Colorectal Cancer Survival and Its Prognostic Factors in Karachi, Pakistan

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ABSTRACT

Objective: To determine the survival rates of colorectal cancer (CRC) in the Pakistani population and determine the prognostic factors for survival among the CRC patients.

Study Design: Retrospective cohort study.

Place and Duration of the Study: The cancer registry of the Aga Khan University Hospital, Karachi, Pakistan, from 2010 to 2016.

Methodology: The abstracted data from the cancer registry was cleaned and updated regarding the vital status at the last follow-up. Survival analyses were performed using the Kaplan-Meier method. Adjusted hazard ratios (aHR) and their 95% confidence intervals (CIs) were estimated using a cox regression model to assess the prognostic factors for survival.

Results: The overall proportion of late-onset CRC (>50 years of age) was 55.3% and early-onset CRC (<=50 years of age) was higher than expected (45.7%). A high level of carcinoembryonic antigen (CEA) (>5 ng/ml) was associated with poor survival compared to patients with CEA levels of ≤5 ng/ml (aHR = 1.68, 95% CI = 1.04, 2.72). Patients, who experienced recurrence, showed poorer survival (aHR = 4.27, 95% CI = 2.55, 7.14). Patients, who did not undergo surgery, showed significantly poorer survival compared to those who underwent surgery (aHR = 5.53, 95% CI = 2.35, 13.03).

Conclusion: The findings suggest that monitoring CEA levels, ensuring prompt surgical treatment and follow-up care for recurrent cases can improve survival outcomes in patients with colorectal cancer.

Key Words: *Colorectal cancer (CRC), Surgery, Recurrence, Grade, Cancer registry.*

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INTRODUCTION

Colorectal cancer (CRC) is a significant public health burden, accounting for a large proportion of cancer cases and deaths each year. It is the second most common malignancy in males and the third most common cancer in females.[1] According to Morgan *et al.*, over 1.9 million new CRC cases and 930,000 deaths were estimated in 2020, and this burden of CRC is expected to increase to 3.2 million new cases and 1.6 million deaths by 2040.[2] According to Karachi Cancer Registry (KCR) 2017-2019 results, the age standardised incidence rate (ASIR) of colorectal cancer in Karachi is 7.70/100,000 among females, and 12.35 /100,000 among males.[3] The cancer survival analysis is important to understand the prognosis and identify the factors that influence the survival outcomes of the patients.

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There are different types of survival data cited in literature which include the ones extracted from clinical trials, population-based cancer registries, and from hospital-based follow-up studies, each having different definitions and methodologies according to their objectives.

There are multiple factors affecting the survival of the patients with colorectal cancer including anatomical site of the tumour, stage, lymph nodes involvement, and preoperative carcinoembryonic antigen (CEA) level.[4] In a study among the Malaysian population, increasing age, the severity of CRC, and male gender were associated with poor survival.[5] In a study conducted in India, increasing age, site, and American Joint Committee on Cancer (AJCC) stages of CRC were significant factors affecting the survival. In another large study among 670,030 CRC cases, lower income and lower education were associated with higher mortality.[6] Overall, the survival rates in the Eastern Mediterranean countries are reported as less compared to Europe and the USA.[7]

In third-world countries such as Pakistan, different factors play role in the pathogenesis and prognosis of CRC, especially with this cancer presenting in the younger age group. There is an urgent need to better understand the aetiopathogenesis of CRC and factors affecting its survival. However, there is a lack

of studies conducted on local data to assess the survival rates of CRC in the Pakistani population. Pakistan does not have a national cancer registry, but there are regional and hospital-based cancer registries working on cancer incidence, behaviour, and survival in that region. This study aimed to fill this knowledge gap by evaluating the survival data and the factors affecting the survival.

METHODOLOGY

This retrospective cohort study was conducted to assess the clinical characteristics and outcomes of patients with CRC in Pakistan. The study population included patients visiting the Aga Khan University Hospital from Karachi, as well as from other provinces of Pakistan, and Pakistanis living outside Pakistan. All data were collected from the Aga Khan University Hospital cancer registry, which uses CNExT, a standardised software program to ensure the accuracy and completeness of cancer data.

