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The relation of presenting symptoms with staging, grading, and postoperative 3-year mortality in patients with stage I–III non-metastatic colon cancer

BOWEL

Osman Bedir[1], Şafak Kızıltaş[2], Osman Köstek[1], Şeyma Özkanlı[3]

[1]Department of Internal Medicine, İstanbul Medeniyet University Göztepe Training and Research Hospital, İstanbul, Turkey
[2]Department of Gastroenterology, Başkent University İstanbul Hospital, İstanbul, Turkey
[3]Department of Pathology, İstanbul Medeniyet University Göztepe Training and Research Hospital, İstanbul, Turkey

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ABSTRACT

Background/Aims: To evaluate the association of presenting symptoms with staging, grading, and postoperative 3-year mortality in patients with colon cancer.

Materials and Methods: A total of 132 patients—with a mean (standard deviation; SD) age of 63.0 (10.0) years and of whom 56.0% were males—with non-metastatic stage I–III colon cancer were included. Symptoms prior to diagnosis were evaluated with respect to tumor localization, tumor node metastasis (TNM) stage, histological grade, and postoperative 3-year mortality.

Results: Constipation and abdominal pain were the two most common symptoms appearing first (29.5% and 16.7%, respectively) and remained most predominant (25.0% and 20.0%, respectively) up to diagnosis. The frequency of admission symptoms significantly differed with respect to tumor location, TNM stage and histological grade. The postoperative 3-year survival rate was 61.4%. Multivariate logistic regression revealed that melena and rectal bleeding increased the likelihood of 3-year mortality by 13.6-fold (p=0.001) and 4.08-fold (p=0.011), respectively.

Conclusion: Our findings revealed differences in presenting symptom profiles with respect to the time of manifestation and predominance as well as to the TNM stage, histological grade, and tumor location. Given that melena and rectal bleeding increased the 3-year mortality risk by 13.6-fold and 4.08-fold, respectively, our findings indicate the association of admission symptoms with outcome among patients with colon cancer.

Keywords: Colon cancer, symptoms, prognosis, mortality

INTRODUCTION

Colon cancer is the third most common tumor worldwide (1). According to the Turkish Ministry of Health 2004–2006 Cancer Statistics, the age-standardized incidence rate of colorectal cancer in Turkey is 17.0 in men and 11.7 in women per 100,000 people (2,3), while recent epidemiological data indicate that colon cancer is more frequent than rectum cancer (4).

Given that most colorectal cancers initially present with non-emergency symptoms, such as rectal bleeding, abdominal pain, or a change in bowel habits (5), earlier diagnosis has been suggested to arise not only from screening but also from the improved recognition of symptomatic cancers (6).

Although several factors, such as pathological staging, vascular and perineural invasion, residual tumor, serum carcinoembryogenic antigen levels, and radial margins, were investigated in terms of predicting outcome, limited data are available on the association of the clinical presentation with outcome in patients with colon cancer (6-8).

Therefore, the present study was designed to evaluate the association of presenting symptoms with staging, grading, and postoperative 3-year mortality in patients with stage I–III non-metastatic colon cancer.

MATERIALS AND METHODS

Study population

Of 258 patients who were diagnosed with non-metastatic stage I–III colon cancer and underwent surgical operation at a tertiary care hospital between 2005 and 2010, 132 patients [mean (standard deviation; SD) age: 63.0 (10.0) years; males: 56.0%, females: 44%] who met

Address for Correspondence: Şafak Kızıltaş E-mail: safakkiziltas@hotmail.com
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the inclusion criteria were included in this retrospective study. Survival data were obtained from the medical records as well as from patients and/or relatives. Patients with recto-sigmoid cancer, stage IV colon cancer, mortality within the postoperative first month or mortality not related to colon cancer, and patients who themselves or relatives could not be reached to obtain data on survival at the time of the study (2013) were excluded (n=126) from the study.

The study was conducted in full accordance with local Good Clinical Practice (GCP) guidelines and current legislation. While the present study was exempt from the requirement of informed consent in relation to its retrospective design, the permission was obtained from Medeniyet University School of Medicine Ethics Committee for the use of patient data for publication purposes (Date of approval: 08/07/2013, Reference number: 2013/0012).

