

Characteristics and outcomes of small bowel adenocarcinoma: 14 years of experience at a single tertiary hospital in Saudi Arabia

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Abstract. Small bowel adenocarcinoma (SBA) is an extremely rare cancer type. In the present study, the patient characteristics and clinical outcomes of patients diagnosed and treated for SBA at a single tertiary hospital were reported. All patients diagnosed and managed between 2007 and 2020 were reviewed. Regression analysis was used to assess variables associated with the metastatic stage at diagnosis. The Kaplan-Meier method was used to estimate survival and the log-rank test was used to determine factors associated with survival outcomes. Out of 137 cases of small bowel primary tumor, 43 consecutive patients with SBA were diagnosed with a median age of 53 years and the majority (76.7%) were males. The common initial presenting symptoms were abdominal pain (58.8%) and bowel obstruction (30.2%). The most common primary site was the duodenum (60.5%) and the majority (65.1%) were diagnosed with stage III/IV disease. Patients with a high neutrophil-lymphocyte ratio (NLR) (≥ 0.85) were more likely to be in the metastatic stage at diagnosis ($P=0.01$). The 3-year overall survival (OS) rates based on stage were 100% (I), 85% (II), 53% (III) and 33.9% (IV) ($P=0.001$). In

addition to the stage, the Eastern Cooperative Oncology Group Performance Status ($P<0.001$), NLR ($P<0.001$), hypoalbuminemia ($P=0.02$) and chemotherapy in a metastatic setting ($P=0.02$) were prognostic factors for OS. In conclusion, NLR is a potential prognostic biomarker for a metastatic stage at diagnosis. Advanced stage, lower performance status score, low albumin level and high NLR are associated with short OS.

Introduction

The small bowel is the longest portion of the gastrointestinal tract; however, the incidence of small bowel cancer is far less than that of colorectal cancer; e.g., in 2022, 11,000 vs. 150,000 new cases, respectively, are predicted to be diagnosed in the US (1). Overall, small bowel cancers account for 3-5% of all gastrointestinal tumors, and the most common histological subtypes are adenocarcinoma, neuroendocrine tumors, gastrointestinal stromal tumors and lymphoma. Small bowel adenocarcinoma (SBA) accounts for 30-40% of all primary small bowel cancers (2-5). The vast majority of SBAs originate from the shortest portion of the small intestine, the duodenum (52-82%), followed by the jejunum (11-25%) (6-9). The mean age group for diagnosis is the fifth and sixth decade of life (10). The risk factors include Peutz-Jeghers syndrome, inflammatory bowel disease, familial adenomatous polyposis, Lynch syndrome, celiac disease, cystic fibrosis and peptic ulcer disease, in addition to environmental and dietary factors (10,11).

Surgical resection and lymph node dissection are the mainstays of localized disease treatment. However, the clinical diagnosis of SBA is challenging and symptoms usually do not occur in localized disease (11). Therefore, a significant number of cases are diagnosed in the advanced stage due to delays in diagnosis, and despite advances in diagnostic tools, the time required for diagnosis has remained unchanged over time (6,9).

The factors associated with short overall survival (OS) are advanced stage, lack of surgery, older age, primary duodenal site and high baseline neutrophil-lymphocyte ratio (NLR) (11-13).

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Abbreviations: SBA, small bowel adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; OR, odds ratio; OS, overall survival; DFS, disease-free survival; PLR, platelet-lymphocyte ratio

Key words: small bowel adenocarcinoma, neutrophil-lymphocyte ratio, hypoalbuminemia, prognostic factors, Saudi Arabia

Overall, there are limited studies regarding the disease characteristics and outcomes of SBA, particularly from the Arab regions, due to the rarity of the disease. In the present study, the patient characteristics and clinical outcomes for patients with SBA treated at our tertiary hospital were described.

