de Próstata e sua Associação com Variáveis Sociodemográficas e Clínicas

Mortalidad en Hombres con Cáncer de Próstata y su Asociación con Variables Sociodemográficas y Clínicas

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ABSTRACT

Objective: The study's purpose has been to evaluate the association of socio-demographic and clinical variables with the general and specific mortality from prostate cancer. **Methods:** This is a retrospective study that was carried out through the analyses of medical records from 1,290 men diagnosed with prostate cancer over the period from 2000 to 2006. **Results:** Considering the 1,290 men, 758 were alive, 308 had died from prostate cancer, and 224 had died from other causes. Those that were associated with death from prostate cancer include: Gleason score > 9, Prostate Specific Antigen (PSA) > 20 and the presence of metastasis. Furthermore, there were those associated with death due to other causes, as follows: widowers, admission to the hospital without diagnosis and without treatment, and also PSA > 50. **Conclusion:** Clinical variables predominated with regards to prostate cancer-specific mortality. On the other hand, socio-demographic variables prevailed towards deaths originated from other causes.

Descriptors: Prostate Neoplasms, Mortality, Men's Health, Public Policies.

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RESUMO

Objetivo: Avaliar a associação de variáveis sociodemográficas e clínicas com a mortalidade geral e específica por câncer de próstata. **Método:** Estudo retrospectivo de 1290 homens diagnosticados com câncer de próstata entre 2000 e 2006. Consultou-se prontuários, Sistema de Registro Hospitalar e Sistema de Informações sobre Mortalidade. **Resultados:** Dos 1290 homens, 758 estavam vivos, 308 morreram por câncer de próstata e 224 por outras causas. Associaram-se ao óbito por câncer de próstata: escore de Gleason > 9, PSA > 20 (entre 2,82 e 5,55 vezes) e presença de metástase. Associaram-se ao óbito por outras causas: estado civil viúvo, ingresso no hospital sem diagnóstico e sem tratamento e PSA > 50. **Conclusão:** Variáveis clínicas predominaram sobre a mortalidade específica por câncer de próstata, já variáveis sociodemográficas em óbitos por outras causas.

Descritores: Neoplasias da Próstata, Mortalidade, Saúde do Homem, Políticas Públicas.

RESUMEN

Objetivo: Evaluar la asociación de las variables sociodemográficas y clínicas con la mortalidad general y específica por cáncer de próstata. **Métodos:** Estudio retrospectivo de 1.290 hombres con cáncer de próstata en el período del 1 de enero de 2000 al 31 de diciembre de 2006. **Resultados:** De los 1.290 hombres, 758 estaban vivos, 308 murieron por cáncer de próstata y 224 por otras causas. Se asociaron con la muerte por cáncer de próstata: Gleason puntuación >9, PSA >20 (entre 2,82 y 5,55 veces) y metástasis. Ellos se asociaron con muerte por otras causas: el estado civil viuda, la admisión al hospital diagnosticar y sin tratar y el PSA >50. **Conclusión:** Las variables clínicas predominaron sobre la mortalidad específica por cáncer de próstata, ya variables sociodemográficas en muertes por otras causas..

Descriptores: Neoplasias de la Próstata, Mortalidade, Salud del Hombre, Políticas Públicas.

INTRODUCTION

Prostate cancer (PC) is the second most malignant tumor in men and the sixth leading cause of death in men worldwide.¹ In Brazil, except for non-melanoma skin cancer, it represents the most prevalent malignant tumor in men, for 28.6% of the cases of male cancers predicted for 2016/2017.² being the second cause of cancer mortality by gender.³ The estimated incidence for 2016 was 61,200, with an estimated risk of 61.82 new cases every 100,000 men.²

Its risk factors are age, black race, and family history.^{2,4,5} Seventy-two percent of cases occur in developed countries and account for 56% of worldwide mortality.⁴ In Brazil, there is a trend towards increased incidence and mortality,⁶ between 1980 and 2006 the increase in mortality from PC corresponded to 100% in cases from cities in the interior of the country, contrasting with an increase of 40.8% in those living in the capitals.⁷ North America and Oceania tend to show a stabilization in the incidence of this neoplasm, and show a reduction in mortality, a result of the detection of the disease in the early stages since the 1990s with the introduction of Prostate Specific Antigen (PSA); of performing radical prostatectomy as a surgical treatment; the evolution of radiotherapy and hormone therapy,^{5,8} reaching a 39% reduction in mortality between

