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# Postoperative Survival in Gastric Cancer Patients and its Associated Factors: A Method Based on a Non-homogenous Semi-Markovian Process

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**Abstract:** This study was designed and carried out to determine the five-year survival rate of gastric cancer patients who had undergone surgical treatment at one of the most important cancer treatment centers, the Iran Cancer Institute and to assess its associated factors. During a study period, patients may often experience events that are likely to affect the final outcome as well. Should these intermediate events and their time of occurrence be overlooked, they may bias the results of the study. It has been suggested that such variables be assigned in the model as time-dependent covariates, but using models with joint distribution of time before death and time before an intermediate event (in this study, relapse), although more difficult, will certainly provide more accurate results. In this study we analyzed the data using a non-homogenous semi-Markovian stochastic process, which basically, regarding life span and intensity rate as the stochastic processes, was a doubly stochastic process and recommend it for analyses of similar data. Two hundred and 81 gastric cancer patients with adenocarcinomatous pathology who had been admitted to and operated on at the Iran Cancer Institute between March 1995 and March 1999 were enrolled in this study. The patients' life expectancy after surgery was determined and its relationship with variables of age at the time of surgery, gender and factors related to the disease such as the cancer site, stage, presence of metastases and sites of metastasis were assessed. In the analyses, methods of Kaplan-Meier, Cox proportional hazards model, non-homogenous Markovian process and Breslow estimator were used. The software used for the analyses were S Plus 2000 and R and an alpha level of 0.05 was considered significant. The five-year survival rate and the median life expectancy in the studied patients were 22.6% and 19.00 months, respectively. The Cox proportional hazards model was used to assess the effect of different variables simultaneously and it showed that age, lymph node metastasis, recurrence and disease stage influenced the chances of survival. It was also shown that lymph node metastasis and disease stage correlated with time of recurrence, while age, distant metastasis and disease stage affected survival after recurrence and age correlated with survival of patients without recurrence. Gastric cancer patients in Iran have a low five-year survival rate. One of the most important reasons seems to be delayed consultation and diagnosis. Most patients are seen first with the disease in the late stages. At this point, most have lymph node, liver, or even distant metastases which makes treatment even more complex. Thus, it is necessary to employ mass media for extensive public education about the early warning signs of the disease and performing periodic examinations.

**Key words:** Survival, gastric cancer, Cox proportional hazards model, semi-Markovian process, doubly stochastic process

## INTRODUCTION

During recent years, improved hygiene in Iran has reduced deaths from infectious diseases and cancers have become a major contributing factor to the Iranian population death rate. Lack of precise and efficient cancer registries makes the number of cancer patients and the annual occurrence of new cases unknown. However, estimates show that the standardized occurrence in 1998 in the capital, Tehran, was 130.9 and 109.8 in 100,000 for men and women, respectively[1]. Considering the probable under estimations, the exact number of cancer deaths

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is not known either, but it has been estimated that in 1998 more than 27 thousand cancer deaths occurred in the 70 million Iranian population[1].

Several reports have stated that gastric cancer is prevalent in Iran, being the second most common cancer in men and the fourth in the general population. Unfortunately, gastric cancer patients in Iran seek medical attention when the disease has reached an advanced stage and is therefore very lethal[1-3].

Determining patients' survival rate is a very important aspect of cancer research. In this regard, several studies have been carried out in different countries. In case of gastric cancer patients, the postoperative five-year survival rate has been reported 29.6% in China, 4.4% in Thailand, 37.0% in the United States, 22.0% in Switzerland and 30.0% in France[4-8].

Various factors affecting survival in these patients have also been investigated; age, disease stage and occurrence of metastasis have been mentioned[4-28].

This study was designed and carried out to determine the five-year survival rate of Iranian gastric cancer patients who received surgical treatment at the most important cancer treatment center in Iran, the Iran Cancer Institute and to evaluate some affecting factors.

Today, many medical and epidemiologic investigations are dedicated to the study of patient survival probability. In these studies, focus lies on patient death due to a definite cause, while some events that can alter final results often happen to patients. Should these intermediate events and their time of occurrence be overlooked, they may bias the results of the study[21-24]. It has been suggested that such variables be entered into the model as time-dependent covariates, but using models with joint distribution of time before death and time before an intermediate event, although not so simple, will certainly provide more accurate results[25-28]. In this study we analyzed the data using a non-homogenous semi-Markovian stochastic process, which basically, regarding life span and intensity rate as the stochastic processes, was a doubly stochastic process[29] and recommend it for analyses of similar data.