Patients, who had a biopsy-proven diagnosis of CRC, were eligible for inclusion in the study. Patients, who were diagnosed with other cancers or if they had missing information about tumour grade, tumour site, or AJCC stage, were excluded.

The variables assessed to predict survival in patients with CRC included patients' sociodemographic data such as age, gender, marital status, family history of CRC, habits of tobacco and alcohol use, and source of payment (out-of-pocket or insurance). Tumour characteristics included histological diagnosis and anatomical site as proximal, distal, or rectum. Grades were categorised as well, moderately and poorly differentiated grades. All cases of CRC were identified using ICD-03 codes. Preoperative serum CEA levels were also abstracted from the data. If patients had multiple CRC tumours within the study period, only the first occurring tumour was considered. The stage at diagnosis was based on the clinical and pathological tumour-lymph nodes-metastasis (TNM) staging system 7th edition. The stage was further categorised into early (Stage 0/I/II) or advanced stage (Stage III/IV). Pre-operative serum CEA levels were also abstracted from the data. Treatment modalities including surgery, chemotherapy, and radiotherapy were also abstracted.

Kaplan-Meier analysis was used to estimate survival rates at 1-, 3-, and 5-year intervals. The log-rank test was used to compare survival rates between groups. Cox proportional hazards regression analysis was performed to calculate hazard ratios (HRs) and their 95% confidence intervals (CIs) for the association between each predictor and survival. In order to identify the independent predictors of colorectal cancer survival, all variables that were significantly associated with survival in the univariate analyses ($p < 0.25$) were included in the multivariable model. This was performed to control for the effects of other variables and to estimate the adjusted hazard ratios (aHR), and 95% confidence intervals (CIs) for each variable, with a level of significance of 0.05. SPSS version 25 (IBM, New York, USA) was used to perform all statistical analyses.

RESULTS

A total of 989 patients with confirmed diagnoses of CRC between 2010 and 2016 who met the inclusion criteria were included in the study. Patients were followed up until death or censored at the end of the study. The mean age was 51.3 years (SD 16.3). The overall proportion of late-onset CRC was 55.3%, and early-onset CRC was 45.7%, higher than expected. Relative 1-year survival rate was 85.6% (95% CI: 84.4%, 86.8%), 3-year survival rate was 77.2% (95% CI: 74.5%, 79.9%), and 5-year survival rate was 72.0% (95% CI: 69.7%, 74.3%).

Table I shows the sociodemographic characteristics, personal habits, mode of payment, and clinical treatment characteristics of the CRC cases. Older age showed poor survival rate compared to the younger age.

Table I: Univariate analysis of patients' sociodemographic characteristics, personal habits, and mode of payment associated with survival in colorectal cancer patients in Karachi, Pakistan (n = 989).

Tumour site - Primary	n	%	Crude HR (95% CI)
Age (years)			
>50	537	54.3	1.45 (1.07, 1.98)
<= 50	452	45.7	Ref.
Gender			
Male	631	63.8	0.95 (0.70, 1.30)
Female	358	36.2	Ref.
Marital Status			
Married	871	88.1	0.77 (0.57, 1.08)
Single/widow/separated	118	11.9	Ref.
Occupation			
Business	108	15.3	2.03 (0.85, 4.83)
Employed	202	28.7	1.89 (0.76, 4.68)
Retd./students	145	20.6	1.70 (0.72, 4.04)
Others	78	11.1	3.32 (1.42, 7.76)
Housewife	172	24.4	Ref.
Province			
Sindh	938	94.8	1.77 (1.28, 2.45)
Other provinces	51	5.2	Ref.
Country			
Pakistan	782	79.1	1.76 (1.28, 2.41)
Outside Pakistan	207	20.9	Ref.
Family history of CRC			
Yes	40	4.0	1.05 (0.53, 2.05)
No/unknown	932	94.2	Ref.
Tobacco use			
Yes	246	24.9	0.88 (0.63, 1.22)
No/unknown	742	75.0	Ref.
Alcohol use			
Yes	39	3.9	0.99 (0.49, 2.02)
No/unknown	949	96.0	Ref.
Payment Source			
Out of pocket	898	90.8	0.90 (0.57, 1.42)
Other sources	91	9.2	Ref.