1991 and 2007, when the mortality rate was equal to that of 1975, a time prior to the clinical use of PSA as tumor marker for PC.⁵

One of its characteristics is to present in an insidious way and to undertake, in the majority, men over 65 years old, 2 with other causes of death concurring for the outcome, being the main ones cardiovascular, respiratory and other primary neoplasias.⁹⁻¹¹

The *Espírito Santo* is a State from the Southeastern Region with a population of 3,514,952 inhabitants, 12 with gross rates of mortality of PC that rose from 1.96 cases/100,000 inhabitants in 1980, when it ranked 16th in the mortality ranking for this disease, to 13.93 cases/100,000 inhabitants in 2014.¹³

Given the aforementioned, this study aims to assess the relationship of socio-demographic and clinical variables with both general and specific PC mortality in men bearing this disease, which were treated at a referral hospital in oncology.

METHODS

It is a retrospective cohort study of secondary data on PC mortality was collected, with data from men diagnosed with neoplasm between January 1st, 2000 and December 31st, 2006, using the Hospital Registry of Cancer from the *Hospital Santa Rita de Cássia/Associação Feminina de Educação e Combate ao Câncer (HSRC/Afecc)*.

The *HSRC/Afecc* is a general and philanthropic hospital for oncology care. It consists of two Centers of Attention of High Complexity in Oncology, as established by the Ordinance No. 741, of December 19th, 2005.¹⁴

Included in the study were men with pathology-proven PC, who had received care in the hospital and were enrolled in the Health Information System from the Hospital Registry of Cancer during the aforesaid period.

In the composition of the sample, the exclusion criteria were the impossibility of determining the initial clinical staging, the registration of only one consultation in the hospital, the cases of residents in other states and the absence of information about the municipality of residence.

The initial sample consisted of 1,500 men; nevertheless, 174 (11.6%) were excluded from the study because they did not present enough information to determine the initial staging; six (0.4%), because they had only one consultation at *HSRC/Afecc*; 25 (1.6%), because they came from other states, and five (0.3%), due to the lack of information about the municipality of origin, thus remaining for the analysis 1,290 men.

For the information collection, the Tumor Registry Form and the medical records of the men served with a diagnosis of the neoplasm were used, as well as the Health Information System-Hospital Registry of Cancer records from the *HSRC/Afecc*. Data on mortality and its underlying cause were obtained by consulting the Mortality Informa-

tion System in the *Espírito Santo* State. The collection of these data occurred over the period from October 2011 to March 2012.

The purpose of the medical records was to collect data that had not been included in the Tumor Registry Record or that had been recorded after the case was registered in the hospital system, a situation that occurs throughout the tumor's birthday. For this purpose, a data collection form was used.

In order to identify the cases with an outcome (death) occurred between 2000 and 2011, we used the Mortality Information System from the *Espírito Santo* State. This database is made up of death certificates collected by the State Health Office and has the objective of providing health managers, researchers and society entities with the most relevant information for the definition of priorities in programs of prevention and control of diseases.¹⁵

The PC was assigned the situations in which C61 was specified as the basic cause of death, according to the 10th edition of the International Classification of Diseases, approved in 1989, the last update in which the ICD C61 corresponding to PC was maintained,¹⁶ occurred in the year 2008.

Herein, the following eleven variables were analyzed: age at diagnosis, race/skin color, education level, marital status, origin and diagnosis and previous treatments (socio-demographic variables); staging, PSA value, histological Gleason score and presence of metastases and treatments and associations of modalities (clinical variables).

Data were organized in the *Microsoft Office Excell 2007 for Windows* program and analyzed using the Statistical Package for Social Sciences (SPSS), version 18.0. To evaluate the mortality, the patients were stratified into death and not death. The death was divided into PC death and death from other causes. The percentages of the qualitative variables were calculated in the groups considered. The chi-square test was used to measure the association between the qualitative variables and the groups considered. The averages, the medians, and the standard deviations were computed. For variables that presented statistical significance of 10% in the chi-square test, the raw odds ratio was calculated and adjusted by the multivariate logistic regression model. Logistic regression considered the non-death category as the standard, and the adjusted odds ratio was estimated for the death categories by PC and death for other causes. The final significance level considered was 5%.