## MATERIALS AND METHODS

In this study, 281 gastric cancer patients with adenocarcinomatous pathology who were admitted and operated on at the Iran Cancer Institute from March 1995 to March 1999 were enrolled. The postoperative life span of these patients was determined. Right censor was applied since the final day to those who survived the study period and other certain dates for those who were lost to follow-up. Two hundred and seven patients deceased during the study period, in 11 of which death had other causes and so were right censored from their death dates.

Individual variables such as age (at the time of surgery), gender (male-female) and those related to the disease such as its site (cardia-antrum-other), stage (I-II-III-IV), presence of metastases (positive-negative), site of metastasis (lymph nodes-liver-distant), type and extent of surgery (Total Gastrectomy (TG), Subtotal Gastrectomy (SG), Distal Gastrectomy (DG), Partial Gastrectomy (PG) and Proximal Gastrectomy (PXG)), number of affected lymph nodes and complementary or secondary treatments received (chemotherapy-radiotherapy-surgery-combination), relapse and the interval between surgery and relapse were assessed for their effect on patients' life expectancy.

Staging was followed by AJCC[30] In the analyses, methods of Kaplan_Meier, Cox proportional hazards model, multi-state stochastic processes, Breslow estimator were used in S_PLUS 2000 and R software and an alpha level of 0.05 was considered significant.

## RESULTS

The studied patients were male in 71.2% of cases and their median age was 68 years (range, 32 to 96 years). The cancer site was the cardia in 39.9% and the anterior in 20.6% of patients. Metastases were found in 166 (59.1%) patients; 77.7% of these patients had metastases in the lymph nodes, 10.8% in the liver and 21.7% had distant metastases. The surgical procedure was total gastrectomy in 52.3% and subtotal gastrectomy in 27.0%, while distal, partial and proximal gastrectomy was performed in 2.8, 8.5 and 9.3%, respectively. For reconstruction, esophagojejunostomy was the choice in 50.9% of patients, 27.6% received gastrojejunostomy, in 13.6% esophagogastrostomy was performed, while colon bypass, Billroth II and colostomy were carried out in 3.3, 3.1 and 1.5%, respectively. Affected nodes were found in 45.9% of patients with a median positive node count of 8 (range, 2 to 18). Pathologic stage distribution included stages IA (2.8%), IB (3.6%), II (17.4%), IIIA (13.9%), IIIB (2.8%) and IV (59.4%). All stage IV assignments were due to an N3 category, a T4 classification, or a T3 classification with M1. While 19.2% of patients had received no secondary treatment, such treatments were tried three times in another 26.0% of them. Relapse was reported in 56.9% of patients and the median disease-free interval was 11.63 months (range, 10.27 to 12.99 months). Using the method of Kaplan_Meier, the five, three and one year survival rates were computed as 22.6, 32.5, 66.8%, respectively and the median life span was 19.00 months.

Table 1: Estimated effects in a Cox model for the total mortality

| Variables | Regression coefficient | Standard error | Wald | Degree of freedom | p-value | Relative risk | 95% CI for relative risk |
|---|---|---|---|---|---|---|---|
| Age (year) | 0.023 | 0.008 | 8.552 | 1 | 0.003 | 1.023 | 1.008-1.039 |
| Stage** | | | 21.667 | 3 | 0.000 | | |
| Stage (2) | 0.382 | 0.391 | 0.957 | 1 | 0.328 | 1.465 | 0.682-3.150 |
| Stage (3) | 1.023 | 0.379 | 7.290 | 1 | 0.007 | 2.783 | 1.324-5.849 |
| Stage (4) | 1.406 | 0.385 | 13.363 | 1 | 0.000 | 4.079 | 1.919-8.667 |
| Lymph node metastases | 0.580 | 0.208 | 7.785 | 1 | 0.005 | 1.787 | 1.188-2.686 |
| relapse | 0.925 | 0.155 | 35.564 | 1 | 0.000 | 2.522 | 1.861-3.419 |

