Sex as an independent prognostic factor in a population-based, non-small cell lung cancer cohort

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BACKGROUND: Males with non-small cell lung cancer (NSCLC) tend to experience worse outcomes, as do those with nonadenocarcinoma histology; however, the independent effects of these factors remain unclear.
OBJECTIVE: To evaluate the independent effect of sex and histology on mortality in a population of patients with NSCLC.
METHODS: All patients with NSCLC in Manitoba from 1985 to 2004 were identified from the Manitoba Cancer Registry. Treatment data were extracted from the Manitoba Health administrative databases and linked to the registry. Cox regression analysis was used to determine the independent effect of sex on survival.
RESULTS: A total of 10,908 patients (6665 male, 4243 female) with NSCLC were identified. Females had a median overall survival of 9.4 months versus 6.8 months for males (P<0.001). The adjusted HR for death for males compared with females was 1.13 (95% CI 1.04 to 1.23; P=0.004). Sex modified the effect of surgical treatment on survival (HR 1.26 [95% CI 1.13 to 1.40]; P<0.001). Adenocarcinoma histology modified the effect of sex on survival (HR 1.36 [95% CI 1.24 to 1.50]; P<0.001) when treatment was accounted for.
CONCLUSION: Females experienced a significantly better survival rate than males independent of treatment, age, year of diagnosis and histology. This was greatest in surgically treated patients and in those with adenocarcinoma.

Key Words: *Adenocarcinoma; Non-small cell; Sex; Survival; Treatment*

Le sexe comme facteur pronostique indépendant dans une cohorte en population de cancer pulmonaire non à petites cellules

HISTORIQUE : Les hommes ayant un cancer pulmonaire non à petites cellules (CPNPC) avaient tendance à présenter des issues plus négatives, de même que ceux qui avaient une histologie sans adénocarcinome. Cependant, les effets indépendants de ces facteurs ne sont pas clairs.
OBJECTIF : Évaluer l'effet indépendant du sexe et de l'histologie sur la mortalité dans une population de patients ayant un CPNPC.
MÉTHODOLOGIE : Les chercheurs ont extrait du Registre du cancer du Manitoba tous les patients ayant eu un CPNPC au Manitoba entre 1985 et 2004. Ils ont tiré les données thérapeutiques des bases de données administratives de Santé Manitoba et les ont liées au registre. Ils ont utilisé l'analyse de régression de Cox pour déterminer l'effet indépendant du sexe sur la survie.
RÉSULTATS : Au total, les chercheurs ont recensé 10 908 patients (6 665 hommes, 4 243 femmes) ayant un CPNPC. Les femmes présentaient une survie médiane globale de 9,4 mois par rapport à 6,8 mois chez les hommes (P<0,001). Le rapport de risque corrigé de décès chez les hommes par rapport aux femmes correspondait à 1,13 (95 % IC 1,04 à 1,23; P=0,004). Le sexe modifiait l'effet du traitement chirurgical sur la survie (RR 1,26 [95 % IC 1,13 à 1,40]; P<0,001). L'histologie de l'adénocarcinome modifiait l'effet du sexe sur la survie (RR 1,36 [95 % IC 1,24 à 1,50]; P<0,001) lorsqu'on tenait compte du traitement.
CONCLUSION : Les femmes présentent un taux de survie significativement plus positif que les hommes, quels que soient leur traitement, leur âge, l'année de leur diagnostic et leur étiologie. Cette différence était plus prononcée chez les patients opérés et chez ceux ayant un adénocarcinome.

Lung cancer is the most common cancer in the world and non-small cell lung cancer (NSCLC) is its largest subtype. The incidence of NSCLC continues to rise; however, since approximately 1985, this increase in incidence has only been apparent in females (1-5). Females tend to present at a younger age and with more advanced disease than males (2,4). Despite this apparent disadvantage, survival after a diagnosis of lung cancer appears to be superior in females compared with males for both NSCLC and small-cell lung cancer (SCLC) (6-12). Furthermore, females are more likely to develop adenocarcinoma than males (11). Sex-specific genetic profiles of tumour tissue have been reported and have been found to correlate with clinical outcome (13). This disparity between the sexes is likely multifactorial and may be due to increased carcinogen sensitivity, a predisposition to specific molecular aberrations, and estrogen-mediated effects through estrogen receptors in lung tissue and other receptors that stimulate cellular proliferation (2-4).