Materials and methods

Patients and methods. A retrospective review of consecutive patients diagnosed with SBA between January 2007 and December 2020 at King Faisal Specialist Hospital & Research Center (Riyadh, Saudi Arabia) was performed. Study data were collected and managed using REDCap electronic data capture tools hosted at King Faisal Specialist Hospital & Research Center (Riyadh, Saudi Arabia) (14,15). Ethical approval was obtained from the Research Ethics Committee at King Faisal Specialist Hospital & Research Center (Riyadh, Saudi Arabia) and the requirement for informed consent from the patients was waived. The data obtained included age at diagnosis, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS), past medical and surgical history, family history, baseline laboratory test results, TNM staging, management and outcomes, including best responses to chemotherapy, time-to-progression and status at the last follow-up. Performance status was evaluated using the Eastern Cooperative Oncology Group Performance Status (ECOG PS) assessment tool (16). The patients were staged according to the American Joint Committee on Cancer Union for International Cancer Control staging system (17). The disease response was evaluated using the Response Evaluation Criteria in Solid Tumors (version 1.1) (18). Disease-free survival (DFS) was defined as the time from surgery until either disease recurrence or death. Progression-free survival (PFS) was defined as the time from the beginning of management (chemotherapy, surgery, radiation therapy or best supportive care) until either disease progression or death, and OS was defined as the time from the beginning of management until death from any cause.

Statistical analysis. Categorical variables are described as frequencies and continuous variables are described as the median and interquartile range. The association of categorical variables with metastasis at diagnosis was examined by χ^2 tests and that of continuous variables by using the Mann-Whitney U-test. Factors tested for associations with the metastatic stage at diagnosis were presenting symptoms, age, sex, history, baseline serum albumin level, pretreatment NLR, platelet-lymphocyte ratio (PLR), tumor markers (CEA and CA19-9 levels) and baseline hemoglobin (Hb) levels. The tumor markers were defined as positive if either CEA ($>4.3 \mu\text{g/l}$) or Ca 19-9 ($>27 \text{ U/ml}$) was present. Hypoalbuminemia was defined as an albumin level $<34 \text{ g/l}$. The best NLR and PLR cutoff was obtained using a receiver operating characteristic (ROC) curve (19,20). Uni- and multivariate logistic regression analysis was used to estimate the association of these variables with the metastatic stage at diagnosis. The Kaplan-Meier method was used to estimate DFS and OS, and a log-rank test was used to determine factors associated with survival outcomes. Statistical analyses were performed using SPSS v.28 (IBM Corporation). $P<0.05$ was considered to indicate statistical significance.

Results

Patient characteristics. Of 137 small bowel primary tumors diagnosed during the study period, 43 cases of SBA were identified and included in the analysis. The median age at diagnosis was 53 years (range, 44-66 years) and the majority of patients (76.7%) were males. The detailed patient and disease characteristics are presented in Table I. The most common primary site was the duodenum (60.5%), followed by the jejunum (27.9%) and ileum (6.9%). The most common diagnostic modalities were EGD (60.5%) and CT scan (23.3%). The diagnosis was established intraoperatively in eight patients. The tumor markers were elevated in 21 patients (48.8%): CEA was elevated in 10 patients (23.3%) and CA19-9 was elevated in 17 patients (39.5%). Furthermore, 18 patients (41.9%) presented with synchronous metastasis and the most common sites for metastases were the liver ($n=10$ patients), followed by peritoneum ($n=8$), lung ($n=8$), lymph nodes ($n=5$) and bone ($n=2$) (data not shown).