Study parameters

Data on patient demographics, family history of malignancy, tumor characteristics [localization, histological type, tumor node metastasis (TNM) stage, histological grade, perineural and perivascular invasion], symptoms at admission (the first symptom appearing, the most predominant symptoms and symptoms experienced at least once up to diagnosis), symptom duration (days from symptom occurrence to the diagnosis), and survival were obtained from the medical records, while the data on the latest status of the patients in terms of survival were obtained via contacting the patients themselves or their close relatives. Symptoms prior to diagnosis were evaluated with respect to tumor localization, TNM stage, and histological grade.

Because the last patient included in the study had a follow-up of 3 years, the patients were classified into two groups as survived ≤ and >3 years after the operation and were included in univariate and multivariate logistic regression analyses to determine the impact of pre-operative symptoms on postoperative 3-year mortality. The association of gender, age, and family history of malignancy with survival was also evaluated.

Statistical analysis

Statistical analysis was made using IBM SPSS Statistics (IBM Corp. Released 2012, IBM SPSS Statistics for Windows, Version 21.0.; Armonk, NY, USA). In addition to descriptive statistics, the Chi-square test for the comparison of categorical data, and univariate and mutually adjusted logistic regression models for elucidating the impact of clinical symptoms on 3-year mortality after surgical treatment were used. Data were expressed as the mean (SD), minimum-maximum, percent (%), and 95% confidence interval (CI) where appropriate. $p<0.05$ was considered statistically significant.

RESULTS

Patient demographics and baseline clinical characteristics

Over a period of 8 years, 132 patients met the inclusion criteria for the study. Overall, 56.0% of our patients were males, and the median age of all the patients was 63 years; 40.2% of patients were aged 60-69 years (Table 1). The tumors were mostly located at the descending (38.6%) or ascending (34.1%) colon, and 69.7% of tumors were adenocarcinomas; the other baseline clinical characteristics related to the cancer are presented in Table 1.

Symptoms preceding diagnosis

Constipation and abdominal pain were the two most common symptoms that appeared first (29.5% and 16.7%, respectively) and remained as the most predominant (25.0% and 20.0%, respectively) of the overall symptoms experienced up to diagnosis (Table 2). While not commonly reported among the first symptoms to appear, melena and rectal bleeding become the predominant symptom experienced by 14.4% and 12.9% of patients, respectively (Table 2). A change in bowel habits (72.7%), loss of appetite (47.0%), and weight loss (46.2%) were the most common symptoms experienced at least once up to diagnosis (Table 2). Half of the patients (49.2%) had received a diagnosis within 90 days of symptom onset (Table 2).

Symptoms with respect to tumor location, TNM stage, and histological grade

The frequency of admission symptoms, other than nausea, change in bowel habits, and loss of appetite were significantly different in the subgroups of patients according to tumor location (Table 3). In summary, the rate of abdominal pain (55.6%, p=0.001), rectal bleeding (55.6%, p=0.001), and weight loss (66.7%, p=0.003) were much higher among transverse colon tumors, while constipation (62.7%, p=0.001) was more frequent among patients with descending colon cancer; melena was noted more frequently in patients with ascending rather than transverse colon tumors (35.6% vs. 11.1%, p=0.001), while it was seen in none of the descending colon tumor patients (Table 3).

When Stage II vs. Stage III tumors were compared, diarrhea (0.0% vs. 100.0%, p=0.002), melena (0.5% vs. 95.0%, p=0.004), rectal bleeding (11.0% vs. 89.0%, p=0.002), change in bowel habits (21.0% vs. 79.0%, p=0.0001), and loss of appetite (19.0% vs. 81.0%, p=0.004) were the admission symptoms with significantly higher percentages among patients at a higher TNM stage, while the rate of vomiting (p=0.01), melena (p=0.02), change in bowel habits (p=0.01), weight loss (p=0.004), and loss of appetite (p=0.002) significantly increased with histological grade (Table 3).

Postoperative three-year survival

Postoperative survival time was less than 1 year in 26 (19.6) and 1–3 years in 25 (18.9) patients, with a 3-year survival rate of 61.4%. No significant difference in terms of mean (SD) age [63.0 (11.0) vs. 62.0 (10.0) years, p=0.51] and family history of malignancy [11 patients (50.0%) for each, p=0.23] was noted between patients who had died in less than 3 years or survived >3 years, postoperatively.