Females appear to respond better to treatment and survive longer than males. In a study of patients with stage I to III NSCLC treated uniformly, females were found to have a more favourable survival rate compared with males at the same stage (14). A larger study of patients with resectable NSCLC supported this finding, but only in patients with adenocarcinoma (15). In advanced disease, re-analysis of clinical trial data suggests an improved overall survival rate with platinum-based chemotherapy in females with adenocarcinoma compared with males (12,16). In contrast, similar analyses, including early stage and advanced NSCLC and SCLC, have shown no overall survival advantage for females (17). Furthermore, in patients with advanced NSCLC, female Asian nonsmokers with adenocarcinoma may be more likely to respond to targeted inhibition of the epidermal growth factor receptor; however, other studies do not support this assertion (18,19). Because treatment at all stages has the potential to influence survival, a complete assessment of the independent effect of sex on survival must consider the treatment pattern and changes in histology over time.

Manitoba is a Canadian province with a stable population of 1.2 million, with approximately 800 new cases of lung cancer diagnosed per year. Health care is provided to all citizens through a public-payer system. The Manitoba Cancer Registry (MCR) captures all malignant diagnoses in the province and all physician billing is captured through administrative databases. We compiled a cohort of all NSCLC patients from 1985 to 2004, which included demographic and treatment data (20). Using this large, robust population-based cohort of NSCLC patients, we tested the hypothesis that female sex is an independent prognostic factor for survival and that adenocarcinoma histology modifies the effect of sex on survival.

METHODS

Databases

Since the early 1970s, physician contact and intervention through billing tariffs and *International Classification of Diseases* (ICD) diagnostic codes have been coded in the Manitoba Health administrative

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databases. The administrative database has been described previously (21). In 1984, a personal health identification number was assigned to each person covered by the provincial health care plan. All neoplastic diagnoses since 1956 have been collected in the MCR through a mandatory reporting system that also captures treatment and demographic data. The accuracy of the MCR was found to be 95% to 98% complete for case ascertainment when examined by the North American Association of Central Cancer Registries (22). Using the personal health identification number, these databases were linked to provide a comprehensive representation of treatment and outcomes.

Cohort and data collection

All patients diagnosed with NSCLC from January 1, 1985 to December 31, 2004, were identified from the MCR using the corresponding ICD-9 or ICD-10 codes. These dates were chosen to include major factors in treatment and outcome before the widespread use of adjuvant and targeted therapy. These data were linked to the administrative database. The following data were extracted: ICD-9 or ICD-10 codes for NSCLC, histology, number of primary lung cancers, diagnosis date, date of birth, date of death, sex, treatment ICD and treatment dates occurring on or following the date of diagnosis. Histology was categorized as squamous carcinoma (ICD-O: 8052/3, 8070/3, 8071/3, 8072/3, 8074/3, 8430/3), adenocarcinoma (ICD-O: 8012/3, 8140/3, 8250/3, 8251/3, 8260/3, 8262/3, 8310/3, 8480/3, 8481/3, 8490/3, 8560/3) or NSCLC not otherwise specified (ICD-O: 8010/3, 8021/3, 8031/3). Stage data were available and extracted for 1999 and 2004. The diagnosis date is recorded in the MCR as the first sample date of pathologically confirmed NSCLC. Treatment information for subjects with multiple primary tumours diagnosed on the same day (ie, simultaneous diagnoses) was recorded as one cancer. Multiple primary lung cancers with different diagnosis dates (sequential diagnoses) were considered as new events, with treatment information recorded from the diagnosis date of the first cancer until the diagnosis date of the subsequent primary lung cancer. Approval from the University of Manitoba Research Ethics Board (Winnipeg, Manitoba) was obtained, as were waivers of informed consent.