Factors associated with metastatic stage at diagnosis. The continuous values of baseline albumin ($P=0.01$), NLR ($P<0.001$) and PLR ($P=0.01$) were associated with the metastatic stage at diagnosis. There was no association of presenting symptoms, age, sex, history of cholecystectomy, CEA level, CA19-9 level or baseline Hb with metastasis at diagnosis (data not shown). The best cutoff for the NLR was >0.85 and that for PLR was >125 (Fig. S1). Univariate logistic regression was significant for hypoalbuminemia [odds ratio (OR): 3.75, 95% CI: 1.01-13.7; $P=0.04$] and high NLR (OR: 20.2, 95% CI: 2.2-182.4; $P<0.01$). There was no significant association between primary disease site (OR: 2.1, 95% CI: 0.77-6.11; $P=0.1$), tumor grade (OR: 1.1, 95% CI: 0.26-4.5; $P=0.9$), PLR (OR: 4.3, 95% CI: 0.95-19.5; $P=0.06$) and tumor markers (OR: 1.2, 95% CI: 0.33-4.6; $P=0.7$) with metastasis at diagnosis. Multivariate analysis indicated that in comparison to patients with a low NLR (<0.85), patients with a high NLR were more likely to be in the metastatic stage, with an OR of 17.6 (95% CI: 1.7-178; $P=0.01$). Furthermore, patients with hypoalbuminemia were more likely to be in the metastatic stage at diagnosis (OR: 5.5, 95% CI: 0.9-31.5); however, the P -value was insignificant ($P=0.06$) (data not shown).

Characteristics of management. A total of 23 (92%) out of 25 patients received treatment for localized disease. Furthermore, 17 patients (68%) underwent surgery (microscopically margin-negative resection, R0 achieved in 13 patients), and 11 patients received chemotherapy: Adjuvant, 5 patients; and upfront, 6 patients (XELOX, 6 patients; and FOLFOX, 5 patients). The median duration of chemotherapy was 3.75 months (range, 0.5-6.0 months). A total of 9 patients developed recurrence, 4 received second-line chemotherapy and 1 underwent cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. None of the patients received chemotherapy beyond the second line. In the metastatic group, 12 out of 18 patients received treatment. A total of 10 patients (55%) received chemotherapy (FOLFOX, 6 patients; XELOX, 3 patients; and nivolumab, 1 patient), the median duration of chemotherapy was 3.5 months (range, 1.0-6.0 months) and the best response was partial response ($n=1$), stable disease ($n=1$),

Table I. Patients and disease characteristics (n=43).

Characteristic	Value
Median age at diagnosis, years	53 (44-66)
Male sex	33 (76.7)
PMH	
Celiac disease	3 (6.9)
Lynch syndrome	1 (2.3)
Familial adenomatous polyposis	1 (2.3)
Multiple colonic polyps (non-APC)	1 (2.3)
PSH	
Cholecystectomy	7 (16.2)
Hemicolectomy	6 (13.9)
Presentation	
Abdominal pain	24 (55.8)
Vomiting	17 (39.5)
Bowel obstruction	13 (30.2)
Anemia	12 (27.9)
Overt gastrointestinal tract bleeding	5 (11.6)
Weight loss	8 (18.6)
Jaundice	5 (11.6)
Baseline laboratory parameters, and normal values	
Hb, g/dl (NR, 11.6-16.6)	10.5 (7.8-12.2)
CEA, μ g/l (NR, 0-4.3)	2.15 (1.6-4.2)
CA19-9, U/ml (NR, 0-27)	30 (12-77)
Albumin, g/l (NR, 34-54)	34 (30.9-38.7)
Bilirubin, mg/dl (NR, 0.1-1.2)	6 (4.0-9.5)
NLR	1.46 (0.75-3.7)
PLR	133.3 (103-267)
ECOG PS	
0/I	22 (51.2)
II	7 (16.3)
III	11 (25.5)
NA	3 (6.9)
Site of primary tumor	
Duodenum	26 (60.5)
Jejunum	12 (27.9)
Ileum	3 (6.9)
Unspecified	2 (4.7)
Tumor grade	
G1	3 (6.9)
G2	33 (76.7)
G3	5 (11.6)
NA	2 (4.7)
Stage	
I	3 (6.9)
II	12 (27.9)
III	10 (23.3)
IV	18 (41.9)

Values are expressed as n (%) or the median (interquartile range). APC, adenomatous polyposis coli; PMH, past medical history; PSH, past surgical history; Hb, hemoglobin; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; G, grade; NA, information not available; NR, normal range.