Table 1. Patient demographics and baseline clinical characteristics (n=132)

Age (year)	**Mean (SD) median (min-max) 63.0 (10.0) 63.0 (40.0-87.0)**
Age groups (years)	**n (%)**
40-49	17 (12.9)
50-59	34 (25.8)
60-69	53 (40.2)
70-80	23 (17.4)
≥80	5 (3.8)
Gender, Female/Male	58 (44.0)/74 (56.0)
Family history for malignancy	22 (16.7)
Tumor localization	
Descending colon	51 (38.6)
Ascending colon	45 (34.1)
Transverse colon	36 (27.3)
Histological type	
Adenocarcinoma	92 (69.7)
Non-adenocarcinoma	17 (12.9)
Signet ring cell carcinoma	8 (6.1)
Mucinous carcinoma	6 (4.6)
Mixed type	3 (2.3)
Histological grade	
GI- well differentiated	9 (6.8)
GII- moderately differentiated	58 (43.9)
GIII- poorly differentiated	20 (4.8)
Missing data	19
TN stage[a]	
Tumoral invasion	
T1	2 (1.7)
T2	36 (31.2)
T3	77 (66.9)
Missing data	17
Lymph node positivity[b]	
N0	35 (33.7)
N1	38 (36.5)
N2	25 (24.0)
N3	6 (5.8)
Missing data	28
Neurovascular invasion	
Perivascular invasion	18 (16.5)
Perineural invasion	17 (15.6)
Missing data	23

TN: tumor node
[a]Patients were evaluated based on tumoral invasion and lymph node positivity, since patients with metastatic tumors were not included in the study
[b]N1: 1-3 pericolic node positive; N2: ≥4 pericolic node positive; N3: arterial node positive

Table 2. Symptoms preceding the diagnosis (n=132)

Symptom first appeared	**n (%)**
Constipation	39 (29.5)
Abdominal pain	22 (16.7)
Change in bowel habits	16 (12.1)
Loss of appetite	15 (11.4)
Nausea/vomiting	14 (10.6)
Melena	8 (6.1)
Rectal bleeding	7 (5.3)
Weight loss	1 (0.8)
Most predominant symptom[b]	
Constipation	33 (25.0)
Abdominal pain	27 (20.5)
Melena	19 (14.4)
Rectal bleeding	17 (12.9)
Change in bowel habits	11 (8.3)
Loss of appetite	5 (3.8)
Nausea/vomiting	5 (3.8)
Weight loss	4 (3.0)
Symptom experienced at least once[b]	
Change in bowel habits	96 (72.7)
Loss of appetite	62 (47.0)
Weight loss	61 (46.2)
Constipation	49 (37.1)
Abdominal pain	47 (35.6)
Nausea	41 (31.1)
Rectal bleeding	36 (27.3)
Vomiting	27 (20.5)
Diarrhea	22 (16.7)
Melena	20 (15.2)
Days from (any) symptom occurrence to diagnosis	
1-30 days	39 (29.5)
31-90 days	26 (19.7)
91-180 days	18 (13.6)
181-365 days	27 (20.5)
1-3 years	15 (11.4)
≥3years	7 (5.3)

[a]at least 3 kg unintentional weight loss not related to other causes
[b]from occurrence to diagnosis

Symptoms with respect to three-year mortality

Upon univariate analysis, all admission symptoms other than constipation were significantly less frequent among the >3-year survivors. Upon univariate logistic regression, abdominal pain (p=0.012), diarrhea (p=0.011), melena (p<0.001), rectal bleeding (p=0.005), weight loss (p<0.001), and loss of appetite

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Table 3. Symptoms with respect to tumor location, TNM stage and histological grade