This research is in accordance with the ethical determinations established in the Resolution No. 466 of December 12th, 2012, of the National Commission of Ethics in Research and was approved by the Research Ethics Committee from the *Universidade Federal do Espírito Santo (UFES)* under the No. 253/11, on October 26th, 2011.

RESULTS AND DISCUSSION

Regarding the 1,290 men treated with PC, 758 (58.8%) were alive at the end of the observation period; 308 (23.9%) had as their outcome the death from PC and 224 (17.4%), the death from other causes not related to this neoplasm.

The illiterates accounted for 16.22% of the sample; 48.58% had not completed primary school and approximately 4% had completed higher education. Considering the deaths from cancer studied, 51% were incomplete first-degree patients, 63% non-whites, 69% from the metropolitan region and 60% referred by the *Sistema Único de Saúde (SUS)* [Unified Health System]. None of the above socio-demographic variables presented statistical significance with the outcomes of deaths due to PC or other causes. The prevalence of death in both PC and other causes was 70 years old and older, with 60% and 68% of cases, respectively ($p=0.001$); (76%), followed by single (8%) and lastly, divorced was responsible for 4% of the deaths. Widows presented a higher prevalence of death due to other causes ($p=0.001$). Cases with diagnosis and without previous treatment led to specific cause deaths, with 65% of cases, but were even higher in deaths from other causes, totaling 73% ($p=0.001$).

Associating the clinical variables with the outcome, it was observed that the initial clinical staging ($p=0.001$) and the Gleason score ($p=0.001$), the PSA value ($p=0.001$) and the presence of metastases ($p=0.001$) presented statistical significance (**Table 1**).

Table 1 - Absolute and relative frequencies of clinical variables according to the outcome in men assisted by the *Hospital Santa Rita de Cássia, Vitória* city, *Espírito Santo* State, from January 1st, 2000 to December 31st, 2006.

Variable	Category	Total		Outcome						p-value
				Non-death		Death by prostate cancer		Death by other causes		
				n	%	n	%	n	%	
Stage	Early (I and II)	919	71%	618	82%	124	40%	177	79%	0.001
	Late (III and IV)	371	29%	140	18%	184	60%	47	21%	
Gleason score	Up to 6	685	54%	457	61%	101	34%	127	58%	0.001
	7	321	25%	176	23%	86	29%	59	27%	
	8	147	12%	74	10%	49	16%	24	11%	
	9	98	8%	38	5%	51	17%	9	4%	
	10	17	1%	5	1%	11	4%	1	0%	
PSA value	< 10	346	30%	262	38%	30	11%	54	26%	0.001
	10 ... 20	274	23%	189	28%	32	11%	53	26%	
	20 ... 50	241	21%	135	20%	65	23%	41	20%	
	50 ... 100	109	9%	45	7%	40	14%	24	12%	
	≥ 100	201	17%	55	8%	114	41%	32	16%	
Metastasis	Yes	302	24%	68	9%	198	64%	36	16%	0.001
	No	983	76%	688	91%	109	36%	186	84%	

Table 2 (socio-demographic variables) and **Table 3** (clinical variables) were the multivariate analysis, considering the two outcomes, PC death and death from other causes, in relation to non-death, for factors that presented statistical significance individually (calculation of gross odds ratio), first for socio-demographic variables, later for clinical variables. The results indicate that the age variable was no

longer associated with mortality in these patients, while the widowed civil status was associated with a 2.62-fold increase in the probability of death from other causes ($p < 0.001$, CI: 1.66-4.12); to enter the *HSRC/Afccc* without diagnosis and without treatment increased by 1.67 times the chance of death by PC ($p=0.034$; CI: 1.04-2.7) and by 3.45 times death due to other causes ($p=0.001$, IC: 1.83-6.48), and to enter with diagnosis and without treatment increased by 1.84 times the chance of death due to other causes ($p=0.027$, CI 1.07-3.15). The Gleason score > 6 increased from 2.21 to 9.97 times the probability of death by PC ($p=0.001$; CI: 3.38-29.28).