*Variable(s) entered at step No. 1: Sex, Age, tumor site, lymph node metastases, liver metastases, distant metastases, stage, relapse, smoking history, type of gastrectomy

Variable removed at step No. 2: Liver metastases
Variable removed at step No. 3: Smoking history
Variable removed at step No. 4: Distance metastases
Variable removed at step No. 5: Sex
Variable removed at step No. 6: Tumor site
Variable removed at step No. 7: Type of gastrectomy

**Baseline is Stage=1

Table 2: Estimated effects in a Cox model for the total mortality with a time-dependent variable (time to relapse)

| Variables | Regression coefficient | Standard error | Wald | Degree of freedom | p-value | Relative risk | 95% CI for relative risk |
|---|---|---|---|---|---|---|---|
| Age (year) | 0.033 | 0.011 | 8.726 | 1 | 0.003 | 1.033 | 1.011-1.056 |
| Stage** | | | 7.097 | 3 | 0.041 | | |
| Stage (2) | 0.323 | 0.656 | 0.243 | 1 | 0.622 | 1.382 | 0.382-4.994 |
| Stage (3) | 0.986 | 0.639 | 2.381 | 1 | 0.123 | 2.681 | 0.766-9.383 |
| Stage (4) | 1.042 | 0.606 | 2.955 | 1 | 0.086 | 2.836 | 0.864-9.309 |
| Distant metastases | 0.666 | 0.273 | 5.970 | 1 | 0.015 | 1.946 | 1.141-3.320 |
| Time to relapse (months)*** | | | 19.198 | 2 | 0.000 | | |
| Waiting time ≤ 6 months | 1.221 | 0.281 | 18.843 | 1 | 0.000 | 3.391 | 1.954-5.884 |
| 6 months≤waiting time≤12 months | 0.432 | 0.245 | 3.120 | 1 | 0.077 | 1.541 | 0.954-2.490 |

*Variable(s) entered at step No. 1: Sex, age, tumor site, lymph node metastases, liver metastases, distant metastases, stage, smoking history, type of gastrectomy, time to relapse, ** Baseline is Stage=1, *** Baseline is Time to relapse = 12 months

The marginal distribution of survival time regardless of the disease-free interval before relapse was studied with the Cox proportional hazards model. Therefore, the function of hazard for person I with covariate vectors of Zi, unspecified baseline hazard function of $h_0(t)$ and regression coefficient of $\beta$ were:

$$h_i(t|Z_i) = h_0(t)\exp(\beta' Z_i)$$

and through calculating the Wald statistic, the variables influencing survival were determined. The effects of these variables on patient survival were simultaneously measured. This showed that variables of age, lymph node metastasis, disease stage and relapse related to patients' life expectancy (Table 1). The risk of death for patients afflicted with stage 2, 3 and 4 of the disease was respectively, 1.47 (95% confidence interval: 0.68 to 3.15), 2.78 (95% confidence interval: 1.32 to 5.85) and 4.08 (95% confidence interval: 1.92 to 8.67) times greater than those with stage 1. Lymph node metastasis and relapse increased this risk 1.79 (95% confidence interval: 1.19 to 2.69) and 2.52 (95% confidence interval: 1.86 to 3.42) times. The risk of death also increased with age; 1.02 (95% confidence interval: 1.01 to 1.04) times per year.

In the next stage, considering the time-dependent covariate related to the interval before relapse and using the model below:

$$h_i(t|Z_i) = h_0(t)\exp(\beta' Z_i + aZ_{2i}(t))$$

we found that chance of survival was not only affected by variables of age, distant metastases, disease stage and disease-free interval before relapse, but also by this time-dependent covariate and a longer survival without relapse decreased the risk of death. This analysis (Table 2) showed that the risk of death for patients afflicted with stage 2, 3 and 4 of the disease was respectively 1.38 (95% confidence interval: 0.38 to 4.99), 2.68 (95% confidence interval: 0.77 to 9.38) and 2.84 (95% confidence interval: 0.86 to 9.31) times greater than those with stage 1. Being free of cancer relapse for less than 6 months, compared to more than one year, increased the risk of death 3.39 (95% confidence interval: 1.95 to 5.88) times. When relapse occurred between 6 to 12 months, this risk was 1.54 (95% confidence interval: 0.95 to 2.49) times greater in comparison to relapse after one year. The increase in risk of death was 1.03 (95% confidence interval: 1.01 to 1.06) times greater per year with aging (Table 2). This is strong