HR: Hazard ratio, CI: Confidence interval.

Table II shows the clinical and treatment variables of the CRC cases. Tumour site analysis showed that the rectum displayed a higher survival rate (HR = 0.41, 95% CI = 0.21, 0.82), while there was no significant association of survival with proximal and distal sites. In histological analysis, signet ring cell adenocarcinoma exhibited a poorer survival (HR = 2.45, 95% CI = 1.31, 4.60), along with other mixed types (HR = 3.04, 95% CI = 1.55, 5.94). Late AJCC Stage had a significantly higher risk (HR = 2.30, 95% CI = 1.63, 3.24). Recurrence demonstrated poorer survival (HR = 13.04, 95% CI = 7.52, 22.63), and lack of surgery also had poor prognosis on survival (HR = 3.10, 95% CI=2.25, 4.26). Patients who did not

receive any chemotherapy also had poor survival (HR = 1.73, 95% CI = 1.29, 2.32). Notably, CEA levels exceeding 5 ng/ml showed poor survival (HR = 2.89, 95% CI = 1.50, 5.57).

Table III shows the results of the final multivariable model, which found that high levels of carcinoembryonic antigen (CEA; greater than 5 ng/ml) were a significant predictor of poor survival in patients with colorectal cancer. A high level of CEA (>5 ng/ml) was associated with poor survival compared to patients with CEA levels of ≤5 ng/ml (HR = 3.07, 95% CI = 1.33, 7.10). Patients who experienced recurrence, showed poorer survival (HR = 15.56, 95% CI = 5.96, 40.61), in comparison to patients who did not experience recurrence. Patients who did not opt surgery for CRC exhibited a significantly elevated risk of death with lower survival (adjusted HR = 5.53, 95% CI = 2.35, 13.03), compared to the patients who opted for the surgery.

The Kaplan-Meier survival curves showed poor survival with colon NOS CRC and recurrence (Figure 1).

Table II: Univariate analysis of pathological characteristics, anatomic sites and stage for survival in colorectal cancer patients in Karachi, Pakistan (n = 989).

Tumour site - Primary	N	%	Crude HR (95% CI)*
Proximal	249	25.8	0.67 (0.35, 1.28)
Distal	313	32.4	0.57 (0.30, 1.09)
Rectum	363	37.6	0.39 (0.20, 0.75)
Colon NOS	40	4.1	Ref.
Histology of tumour			
Mucinous adenocarcinoma	126	12.7	1.04 (0.65, 1.67)
Signet ring cell adenocarcinoma	71	7.2	2.45 (1.31, 4.60)
Other (mixed, medullary, Adenosquamous)	62	6.3	3.04 (1.55, 5.94)
Adenocarcinoma	726	73.4	Ref.
AJCC Stage			
Late Stage (III and IV)	348	35.2	2.30 (1.63, 3.24)
Early Stage (0, I, and II)	598	60.5	Ref.
Recurrence			
Yes	185	36.1	13.04 (7.52, 22.63)
No	328	63.9	Ref.
Surgery			
Not performed	299	30.3	3.10 (2.25, 4.26)
Performed	689	69.7	Ref.
Radiation			
No	753	76.8	1.70 (1.16, 2.48)
Yes	227	23.2	Ref.
Chemotherapy			
No	430	43.5	1.73 (1.29, 2.32)
Yes	558	56.4	Ref.
Serum CEA level (ng/ml)			
>5	343	63.5	2.89 (1.50, 5.57)
<= 5	197	36.5	Ref.