Table 2 - Results of the multivariate logistic regression analysis for the statistically significant socio-demographic variables by individual (raw odds ratio), *Vitória* city, *Espírito Santo* State, 2006.

Variable	Category	Death by prostate cancer				Death by other causes			
		p-value	OR	LI	LS	p-value	OR	LI	LS
Age group	≤ 49 y/o	1				1			
	50 to 69 y/o	0.561	0.7	0.21	2.32	0.62	1.68	0.21	13.49
	≥ 70 y/o	0.829	1.14	0.35	3.75	0.21	3.77	0.47	30
Marital status	Married	1				1			
	Single	0.419	1.19	0.78	1.82	0.77	0.92	0.54	1.57
	Divorced	0.92	1.03	0.53	2.01	0.87	0.94	0.42	2.07
	Widower	0.702	1.11	0.66	1.84	0	2.62	1.66	4.12
Diagnosis and previous treatment	Without both diagnosis and treatment	0.034	1.67	1.04	2.7	0	3.45	1.83	6.48
	With diagnosis and without treatment	0.25	0.8	0.55	1.17	0.02	1.84	1.07	3.15
	With both diagnosis and treatment	1				1			

The PSA value > 20 ng/dL increased between 4.20 and 18.10 times the chance of death by PC ($p= 0.001$, CI: 2.60-6.79 and 11.02-29.73), and > 50 ng/dL, between 2.59 and 2.82 times that of death due to other causes ($p=0.001$; CI: 1.67-4.77). The initial clinical stage 4 increased by 21.48 times the probability of death by PC ($p=0.004$; CI: 2.66-173.20), while the presence of metastasis increased by 18.38 times the death rate ($p=0.001$, CI: 13.06-25.86), and 1.96 times that of death due to other causes ($p=0.002$; CI: 1.27-3.03).

Table 3 - Results of the multivariate logistic regression analysis for the statistically significant clinical variables by individual (raw odds ratio), *Vitória* city, *Espírito Santo* State, 2006.

Variável	Categoria	Óbito por câncer de próstata				Óbito por outras causas			
		P-valor	OR	LI	LS	P-valor	OR	LI	LS
Escore de Gleason	Até 6		1,00				1,00		
	7	0,000	2,21	1,58	3,09	0,300	1,21	0,85	1,72
	8	0,000	3,00	1,97	4,56	0,545	1,17	0,71	1,93
	9	0,000	6,07	3,79	9,74	0,677	0,85	0,40	1,81
	10	0,000	9,95	3,38	29,28	0,765	0,72	0,08	6,22
Valor do PSA	< 10		1,00				1,00		
	10 --- 20	0,150	1,48	0,87	2,52	0,153	1,36	0,89	2,08
	20 --- 50	0,000	4,20	2,60	6,79	0,096	1,47	0,93	2,32
	50 --- 100	0,000	7,76	4,39	13,72	0,001	2,59	1,46	4,60
	≥ 100	0,000	18,10	11,02	29,73	0,000	2,82	1,67	4,77
Estadiamento clínico inicial	1		1,00				1,00		
	2	0,572	1,82	0,23	14,48	0,231	0,51	0,17	1,54
	3	0,185	4,15	0,51	34,04	0,109	0,37	0,11	1,25
	4	0,004	21,48	2,66	173,20	0,861	0,90	0,28	2,91
	Metástase	Sim	0,000	18,38	13,06	25,86	0,002	1,96	1,27
	Não		1,00				1,00		

Table 4 (socio-demographic variables) and **Table 5** (clinical variables) present a multivariate analysis model, considering all variables at the same time (adjusted odds ratio). The Gleason score 9 (OR: 2.98, $p=0.001$) and 10 (OR: 9.55, $p=0.013$), PSA value > 20 (between 2.82 and 2.82) were statistically significant for PC death, and 5.55 times, $p=0.001$) and presence of metastasis (OR: 12.18; $p < 0.001$). Marital status (OR: 1.96, $p=0.01$), admission to *HSRC/Afccc* without diagnosis and without previous treatment (OR: 2.60, $p=0.007$) were associated with death due to other causes. PSA value between 50 and 100 ng/dL (OR: 2.41, $p = 0.005$) and > 100 ng/dL (OR: 1.92; $p=0.041$).