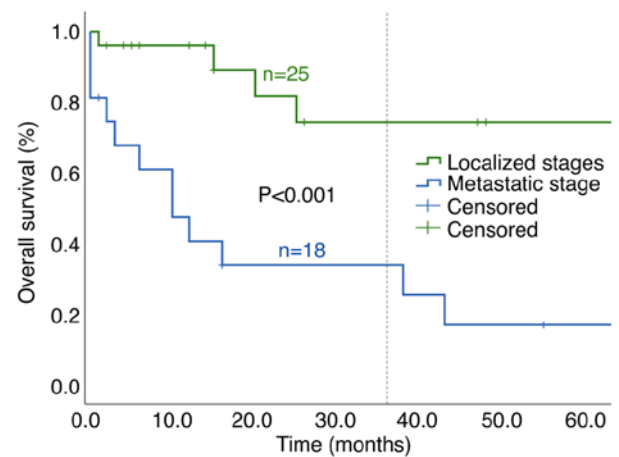


Figure 1. Kaplan-Meier curves of overall survival of patients with localized and metastatic small bowel adenocarcinoma.

progressive disease (n=5) and unknown in 3 patients. A total of 6 patients underwent surgery (R0, 2 patients) and 2 received radiation therapy. Furthermore, 3 patients received second-line chemotherapy (data not shown).

Survival outcomes. The median duration of follow-up was 12 months (range, 2-47 months). The median DFS for patients who achieved complete resection (R0 vs. R1) was 49 vs. 5 months ($P=0.02$). The median OS for localized disease vs. metastatic stage was not reached vs. 10 months and the 3-year OS was 74.3 vs. 33.9%, respectively ($P<0.001$; Fig. 1). The 3-year OS rates based on disease stage were 100% (I), 85% (II), 53% (III) and 33.9% (IV) ($P=0.001$). Furthermore, a lower ECOG PS ($P<0.001$), low baseline NLR ($P<0.001$) and no hypoalbuminemia ($P=0.02$) were associated with better OS (Fig. 2A-D). Chemotherapy administration for metastatic disease was associated with better PFS and OS; the median PFS was 6 vs. 1 month ($P=0.03$) and the median OS was 38 vs. 3 months ($P=0.02$). There was a trend of better survival with low CA19-9 and low PLR, but it did not reach statistical significance ($P=0.051$ and $P=0.33$, respectively). There was no association between grade and OS ($P=0.92$). Furthermore, there was no significant difference in OS by primary site (duodenum, jejunum or ileum). The 1-year OS rate was 77, 73 and 66.7%, respectively ($P=0.60$) (data not shown).

Discussion

The findings of the current study are consistent with previous reports and support recent findings related to the association of the baseline NLR with OS. Furthermore, the results indicated that a high baseline NLR was independently associated with a more advanced stage at diagnosis. Early-stage disease, better performance status, low NLR, normal albumin level and chemotherapy in the advanced stage were associated with better OS.

Older age at diagnosis in the patients of the present study did not correlate with survival outcomes. However, the median age in the present cohort was 53 years, which is relatively younger than the worldwide median age at diagnosis for SBA, perhaps due to the younger age distribution in the local popu-