	Tumor localization				Tumor TNM stagea			Histological grade			
Symptoms, n (%)	**Ascending colon**	**Descending colon**	**Transverse colon**	**p***	**Stage II**	**Stage III**	**p***	**Grade I**	**Grade II**	**Grade GIII**	**p***
Abdominal pain	6 (13.6)	21 (42.0)	20 (55.6)	0.001	14 (36)	25 (64.0)	0.51	3 (8.0)	23 (59.0)	13 (33.0)	0.47
Diarrhea	14 (31.0)	0 (0.0)	8 (22.0)	0.001	0 (0.0)	18 (100.0)	0.002	0 (0.0)	8 (44.0)	10 (56.0)	0.21
Constipation	5 (11.1)	32 (62.7)	12 (33.3)	0.001	13 (35.0)	24 (65.0)	0.61	2 (5.0)	15 (41.0)	20 (54.0)	0.13
Nausea	13 (28.9)	16 (31.4)	12 (33.3)	0.91	11 (30.0)	26 (70.0)	0.74	0 (0.0)	20 (54.0)	17 (46.0)	0.09
Vomiting	14 (33.3)	5 (9.8)	8 (22.2)	0.02	5 (22.0)	18 (78.0)	0.21	5 (22.0)	8 (35.0)	10 (43.0)	0.02
Melena	16 (35.6)	0 (0.0)	4 (11.1)	0.001	1 (5.0)	19 (95.0)	0.004	0 (0.0)	6 (30.0)	14 (70.0)	0.01
Rectal bleeding	1 (2.2)	15 (29.4)	20 (55.6)	0.001	4 (11.0)	31 (89.0)	0.002	1 (3.0)	23 (66.0)	11 (31.0)	0.09
Change in bowel habits	29 (61.4)	41 (80.4)	26 (72.2)	0.21	18 (21.0)	66 (79.0)	0.0001	3 (4.0)	44 (52.0)	37 (44.0)	0.01
Weight loss	13 (28.9)	24 (47.1)	24 (66.7)	0.003	14 (25.0)	42 (75.0)	0.12	2 (4.0)	23 (41.0)	31 (55.0)	0.004
Loss of appetite	17 (37.8)	26 (51.0)	19 (52.8)	0.31	11 (19.0)	46 (81.0)	0.004	2 (4.0)	23 (40.0)	32 (56.0)	0.002

TNM: tumor node metastasis; Grade I: well differentiated; Grade II: moderately differentiated; Grade III: poorly differentiated
[a]Although 2 patients had T1 stage tumors, lymph node evaluation revealed TNM stage III category in these patients and thus none of the patients was in TNM stage I category.
*Chi-square test

Table 4. Univariate and multivariate regression analyses for symptoms predicting 3-year mortality

	Survivors for >3 yrs (n=81)	Decedents (n=51)	Univariate analysisa			Multivariate analysisb		
Symptoms at admission	**n (%)**	**n (%)**	**OR**	**95% CI (LB; UB)**	**p**	**OR**	**95% CI**	**p**
Abdominal pain	22 (27.2)	25 (49.0)	2.58	1.24; 5.38	0.012	1.13	0.34; 3.73	0.841
Diarrhea	8 (9.9)	14 (27.5)	3.45	1.33; 8.97	0.011	1.66	0.50; 5.47	0.405
Constipation	32 (39.5)	17 (33.3)	0.77	0.37; 1.59	0.485		Not included	
Nausea-vomiting	18 (22.2)	23 (45.1)	2.07	0.995; 4.32	0.051*	1.30	0.45; 3.71	0.627
Melena	4 (4.9)	16 (31.4)	8.80	2.74; 28.25	<0.001	13.60	3.00; 61.66	0.001
Rectal bleeding	15 (18.5)	21 (41.2)	3.08	1.40; 6.79	0.005	4.08	1.38; 12.05	0.011
Change in bowel habits	56 (69.1)	40 (78.4)	1.62	0.72; 3.67	0.248		Not included	
Weight loss	25 (30.9)	36 (70.6)	5.38	2.50; 11.55	<0.001	1.70	0.35; 8.31	0.510
Loss of appetite	24 (29.6)	38 (74.5)	6.94	3.15; 15.30	<0.001	4.47	0.98; 20.35	0.053

CI: confidence interval; LB: lower bound; UB: upper bound; OR: odds ratio by logistic regression analysis
*included in the multivariate analysis since the univariate p value was marginal

(p<0.001) were found to be risk factors of death in 3 years. On the other hand, after adjusting by mutually adjusted multivariate logistic regression, only having melena and rectal bleeding on admission were confirmed to be independent predictors of 3-year mortality, which increased the likelihood of mortality in the postoperative 3 years by 13.6-fold (p=0.001) and 4.08-fold (p=0.011), respectively (Table 4).