Table 4 - Results of the multivariate logistic regression analysis for the statistically significant socio-demographic variables (adjusted odds ratio), *Vitória* city, *Espírito Santo* State, 2006.

Variable	Category	Death by prostate cancer				Death by other causes			
		p-value	OR	LI	LS	p-value	OR	LI	LS
Age group	≤ 49 y/o		1				1		
	50 to 69 y/o	0.275	0.43	0.1	1.95	0.612	1.73	0.21	14.23
	≥ 70 y/o	0.82	0.84	0.19	3.76	0.238	3.55	0.43	29.1
Marital status	Married		1				1		
	Single	0.585	1.17	0.66	2.07	0.78	0.92	0.53	1.62
	Divorced	0.883	0.93	0.37	2.33	0.946	1.03	0.44	2.4
	Widower	0.729	0.89	0.44	1.76	0.01	1.96	1.18	3.26
Diagnosis and previous treatment	Without both diagnosis and treatment	0.401	0.75	0.38	1.48	0.007	2.6	1.3	5.19
	With diagnosis and without treatment	0.398	0.79	0.46	1.36	0.249	1.42	0.78	2.59
	With both diagnosis and treatment	1				1			

Table 5 - Results of the multivariate logistic regression analysis for the statistically significant clinical variables (adjusted odds ratio), *Vitória* city, *Espírito Santo* State, 2006.

Variable	Category	Death by prostate cancer				Death by other causes			
		p-value	OR	LI	LS	p-value	OR	LI	LS
Gleason score	Up to 5	1				1			
	7	0.374	1.22	0.79	1.88	0.466	1.16	0.76	1.71
	8	0.708	1.11	0.64	1.95	0.846	0.95	0.54	1.65
	9	0.001	2.98	1.59	5.58	0.803	0.9	0.4	2.03
	10	0.013	9.95	1.62	56.32	0.551	1.76	0.15	20.55
PSA value	< 10	1				1			
	10 --- 20	0.301	1.38	0.75	2.52	0.382	1.22	0.78	1.89
	20 --- 50	0	2.82	1.62	4.92	0.32	1.28	0.79	2.07
	50 --- 100	0	4.67	2.4	9.07	0.005	2.41	1.3	4.48
	≥ 100	0	5.55	2.97	10.4	0.041	1.92	1.03	3.57
Initial clinical stage	1	1				1			
	2	0.911	0.88	0.1	7.94	0.291	0.49	0.13	1.85
	3	0.998	1	0.11	9.52	0.14	0.24	0.08	1.43
	4	0.915	0.88	0.09	8.48	0.285	0.44	0.1	1.97
	Metastasis	Yes	0	12.18	7.36	20.15	0.056	1.82	0.98
	No	1				1			

The greater the Gleason score and the presence of metastasis, the larger the risk of death due to specific cause; PSA greater than 20 increased the probability of death by PC, however when over 50 was associated with death from other causes, as well as being widowed and admitted to the hospital without diagnosis or treatment. Clinical variables predominated on prostate cancer-specific mortality and sociodemographic variables on deaths from other causes.

Age is a well-established risk factor in the natural history of the disease, less than 1% of the diagnoses occur before the age of 50,² which is not true when the age is above 65 years old.^{2,17,18} Considered a cancer of the elderly, it has slow progression, about 15 years for the growth of 1 cm to the cube, it is possible that the increase in its incidence is due in part to the increase in life expectancy and the evolution of diagnostic methods and health information systems.¹⁹ In this study, more than half of all cases were 70 years old or older.

Ethnicity/skin color is a potential risk factor.²⁰ PC is 1.6 times more common in black men, it is possible that this difference is due to lifestyle and factors associated with the detection of the disease.² There is no reason in order to see this variable with a purely biological view, it is a social variable, with marks of inequity in health,²¹ and influences other variables, such as schooling,²² and even mortality.²³

Low level of education in patients with PC is a common finding in profile studies,^{17,18} when inferior to full secondary education and associated with intermediate risk tumors²⁴ are factors that increase the chance of mortality, including other causes. The higher level of schooling favors the PSA test,²⁵ which may aid in early detection and follow-up. In the present study, of the patients who died of PC, more than half had not completed the first degree.