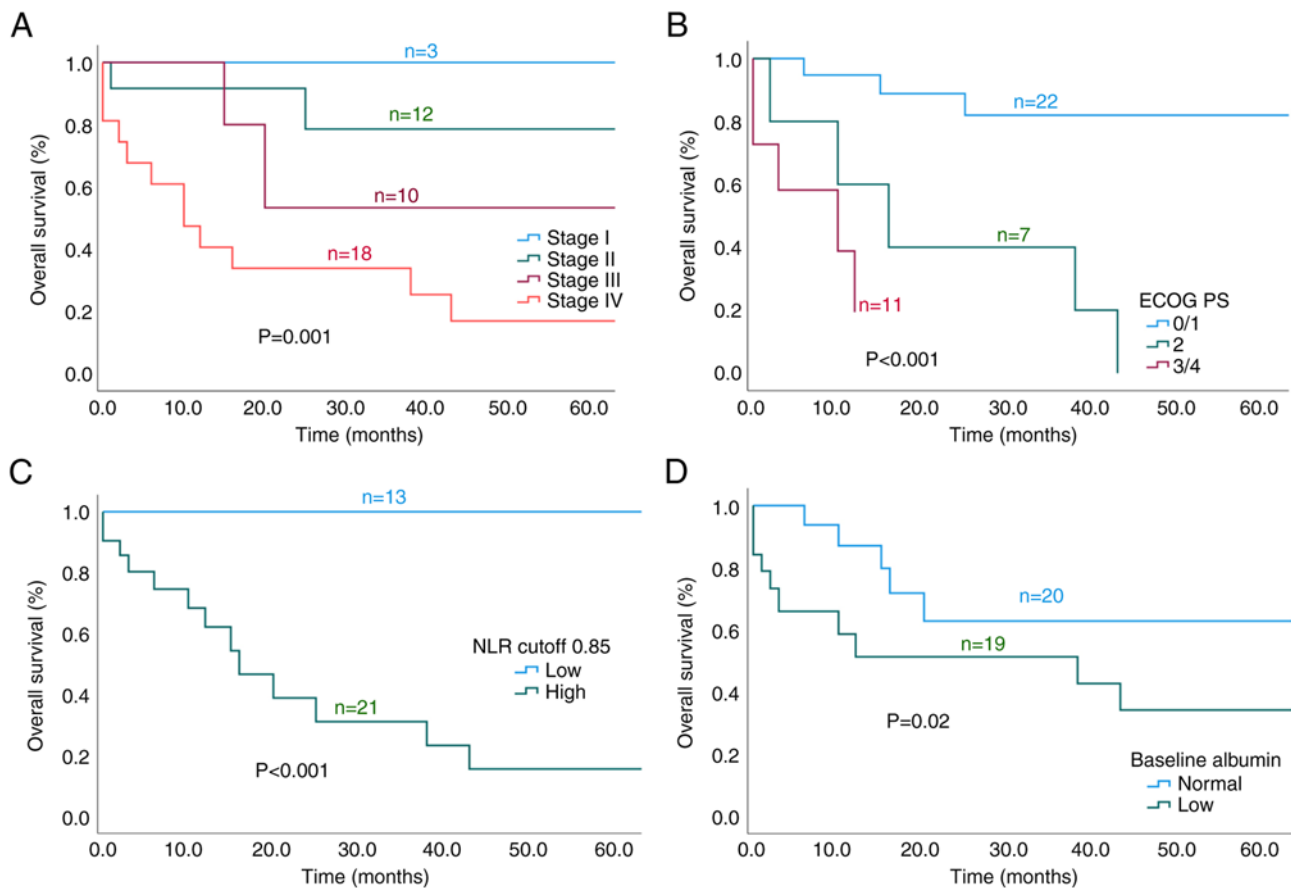


Figure 2. Kaplan-Meier curves of overall survival in patients with small bowel adenocarcinoma stratified by (A) stage, (B) ECOG PS, (C) NLR and (D) albumin level. ECOG PS, Eastern Cooperative Oncology Group Performance Status; NLR, neutrophil-lymphocyte ratio.

lation. In contrast to the young age at diagnosis in the present cohort (50% were younger than 55 years), other studies have found SBA to primarily be a disease of the elderly (3,12,13,21). SBA tends to occur more frequently in males (6,7,9,10,22), consistent with the present cohort. However, certain studies reported a relatively equal distribution by sex (12,13,21). There was no association between sex and survival outcomes in the present cohort; however, male sex was previously reported to be associated with worse survival outcomes in SBA (3,23).