DISCUSSION

Our findings in a cohort of patients with non-metastatic stage I–III colon cancer revealed that constipation and abdominal pain were the most common symptoms that appeared first, while a change in bowel habits was experienced by the majority of patients at least once up to diagnosis; while melena and rectal bleeding were the later symptoms that increased the likelihood of mortality in the postoperative 3 years by 13.6-fold (p=0.001) and 4.08-fold (p=0.011), respectively.

Our findings are consistent with the general profile of patients with colon cancer described in the first prospective long-term registry study (A Turkish Oncology Group trial) on the epidemiology of colorectal cancer in Turkey, which revealed male predominance (60.7%), a mean age of 59.63 years, a median 3.0 months duration between the first symptoms and diagnosis, and the involvement of ascending colon, descending colon, and transverse colon in 9.7%, 8.1%, and 7.1% of patients with colon cancer (4).

While findings in our cohort were also similar to other cohorts of patients with colon cancer in the past studies in terms of

demographics and tumor location, the symptom profile seems to differ with respect to quality as well as frequency, with a lesser incidence of abdominal pain and rectal bleeding among symptoms noted until diagnosis or that had occurred first, respectively (1,6,7,9).

In terms of the admission symptoms, abdominal pain (one of the earliest symptoms) and rectal bleeding (a later symptom predicting mortality) were more common in transverse colon tumors, while melena, the most significant predictor of 3-year postoperative mortality, was the only admission symptom that was more common in patients with ascending colon tumors.

Hence our findings emphasize a close association of the quality of admission symptoms with progression of the disease and a potential role for fecal occult blood test screening in earlier detection of the disease prior to manifestation of overt rectal bleeding (6) in transverse colon tumors.

In our cohort, diarrhea, melena, rectal bleeding, a change in bowel habits, and loss of appetite were the more commonly encountered admission symptoms in higher TNM stages. Significant differences in the manifestation of symptoms with respect to TNM staging have also been reported in other studies, with an increased incidence of abdominal pain, weight loss, and a change in bowel habits shown in advanced TNM stages, which correlate with more aggressive tumor characteristics and an adverse clinical outcome (7,8,10-13).

Melena (more common in ascending colon tumors) and rectal bleeding (more common in transverse colon tumors) were the only admission symptoms in our cohort that were shown to increase the postoperative 3-year mortality risk, by 13.6-fold and 4.08-fold, respectively. This seems consistent with the higher prevalence of these symptoms at later TNM stages. Likewise, a worse prognosis in terms of overall survival in patients with right-sided than left-sided colon cancers was also reported in a recent meta-analysis (14). Also, tumor location was shown to be an independent prognostic factor of 5-year recurrence-free survival and 5-year overall survival in Stage III colon cancer, with a gradual decrease in survival from cecum to sigmoid colon cancer (15).

While, all admission symptoms other than constipation were significantly less frequent among the >3-year than <3-year survivors in the univariate analysis; only abdominal pain, diarrhea, melena, rectal bleeding, weight loss, and loss of appetite were associated with a higher risk for postoperative 3-year mortality in the univariate logistic regression in the present study. Moreover, after mutual adjustment in the multivariate logistic regression, only having melena and rectal bleeding on admission were confirmed to be independent predictors that increased the likelihood of postoperative 3-year mortality by 13.6-fold (p=0.001) and 4.08-fold (p=0.011), respectively.

Our findings indicate the association of admission symptoms with mortality from colon cancer. The difference in mortality from colorectal cancer with respect to the nature of the first clinical manifestations was also shown in a past study conducted with 349 patients with primary colorectal cancer, in which, unlike our findings, rectal bleeding was indicated to be the most common symptom that occurred first or up to diagnosis and was associated with lower mortality (6). Given that patients with sigmoid-rectal cancers were not included in our study population, rectal bleeding was not among the first noted symptoms in our cohort.