Table 3: Estimated effects in a Cox model for the relapse intensity with Breslow Estimation Method

| Variable | Regression coefficient | Standard error | Wald | Degree of freedom | p-value | Relative risk | 95% CI for relative risk |
|---|---|---|---|---|---|---|---|
| Stage** | | | 12.122 | 3 | 0.006 | | |
| Stage (2) | 0.690 | 0.402 | 2.949 | 1 | 0.086 | 1.994 | 0.907-4.381 |
| Stage (3) | 0.665 | 0.414 | 2.578 | 1 | 0.108 | 1.944 | 0.864-4.377 |
| Stage (4) | 1.282 | 0.406 | 9.955 | 1 | 0.002 | 3.604 | 1.625-7.992 |
| Lymph node metastases | 0.749 | 0.225 | 11.074 | 1 | 0.001 | 2.114 | 1.360-3.286 |

*Variable(s) entered at step No. 1: Sex, age, tumor site, lymph node metastases, liver metastases, distant metastases, stage, smoking history, type of gastrectomy, ** Baseline is Stage=1

Table 4: Estimated effects in a Cox model for the mortality after relapse with Breslow Estimation Method

| Variable | Regression coefficient | Standard error | Wald | Degree of freedom | p-value | Relative risk | 95% CI for relative risk |
|---|---|---|---|---|---|---|---|
| Age (year) | 0.036 | 0.011 | 11.281 | 1 | 0.001 | 1.037 | 1.015-1.059 |
| Stage** | | | 6.752 | 3 | 0.045 | | |
| Stage (2) | 0.475 | 0.647 | 0.539 | 1 | 0.463 | 1.608 | 0.452-5.718 |
| Stage (3) | 0.994 | 0.634 | 2.453 | 1 | 0.117 | 2.701 | 0.779-9.366 |
| Stage (4) | 1.119 | 0.596 | 3.517 | 1 | 0.061 | 3.061 | 0.951-9.851 |
| Distant metastases | 0.528 | 0.259 | 4.166 | 1 | 0.041 | 1.695 | 1.021 -2.815 |

*Variable(s) entered at step No. 1: Sex, age, tumor site, lymph node metastases, liver metastases, distant metastases, stage, smoking history, type of gastrectomy, **Baseline is Stage=1

Table 5: Estimated effects in a Cox model for the mortality without relapse with Breslow Estimation Method

| Variable | Regression coefficient | Standard error | Wald | Degree of freedom | p-value | Relative risk | 95% CI for relative risk |
|---|---|---|---|---|---|---|---|
| Age (year) | 0.040 | 0.012 | 11.276 | 1 | 0.001 | 1.040 | 1.017-1.065 |

*Variable(s) entered at step No. 1: Sex, age, tumor site, lymph node metastases, liver metastases, distant metastases, stage, smoking history

evidence to consider an intermediate situation for analyzing survival.

In the next stage, three different situations were considered for each patient (Fig. 1); zero was assigned for survival without relapse, 1 for relapse and 2 for death. The probability of transition to these situations and their respective rates were taken into account and the effect of various factors on these transitions and the interval between them were assessed (Appendix 1).

Analysis of variables influencing the period remaining in status zero (alive) without transition to status 1 (relapse) showed that lymph node metastasis and disease stage affected the delay in relapse. The risk of occurrence, according to these analyses, for patients in stage 2, 3 and 4 was, respectively 1.99 (95% confidence interval: 0.91 to 4.38), 1.94 (95% confidence interval: 0.86 to 4.38) and 3.60 (95% confidence interval: 1.63 to 7.55) times greater than for those in stage 1. With lymph node metastases, risk of relapse increased 2.11 times (95% confidence interval: 1.36 to 3.29) (Table 3).