Analysis

The primary outcome was survival from the date of diagnosis of females compared with males. Based on a two-sided α of 0.05 and a β of 0.20, the required number of events to detect an estimated unadjusted HR of 1.3 between males and females was calculated to be 5119. To capture all possible treatments, subjects were considered to have undergone surgery, chemotherapy or radiotherapy (RT) if the appropriate tariff code was found in either the MCR or administrative database at any point on or after the diagnosis date. The percentage of patients in each yearly cohort whose initial treatment was chemotherapy, RT or surgery was calculated. Subjects were included in only one treatment category. Patients with no record of treatment in either the MCR or administrative database were considered to have received only supportive care. Diagnoses made at autopsy or from a death certificate were included in the supportive care group. Patients with missing data for date of death were considered to be alive and censored for survival analysis at October 1, 2007. Treatment pattern, demographics and survival according to treatment group for this cohort have previously been reported (20).

Analysis consisted of multiple linear regression models with generalized estimating equations and robust variance estimation to account for within-year correlations (23). Quantile linear regression was used to estimate changes in median survival over time (24). The final multivariable model for median survival included treatment group, age, sex and year of diagnosis with a linear spline term at 1995, and accounted for a sex-treatment group interaction and a histology-sex interaction. Model fit was determined by residual analysis and removal of collinear variables. There were no missing data encountered. HRs for death were estimated using the Cox proportional hazards model. The final Cox model included sex, the interaction between treatment group and sex, and the interaction between histology and sex, and was stratified according to age, treatment group, year of diagnosis and histology. Cox model selection was based on minimization of Akaike's information criterion and underlying scientific knowledge of the disease. The proportional hazards assumption was met on the basis of Schoenfeld's residuals. Database administration was performed using SAS version 9.1 (SAS Institute Inc, USA), and data analysis was performed using STATA version 10.0 (StataCorp, USA) (25).

TABLE 1
Patient characteristics

	1985 to 1994 (n=5267)	1995 to 2004 (n=5641)	Total (n=10,908)
Female sex	33.6	43.8	38.9
Age, years, mean	67.9	69.5	68.7
Histology			
Adenocarcinoma	45.8	49.5	47.7
Squamous carcinoma	36.2	25.9	30.9
Other	18.0	24.6	21.4
Treatment group			
Surgery	33.0	28.9	30.9
Chemotherapy	3.6	9.6	6.7
Radiation therapy	35.9	29.5	32.6
Supportive care	27.5	32.0	29.8

Data presented as % unless otherwise indicated

RESULTS

Demographics

A total of 10,908 cases of NSCLC were identified from the MCR, with 9615 deaths as of October 1, 2007. Of these patients, 38.9% (n=4243) were female (Table 1). The mean age at diagnosis was 69.2 years for males and 67.9 years for females (P<0.0001). The mean age increased by 0.18 years per annum for both sexes (P<0.001). A change in the sex distribution was found, with 30.7% female in 1985 increasing to 47.8% in 2004 (annual per cent change [APC] 1.00; P<0.0001).

The proportion of female patients in each treatment group increased with each year from 1985 except those treated with upfront chemotherapy (surgery APC 1.1 [95% CI 0.8 to 1.4]; P<0.001; chemotherapy APC 0.2 [95% CI –0.5 to 0.9]; P=0.637; RT APC 0.8 [95% CI 0.6 to 1.1]; P<0.001; and supportive care APC 1.1 [95% CI 0.8 to 1.4]; P<0.001).

Survival

The unadjusted median overall survival rate was higher for females than for males, with an unadjusted HR of death for males relative to females of 1.29 (95% CI 1.24 to 1.34; P<0.001). The Kaplan-Meier survivor function is shown in Figure 1. Survival of females was significantly better than for males by log-rank test stratified according to treatment group, age, year of diagnosis and histological subtype (P<0.0001). In patients with adenocarcinoma, the unadjusted HR for death of males relative to females was 1.51 (95% CI 1.42 to 1.60; P<0.001) (Figure 2). In contrast, in those with nonadenocarcinoma histology, the unadjusted HR for death between males and females was 0.99 (95% CI 0.93 to 1.05; P=0.751) (Figure 2).

Multivariable quantile linear regression was used to determine the median survival of males and females according to treatment group, controlling for age, histology and year of diagnosis (Table 2). For males, median survival did not change significantly over time (0.03 months per annum [95% CI –0.10 to 0.15]; P=0.662), whereas the median survival increased over time for females after 1995 (–0.02 months per annum from 1985 to 1995 [95% CI –0.38 to 0.34]; P=0.918; 0.38 months per annum from 1995 to 2004 [95% CI 0.04 to 0.71]; P=0.029) as shown in Figure 3. With treatment group in the model, age and year of diagnosis did not significantly impact survival; however, sex and treatment group remained strong predictors of survival.