Prevalence of patients with married or cohabiting PC was characteristic of other studies.^{17,18} More than half of the men affirm that the family contributes positively to their health habits, helping in times of aggravation and clinical stability.²⁶ The state a widowed civilian patient presented as

a variable associated with mortality from other causes and may be related to the absence of the figure of a caregiver for this man, a fact that may make it impossible to attend the health unit regularly to care for chronic diseases.

The primacy of the region of metropolitan origin, in all categories (67.8%), is possibly related to greater access and accessibility to diagnosis, when compared to other regions. A study of mortality trends in the capitals and in the interior of Brazil diverges from the above when it finds, in all Brazilian regions, much worse mortality rates among men from the interior region.⁷

Patients from the SUS did not show statistical significance regarding mortality from either PC or other causes, but their characteristics differ from those of patients admitted by the private system or by agreement. Usually, these patients receive the diagnosis at the home service and initiate some treatment modality, aiming to administer a complement of their treatment in the hospital.

When access is assessed, those who arrive at the hospital without diagnosis and without treatment present a greater chance of mortality from other causes, which may show a fragility of the health system as a whole, since the man who has difficulty in early diagnosis and treatment opportunity for the PC possibly also have the other diseases.

The same interpretation can be made when assessing the association of the PSA value with mortality. The increase in this value is associated with an increase in mortality due to neoplasm, as can be expected, since it is a disease with a higher risk of progression,²⁴ although it is also associated with an increased risk of mortality from causes other than the PC, lack of access to routine consultations for screening for age-related diseases in the primary health care network. Another possibility is that patients who presented high PSA (above 50 ng/dL) and died due to other causes have omitted their true cause, due to misconception on the death certificate, lack of hospital follow-up, lack of family knowledge or by occurrence of death in other locations, without access to the patient's medical records, where direct complications of the underlying disease may have been confounding factors.

The early diagnosis of PC allows the implementation of a timely and radical treatment, which often contributes to the complete recovery of patients.²⁷ In the present study, men with initial staging (I and II) died more from other causes, and those with late staging III and IV) died of PC. The variable metastasis presented similar behavior; men with metastasis died more per PC, and those without metastasis, for other causes.

The Gleason Score is a graduation referring to the PC architecture standard, in which 1 would be the best-differentiated degree. Scores from 8 to 10 have a greater chance of recurrence and greater lethality compared to scores 2 to 6.²⁸ Their scores were directly related to the probability of the individual dying as a result of the neoplasm, and not due to other causes.

In 2008, the Health Ministry proposed the *Política Nacional de Atenção Integral à Saúde do Homem (PNAISH)* [National Policy for Integral Attention to Man's Health], reflecting a yearning for society to recognize that health problems are a public health problem, and increase the life expectancy of men by reducing morbidity and mortality from preventable and preventable causes.²⁹ Noting the vulnerability of the individual, *PNAISH* also provides comprehensive care for each stage of life, with primary prevention campaigns in youth and adult life and the screening of common problems in old age.

This policy reflects the needs of the man with PC in *Espírito Santo* State, a situation that probably reflects a national need. Variables associated with PC that result in increased mortality from this disease also reflect a general mortality, probably due to the lack of access to adequate resources or public policies focused on primary care and campaigns for the early diagnosis of chronic noncommunicable diseases, such as cardiovascular diseases, diabetes, and oncology. It is expected that further studies, after the implementation of the *PNAISH*, will reflect an improvement in the health conditions of this population group, showing a reduction in mortality parameters and a higher life expectancy for men.

Further information is required from the target population on the tests and methods used in the early detection of prostate cancer. The education in the health of the man must begin from the primary formation, contributing to generations more attentive to the health and without misconceptions about the accomplishment of the exams. Educating in health and promoting greater accessibility are undoubtedly fundamental points for the success of any public policy.

The fulfillment and valorization of public health policies for men, where there is an increase and a more flexible schedule in the service with free demand, can be a more effective gateway in health care, without interfering in the daily work of this population. It is also suggested an active search through family health teams with the encouragement and empowerment of men towards their health, followed by itinerant outpatient clinics with trained health personnel to carry out the PC monitoring efforts.

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