Data from a cohort study using the Clinical Practice Research Database revealed that patients with colorectal cancer who presented without rather than with rectal bleeding, a relevant alarm symptom, had a higher mortality rate (HR=1.74, 95% CI=1.42 to 2.13, p<0.001) (16). Analysis of the data on patients with colon cancer from the Icelandic Cancer Registry (1995–2004) in a population-based study revealed the increased likelihood of a lower tumor grade and lower frequency of vessel invasion among patients presenting with visible blood in stools on admission, while blood in stools was also shown to predict survival (HR=0.54) (8).

Given the lower survival from diagnosis to death in patients with cancer without rather than with any record of relevant alarm symptoms in general (16), a higher alertness among physicians to the possibility of colorectal cancer in the case of rectal bleeding seems to be associated with the better survival in these patients (6,17).

Notably, for data from a past study on the correlation between symptoms at admission and the outcome among patients with colon cancer, a multivariate analysis controlling for age, stage, and the duration of complaints showed that melena was strongly associated with mortality (p=0.04, OR=7.4), while rectal bleeding was with survival (p=0.004, OR=0.25) (7). However, and consistent with our findings and via multivariate analysis on the adjusted mortality, rectal bleeding was reported to be associated with mortality and no longer with survival (p=0.02, OR=2.5) (7). Also, consistent with the symptom profile in our cohort, abdominal pain, a change in bowel habits, and weight loss were the most common symptoms, while rectal bleeding was the 4th most common symptom (7).

Hence, our findings support the association of clinical presentation with outcome among patients with colon cancer, and the importance of certain admission symptoms, such as melena and rectal bleeding, in predicting the outcome among patients with colon cancer (7).

Half of our patients had received a diagnosis within 90 days of symptom onset, while the 3-year survival rate was 61.4%. Similarly, past studies in patients with colon cancer revealed a mean of 1.8 months duration of complaints prior to diagnosis

and an overall mortality of 39.4% within a median of 36 months to follow-up (7) as well as 90 days from symptom onset to diagnosis in nearly half of patients and an overall mortality of 59% within a median of 421 days of diagnosis (6).

Neither constipation nor abdominal pain was among the significant predictors of mortality risk in our cohort, despite the fact that they were the two most common symptoms that appeared first and remained predominant up to diagnosis. This seems consistent with the published data on the lack of s relationship between the duration of symptoms and mortality in patients with colorectal cancer, even when corrected for possible confounders (6,16,18-22).

Although the duration of symptoms was not associated with the outcome and no relationship has been suggested between diagnostic delay and colorectal cancer survival (22), both rectal bleeding (significant predictor of mortality risk) and abdominal pain (one of the earliest symptoms) were more common in our patients with transverse colon tumors. Thus, our findings support the finding that the symptomatic phase in colon cancers might have sufficient duration to offer the possibility of earlier diagnosis, leading to mortality benefits (6).

Certain limitations to this study should be considered. First, due to the small sample size and retrospective single-center design of the present hospital-based study, establishing a temporality between cause and effect as well as generalizing our findings to the overall patient population with colon cancer would be difficult. Second, due to the inadequacy of the available registration system, a number of patients or their relatives could not be reached to obtain data on survival and thus could not be included in the final analysis. This appears to be a definite, albeit inevitable, weakness of the study. Third, the accuracy of data on admission symptoms seems questionable given the possible neglect of symptom reporting either by the patients or physicians as well as the likelihood of the inability of some patients to specify the exact time of symptom onset prior to diagnosis. Nevertheless, despite these certain limitations, given the paucity of the information available in this area, our findings represent a valuable contribution to the literature.

In conclusion, the present analysis of a retrospective cohort of patients with non-metastatic stage I–III colon cancer over a period of 8 years revealed a difference in presenting symptom profiles with respect to the time of manifestation and predominance as well as in terms of TNM stage, histological grade, and tumor location. Given that melena and rectal bleeding increased the 3-year mortality risk by 13.6-fold and 4.08-fold, respectively, our findings indicate the association of admission symptoms with outcome among patients with colon cancer. Further large-scale, population-based studies are needed to provide conclusive evidence on this topic, which, although promising, is still scarce.

Ethics Committee Approval: Ethics Committee Aproval was received for this study from the ethics committee of Medeniyet University School of Medicine.

Informed Consent: Written inform consent was obtained from patient who participated in this study.

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