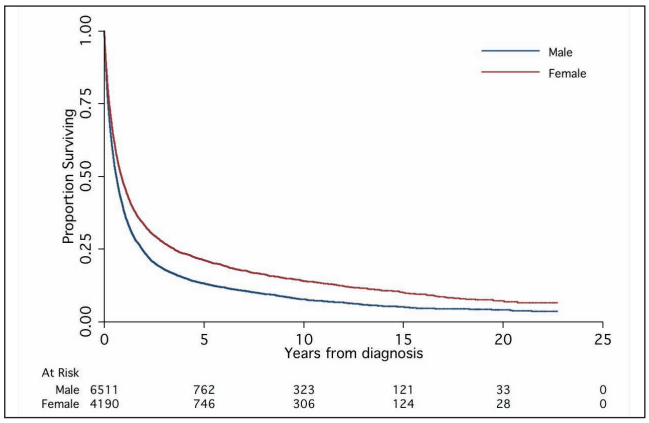

Figure 1) *Kaplan-Meier survival function. Unadjusted male versus female*

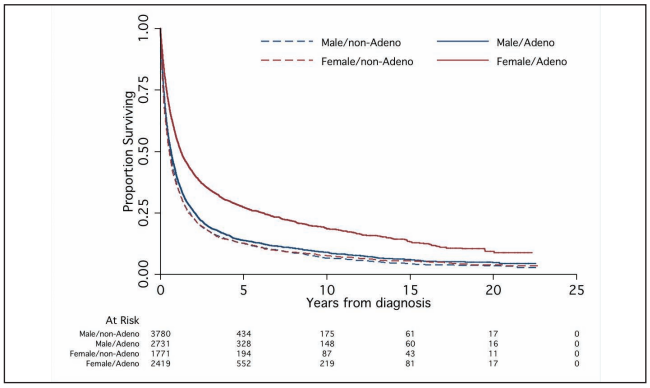

Figure 2) *Kaplan-Meier survival function. Unadjusted male versus female, stratified according to histology. Adeno Adenocarcinoma*

Using the multivariable Cox model with the best fit, the HR for death for males relative to females was 1.13 (95% CI 1.04 to 1.23; P=0.004), accounting for age, treatment group, year of diagnosis and histology. Sex modified the effect of treatment on survival such that males undergoing surgery had an HR for death of 1.26 (95% CI 1.13 to 1.40; P<0.001) relative to females undergoing surgery. This effect modification was not apparent in patients undergoing primary chemotherapy (HR 1.06 [95% CI 0.89 to 1.26]) or RT (HR 1.08 [95% CI 0.99 to 1.17]).

There was a statistically significant interaction between sex and histology, with an HR of 1.20 (95% CI 1.10 to 1.32; P<0.001) for nonadenocarcinoma relative to adenocarcinoma (Figure 2). The combination of these effects estimated that male patients with adenocarcinoma who underwent surgery had an HR for death of 1.51 (95% CI 1.38 to 1.66; P<0.001) relative to female patients with adenocarcinoma who underwent surgery. Similarly, for patients with adenocarcinoma not treated with surgery, sex significantly modified the effect of primary chemotherapy (HR 1.27 [95% CI 1.08 to 1.50]; P=0.004) and primary RT (HR 1.30 [95% CI 1.19 to 1.42]; P<0.001) on survival.

Sensitivity analysis of the nonadenocarcinoma group confirmed the adjusted effect of sex on survival in this group. Accounting for treatment group, age, year of diagnosis and interactions, males experienced significantly worse survival than females (HR 1.15 [95% CI 1.02 to 1.24]; P=0.015).

DISCUSSION

The survival of females with NSCLC in this particular population-based cohort was superior to males from 1985 to 2004. This remained true after accounting for age, histology, treatment group and the changes in these variables (including sex) over time. Female sex was, therefore, found to be a good, independent prognostic factor in NSCLC.