Survival of patients with relapse, i.e. remaining in status 1 without transition to status 2 (Fig. 1), was studied using the Breslow estimator. In these cases, variables of age, distant metastasis and disease stage influenced survival. We found that risk of death for this group increased 1.040 (95% confidence interval: 1.02 to 1.06) times per year with age. The risk of death for patients in stage 2, 3 and 4, in comparison to those in stage 1, was respectively, 1.61 (95% confidence interval: 0.45 to 5.72),

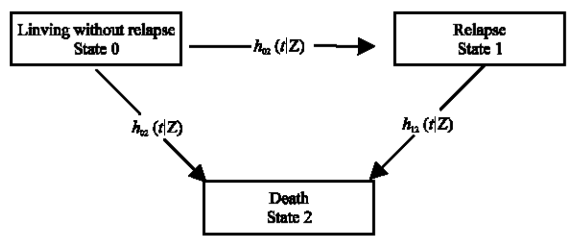


Fig. 1: A three state stochastic process

2.70 (95% confidence interval: 0.78 to 9.37) and 3.06 (95% confidence interval: 0.95 to 9.85) times greater (Table 4). In case of patients without relapse, i.e. remaining in status zero without transition to status 2 (Fig. 1), analysis of survival using the Breslow estimator only found age related to this period (Table 5). In this group, risk of death increased 1.040 times per year with age (95% confidence interval: 1.02 to 1.07).

## DISCUSSION

The five-year survival rate in this study was 22.6% which is lower than that found in many other countries such as the United States, Switzerland, France and China[4,6-9]. This may be explained by the fact that Iranian patients generally seek medical attention when the disease has reached an advanced stage. Therefore, diagnosis is made when the chance of a full cure is slim. In this study, comparison of survival and median life span

## APPENDIX 1

The life expectancy of these patients is not only affected by different variables, but also by the presence or absence of cancer recurrence. However, the period of life in the absence of recurrence can in turn be affected by some variables. For this reason, as stated in this article, we propose the application of a more advanced model for the analysis of such data. In this model, transitions shown in Fig. 1 may occur. Transition intensities of $h_{01}(t|Z)$, $h_{02}(t|Z)$ and $h_{12}(t|Z)$ can be assigned similar to the Cox model:

$$h_{kji}(t|Z_i) = h_{kj0}(t)\exp(\beta'_{kj}Z_i)$$

in which k=0,1, j=1,2 and k≠j. Considering X a Markovian process with three states of 0, 1 and 2 and the absorbing state being 2, the probability of transition from one status to another for a definite Z value is:

$$P_{kj}(s, t|Z) = P\{X(t) = j|X(s) = k, Z), s \le t$$

and so, the probability of survival would be:

1) $$S(t|Z) = P_{00}(0, t|Z) + P_{01}(0, t|Z) =$$

$$P_{00}(0, t|Z) + \int_0^t P_{00}(0, u^-|Z)h_{01}(u|Z)P_{11}(u^+, t|Z)du$$

The estimation of the first part of the above equation using the Breslow estimator[26] is:

$$\hat{P}_{00}(0, t|Z) = \prod_{u \le t}(1 - d\hat{H}_{01}(u|Z) - d\hat{H}_{02}(u|Z))$$

in which

$$\hat{P}_{00}(0, t|Z) = \hat{P}_{00}(0, t^-|Z)(1 - d\hat{H}_{01}(t|Z) - d\hat{H}_{02}(t|Z))$$

so that $$\hat{H}_{kj}(t|Z) = \hat{H}_{kj0}(t)\exp(\hat{\beta}'Z)$$

and $\hat{H}_{kh0}$ is the Breslow estimator for .

$$H_{kj0} = \int_0^t h_{kj0}(u)du$$

Therefore, the estimate of $P_{00}(0,t|Z)$ is dependent upon the probabilities of no transition from status 0 to states 1 and 2 during t. The estimation of the second part of equation 1 is:

$$\sum_{u \le t}\hat{P}_{00}(0, u^-|Z)\hat{P}_{11}(u^+, t|Z)d\hat{H}_{01}(u|Z)$$

in which .