*AJCC: American Joint Committee on Cancer, Colon NOS: Colon non-specific, CEA: Carcinoembryonic antigen, HR: Hazard ratio, CI: Confidence interval, *Univariate Cox Proportional Hazard Regression analysis.*

Table III: Multivariable Cox regression analysis of predictors of survival in colorectal cancer (CRC) patients in Karachi, Pakistan (n = 989).

Variables	Adjusted HR (95% CI) *
Serum CEA level (ng/ml)	
>5	3.07 (1.33, 7.10)
<=5	Ref.
Recurrence	
Yes	15.56 (5.96, 40.61)
No	Ref.
Surgery performed	
No	5.53 (2.35, 13.03)
Yes	Ref.

**Multivariable analysis using Cox Hazard Regression, adjusted for age, gender, tumour grades and treatment modalities.*

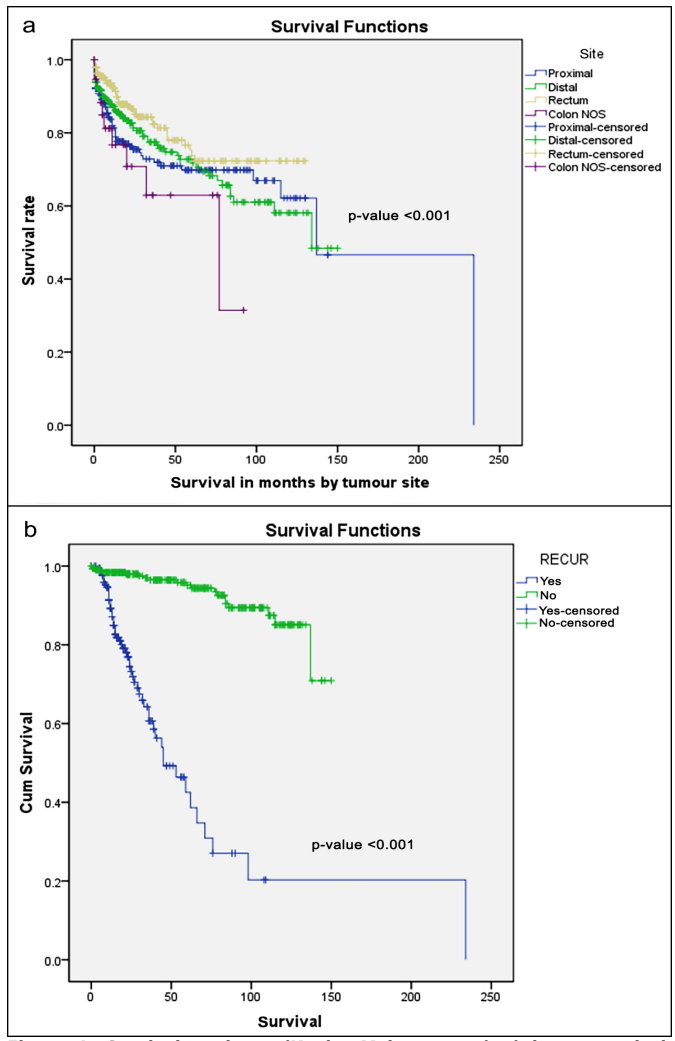

Figure 1: Survival analyses (Kaplan-Meier curves) a) by anatomical site b) by recurrence of CRC and results of log rank test to compare survival rates between groups.