TABLE 2
Median survival according to treatment group and sex

Treatment group	Patients, n (deaths, n)	Survival, months, median	95% CI	P
Surgery				
Male	1950 (1549)	33.4	32.9–33.9	<0.001
Female	1420 (918)	53.3	52.8–53.9	
Chemotherapy				
Male	396 (380)	8.5	7.6–9.4	0.010
Female	338 (320)	10.1	9.2– 1.0	
Radiation therapy				
Male	2279 (2244)	6.0	5.5– 6.5	0.042
Female	1276 (1238)	6.6	6.0–7.1	
Supportive care				
Male	2040 (2007)	1.9	1.3–2.4	0.287
Female	1209 (1166)	2.2	1.6–2.8	
Overall				
Male	6665 (6180)	6.8	6.0–7.6	<0.001
Female	4243 (3642)	9.4	8.7–10.1	

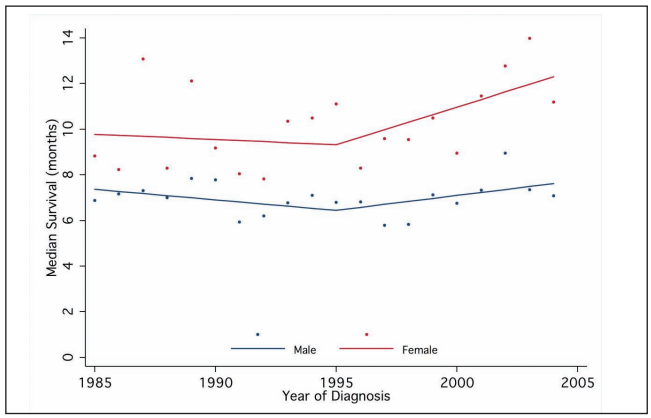

Figure 3) *Median survival duration for males and females according to year of diagnosis*

The superior survival rate of females with NSCLC treated with upfront surgery has been previously examined, although not all studies have demonstrated a difference (Table 3) (6,7,15-17,26-31). In addition, investigators who examined histology have generally shown that this difference in survival was greater in individuals with adenocarcinoma (7,15,16,28-30). Our population-based results of 10,908 patients demonstrate that sex impacts survival regardless of treatment group and that this effect is strongest in individuals treated surgically. Females treated with upfront surgery, on average, survived nearly 20 months longer than males, accounting for age and year of diagnosis. Our large sample size and ability to control for year of diagnosis and nonsurgical treatments may have enabled detection of these differences while other studies could not. We have previously reported a disproportionate increase in the percentage of females undergoing upfront surgical resection, which could influence our results (20). The percentage of females in the entire cohort increased by 1% per year and by 1.1% per year in the surgical group; therefore, this disproportionate increase is minor compared with the large relative survival advantage we have noted for females with NSCLC in the present analysis. We have also reported an increase in survival rate for this population after 1997, and suggested that this was due to improvements in clinical care (20). Controlling for sex, histology and treatment, the independent effect of year of diagnosis on survival was not statistically significant in the present analysis, yet it remained an essential component of the multivariable model and is graphically

TABLE 3
Published data for sex and histology as prognostic factors in non-small cell lung cancer