$$\hat{P}_{11}(s, t|Z) = \prod_{s \le u \le t}(1 - d\hat{H}_{12}(u|Z))$$

Therefore, if t is the time of transition from status 0 to status 2:

$$\hat{P}_{01}(0, t|Z) = \hat{P}_{01}(0, t^-|Z)(1 - d\hat{H}_{12}(t|Z)),$$

if t is the time of transition from status 1 to status 2:

$$\hat{P}_{01}(0, t|Z) = \hat{P}_{01}(0, t^-|Z)(1 - d\hat{H}_{12}(t|Z)),$$

and if t is the time of transition from status 0 to status 1:

$$\hat{P}_{01}(0, t|Z) = \hat{P}_{01}(0, t^-|Z) + \hat{P}_{00}(0, t^-|Z)d\hat{H}_{01}(t|Z)$$

As expected, estimating the probability of survival until t is:

$$\hat{S}(t|Z) = \hat{P}_{00}(0, t|Z) + \hat{P}_{01}(0, t|Z)$$

It is possible to estimate the variance $\hat{P}_{kj}(s, t|Z)$ of using these recursion equations[24].

The estimation of regression models for $h_{01}(t)$, $h_{02}(t)$ and $h_{12}(t)$ is presented, respectively in Table 3, 4 and 5.

Between genders showed that men survived longer, although the difference was not statistically significant. This finding agreed with results of studies carried out in other countries and the life span difference between male and female gastric cancer patients was not statistically significant[31-33].

As we expected, life expectancy significantly decreased with age (p<0.001). A study performed in the United States also showed that older age groups have a shortened life expectancy in comparison to the young[15]. This fact has been verified by studies performed in Japan and Italy as well[16,30].

One hundred and 66 patients (59.1%) were afflicted with metastasis and their life expectancy was much shorter compared to other patients. Presence of metastases usually indicates an advanced disease and therefore a smaller chance of survival. This finding has been confirmed by all studies performed in this regard[4-6,9,10,30-33]. Of these 166 patients, 45.9% had metastasis to the lymph nodes and in 6.4% the liver was involved. The site of metastasis did not influence life expectancy, however, distant metastasis significantly decreased life expectancy; this was expected because these patients are classified in stage IV.

The disease stage greatly affected life expectancy; the five-year survival rate for patients in stage 1 was 52.96%, while it was only 16.72% for those in stage 4. Unfortunately 59.4% of patients were first seen with a stage 4 disease and therefore the life expectancy was shortened in general. In Thailand, 68.9% of patients were initially diagnosed with a stage 4 cancer and so the five-year survival rate was as low as 4.4% and in Malaysia, where 82% of patients were first diagnosed with a stage 4 disease, only 16% were operable or curable[5,13]. The effect of disease stage on life expectancy has been reflected in reports concerning Western and developed countries as well[3,19,32].

Multivariate analysis for detecting the simultaneous effect of different variables on life expectancy showed that age, lymph node metastasis, cancer stage and cancer recurrence influenced life expectancy significantly. Advancing age and a more advanced stage proved to lower the chance of survival, just as lymph node metastasis and recurrence did, while gender and cancer site had no significant effect. These findings have been confirmed by studies performed in Japan[10,33] and Switzerland[7]. In addition to these variables, metastasis to the liver and tumor site were found related in studies carried out respectively in China[9] and the United States[19].

In the past decade, a considerable amount of literature concerning the non-homogenous Markovian process has been published. However, non-homogenous Markovian or semi-Markovian processes has been limited due to their complexity. In the analysis of multiple events, when the interval between events is the subject of attention, it is important to find out whether the events follow a sequence, or such sequential order is lacking. An example of non-sequential events is the competing risks model. In the present study, cancer recurrence and death are two events that compete in time of occurrence. In such analyses, counting processes provides the researcher with a valuable tool to investigate not only sequential or non-sequential events, but also a combination of them simultaneously[28].

In the present study, we first see that variables such as age, disease stage, recurrence and lymph node metastases affect patients survival. However, further careful analyses showed that most of these variables (disease stage, presence of metastases and recurrence) have no significant effect on survival unless there is cancer recurrence and only age can be considered to have an effect.

The application of such a complex model instead of the conventional proportional hazards model can have advantages when time-dependent covariates are taken into account. Firstly, it allows us to compute the occurrence of different situations. Secondly, it leads us to a unbiased estimation of the probability of transition from one status to another. Thirdly, the effect of any previous status can be applied to the probability of transition to the next state. Fourthly, this method provides the means to distinguish between an uncompleted final event (death) and loss to follow-up.

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