DISCUSSION

This study evaluated the survival rates of colorectal cancer (CRC) patients in Karachi, Pakistan, and identified factors that affect survival in this population. The 1-, 3-, and 5-year survival rates were 85.6%, 76.0%, and 71.0%, respectively. This is comparable to the survival rates reported in other countries, such as Sweden (83%), Denmark (77.7%), England (74.7%), Australia (84.9%), and Norway (82.4%),[8] but higher than the survival rates reported in China and India. Yuan *et al.* in 2013 reported a 3-year survival rate of CRC cases in China to be 74%,[9] whereas the reported survival rates from the neighbouring country India, for one and three year survival rates of CRC cases were 63.04% and 42.20%, respectively.[9] Discrepancies in the survival and distribution of stages might emerge due to disparities in the time taken for diagnosis and recognition of symptoms, or variations in the meticulousness of staging protocols. Comparing survival rates for colorectal cancer (CRC) across different countries can be challenging due to variations in patient demographics, disease characteristics, management,

and implementation of CRC screening programmes. Nevertheless, there is a clear evidence of the global geographical discrepancy in CRC survival.[10]

Amongst the prognostic factors, stage, grade, tumour site, co-existing cancers, socio-economic status, and earlier diagnosis and treatment, newer chemotherapy regimens, recent advances in surgical modalities, and radio-therapy have been found to have a significant impact in improving the survival of colorectal cancer in various studies.[11-14]

The present study also looked at the factors affecting survival in the Pakistani population. Results of univariate analysis revealed several factors including higher stage, type of tumour, surgery, and chemotherapy affecting survival, while multivariable analysis revealed three factors affecting the survival including high CEA before surgery, recurrence, and advanced CRC stage. Preoperative CEA level as a poor survival prognostic factor was also found in other studies.[15,16] The role of serum CEA as a prognostic indicator in colon cancer has been extensively investigated. There has been lot of interest regarding preoperative *versus* postoperative elevation in the levels of CEA, and which one is more prognostic of survival. Majority of the studies have established that raised preoperative CEA levels are associated with advanced stage of colonic cancer, increased risk of recurrence, and poor survival.[17,18] A study by Wang *et al.* showed that carcinoembryonic antigen (CEA) levels are associated with and are potential biomarkers for postoperative CRC recurrence which is an important factor for poor survival rates.[19] These study findings are consistent with other studies.[20]

Patients who did not undergo surgery for CRC had poor survival rate similar to those who underwent emergency surgery for CRC as show in a study by Zhou *et al.*[21] It is consistent with studies reported to show that curative surgery is associated with long-term survival in resource-constrained low and middle income countries (LMICs).[22-24] There are many barriers for prompt surgical evaluation and treatment of CRC in LMICs. The out-of-pocket payment is 90.8% which could also be a reason for lack of timely surgery. Surgical care should be a priority to address the increasing burden of CRC in resource-limited settings.

As it was a retrospective data from the cancer registry and medical records, information related to variables like body mass index (BMI), and socio-economic status was lacking. For the vital status, it was not possible to cross-check with mortality data of all the censored patients as their CNIC numbers were not entered in the cancer registry. There is an unmet need to routinely collect and record CNIC data of all patients in the cancer registry and link it with mortality data to confirm the vital status and asses survival outcomes accurately.

CONCLUSION

There was a significant association between high CEA levels, recurrence of CRC after surgery, and lack of surgery with poor survival among the young adults. Based on the findings, there is a need for early detection through awareness campaigns and screenings for early-onset cases. Patients with high preoperative CEA levels should be carefully monitored for recurrence. Moreover, closely monitoring CEA levels, timely surgical interventions, and rigorous follow-up care for recurrence are recommended to enhance patient survival rates. Larger studies are needed with focus on developing and implementing effective screening and early detection programmes to improve the survival rates in this population.

ETHICAL APPROVAL:

Ethical approval for this study was granted by the Ethical Review Committee (ERC) of the Aga Khan University (ERC reference # 6078). Furthermore, all the patients who visited the hospital, received comprehensive information about the potential utilisation of their data for research purposes within the hospital's cancer registry.

PATIENTS' CONSENT:

Patients were presented with the option to grant consent for this study's publications on the informed consent form in all the cases, ensuring the confidentiality and anonymity of their information.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

US: Designed the study, got ERC approval, cleaned and analysed the CRC data form.
SQ, RI: Data abstraction and manuscript writing.
MM: Feedback on the manuscript as the subject expert.
IA: Data analysis.
All authors approved the final version of the manuscript to be published.

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