Author (reference), year	Study information	Sex	Histology	Comments
Wheatley-Price et al (16), 2010	Pooled analysis of 5 clinical trials (n=2349)	Median OS (months): 9.6 (F) vs 8.6 (M); HR 0.83; P=0.0005	Adeno HR 0.70; P<0.0001; Non-adeno HR 0.97; P=0.61	All patients had advanced disease
Wheatley-Price et al (17), 2010	Pooled analysis of 3 clinical trials (n=1108)	PFS HR 0.83; P=0.02; OS HR 0.89; P=0.17	Not reported	
Chang et al (15), 2009	National Cancer Center Hospital, Tokyo (n=2770)	5-year OS: 81% (F) vs 70% (M)	5-year OS: adeno 84% (F) vs 75% (M); P<0.001 Nonadeno 64% (F) vs 58% (M); P=0.299	Only surgical patients included; no difference after propensity matching
Caldarella et al (7), 2007	Tuscan Cancer Registry (n=2523)	5-year OS: 10.5% (F) vs 9.4% (M) P=0.3	5-year OS: 16% (adeno) vs 11% (squam); P=0.02	OS difference apparent in surgical patients: 36.5% (F) vs 29.4% (M)
Albain et al (26), 2007	Pooled analysis of 6 clinical trials (n=1324)	Median OS (months): 11 (F) vs 8 (M); HR 0.86; P=0.02	Not reported	All patients had advanced disease
Efficace et al (27), 2006	Prospective cohort, Belgium (n=391)	HR 0.76; P=0.03	Not reported	All patients had advanced disease
Wakelee et al (28), 2006	Evaluation of clinical trial ECOG 1594 (n=1157)	Median OS (months): 9.2 (F) vs 7.4 (M); P=0.004	Not significant	All patients had advanced disease
Batevik et al (6), 2005	Haukeland University Hospital, Norway (n=351)	5-year OS: 66.1% (F) vs 45.7% (M); HR 0.50; P<0.001	Not reported	Only surgical patients included
Hoang et al (29), 2005	Pooled analysis of 2 clinical trials (n=1436)	Not significant	Not significant	Includes ECOG 1594 data
Visbal et al (30), 2004	Prospective cohort, Mayo Clinic, Minnesota, USA (n=4618)	5-year OS: 19% (F) vs 15% (M), HR 0.83	OS in those with adeno HR 0.73; P<0.01	
Albain et al (31), 1991	Pooled analysis of 14 clinical trials (n=2531)	HR 0.77; P<0.00005	Not reported	All patients had advanced disease

HR (reported as risk of death for females relative to males). adeno Adenocarcinoma; ECOG Eastern Cooperative Oncology Group; F Female; M Male; OS Overall survival; PFS Progression-free survival; squam Squamous carcinoma; vs Versus

notable (Figure 3). This suggests that improvements in clinical outcome over time are largely driven by changes in disease demographics (ie, increasing percentage of females, adenocarcinoma and surgical treatments) rather than merely improvements in clinical care.

Our results confirm that sex interacts with histology to additionally impact survival, suggesting that the host-tumour interaction plays a significant role in determining outcome. Possible mechanisms for this interaction may include estrogen-specific effects on adenocarcinoma or differences in the genetic profiles of the adenocarcinomas that develop in males and females. In contrast to previous studies, we have determined that sex remains an independent prognostic factor regardless of histology. The improved outcome for females is not only due to the increasing proportion with adenocarcinoma but also to an underlying biological difference between the sexes and/or the lung cancers that develop in each sex.

The current analysis was chosen based on a number of strengths. First, a large, unique database that enabled the capture of patient-level treatment information for the entire population was used. By including treatment group in our survival models, we were able to determine the independent effect of sex on survival. Although our data do not contain cancer stage information for all years, treatment group and stage were very closely related (kappa 0.75 to 0.78) for the years that stage data were available. The MCR also enables nearly complete case ascertainment and follow-up. Furthermore, the long follow-up period in our study allowed for the median survival to have been reached in each year of study. By regressing median survival across years of diagnosis, we were able to describe the time trend of survival for sequential cohorts of patients with NSCLC. It should be noted that although our cohort contained data regarding treatment, histology, survival and demographics, we were not able to obtain clinical details (such as smoking status) or molecular markers, which may have contributed additional prognostic information.

We demonstrated an independent and significant positive effect of female sex on survival in NSCLC in addition to a strong interaction between sex and adenocarcinoma. These effects were strongest in early stage disease in which patients are treated surgically, where the underlying biological differences may reduce the risk of recurrence and, therefore, have a greater impact. The mechanisms behind this difference remain unclear, yet the same factors that increase the sensitivity of females to tobacco-smoke carcinogens may also be responsible for the decreased risk of death after the development of disease and the interaction with histology (32). The biological difference may also relate to the potential advantages noted in subgroup analyses of large clinical trials with targeted therapy on the nonsmoking Asian female population (18). Because sex, histology and treatment group have such a significant effect on survival, this effect must be accounted for in the design, analysis and interpretation of clinical trials for NSCLC. Finally, we must consider these findings when counselling patients and not assume that treatment will be equally effective for male and female patients with NSCLC.

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AUTHOR CONTRIBUTIONS: MWP designed the study, analyzed the data and wrote the manuscript; GM compiled and analyzed the data; SN designed the study and revised the manuscript.

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