A total of 30.2% of the patients of the current study presented with bowel obstruction or overt bleeding (11.6%), perhaps due to late presentation. These rates are similar to those of previous studies (6,24-26). Of note, 16.2% of the patients of the present study had a history of cholecystectomy; in two-thirds of them, the duodenum was the primary site and it was the jejunum in one-third. The Swedish registry included a quarter million patients who underwent cholecystectomy and reported a significant increase in small intestine cancers after surgery that correlated with the distance from the common bile duct (4,27).

The findings of the present study were similar to those of previous studies that reported the benefit of R0 resection in terms of prolonged survival outcomes in metastatic settings (10,11). Patients with advanced stage and poor ECOG PS had worse OS, consistent with other reported series (2,8,21,22,25,28).

Nearly half of the patients of the present study had increased tumor markers, which were not associated with

survival outcomes. Of note, high CA19-9 was associated with a trend of longer survival that was more pronounced in advanced settings, but it was not statistically significant ($P=0.06$). However, high CA19-9 was associated with shorter OS, particularly in the advanced stage (12,29). Hypoalbuminemia in the present cohort exhibited an association with a more advanced stage at diagnosis and a significant association with worse OS, consistent with the report by Sakae *et al* (28). Furthermore, a previous report also indicated that high lactate dehydrogenase is a prognostic factor for poor OS (28).

The NLR reflects the underlying inflammatory and immunity processes, two essential parts of the hallmarks of cancer (30). The NLR has been proven to have prognostic survival value in a variety of solid tumors, including gastrointestinal malignancies (31,32). Recently, two studies indicated that a high NLR is associated with poor survival outcomes in patients with SBA (13,33). Yanko *et al* (13) used 4.5 as the optimal cutoff for the NLR. They selected 4.5 based on the high median NLR in their cohort and the optimal NLR cutoff (median 3.5-4.5) of a previous study (34). However, that study included metastatic diseases and did not consider cancer site specificity (34). In the cohort of the present study, the median NLR was 1.46 and it was prespecified that the optimal NLR would be obtained from the ROC curve (19,20). However, in the present cohort, patients with $NLR > 4.5$ had worse survival, with a 3-year OS of 16.7 vs. 63% ($P<0.001$). Of note, a high

NLR in this cohort demonstrated an association with the metastatic stage at diagnosis, reflecting the aggressiveness of the disease. Despite the small sample size, the present results support the value of the NLR as an available biomarker that may be incorporated into the management of SBA. Further research is required to investigate the value of NLR in this setting and with immunotherapy (35). A low PLR was associated with a trend toward better OS, but it was not statistically significant. The median OS for low vs. high PLR was 65 vs. 38 months ($P=0.33$).

It should be acknowledged that the small sample size and retrospective nature of the present study are significant limitations. However, to the best of our knowledge, the present study was the first to explore the clinical characteristics and outcomes for SBA in a population from any Arab country, in this case Saudi Arabia.

In conclusion, the NLR is associated with a more advanced stage at the time of diagnosis of SBA. In addition to the ECOG PS, the stage at diagnosis, hypoalbuminemia and NLR are promising prognostic factors for survival.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

BA, AB, AS, MAE and AHA conceived the study and wrote the proposal. BA, MA, AS, MAE and SB collected the data. BA, MA, AB, SB and AHA analyzed the data. BA, MA and AHA confirm the authenticity of all of the raw data. BA wrote the first draft of the manuscript. All authors critically revised the manuscript for important intellectual content and have read and approved the final version.

Ethics approval and consent to participate

All methods followed the relevant guidelines and regulations. The study was approved and the requirement for informed patient consent was waived by the Research Advisory Council at King Faisal Specialist Hospital and Research Centre (Riyadh, Saudi Arabia; no. 2221168).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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