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Original Research Article

Influence of nutritional anemia on outcomes of colorectal cancer hospitalizations: a national inpatient sample database study

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ABSTRACT

Background: Colorectal carcinoma (CRC) is one of the leading causes of cancer related death globally. Prevalence of Nutritional Anemia is high among CRC patients. We aim to evaluate the role of Nutritional anemia on outcomes of CRC hospitalization.
Methods: We conducted a retrospective cohort study using the Nationwide Inpatient Sample (NIS) database, including all adult CRC patients hospitalized in the United States from 2016 to 2019. Patients were stratified into those with and without nutritional anemia (16.19% vs 83.81%) which included iron, B12, folate deficiency and other nutritional anemia per ICD-10 coding. Mortality was the primary outcome whereas length of stay (LOS), total charges, acute kidney injury (AKI), pulmonary embolism (PE), deep vein thrombosis (DVT), colonoscopy, abdominal surgery and lower gastrointestinal (GI) bleeding were secondary outcomes. Multivariate regression model was used to estimate the outcomes of CRC hospitalization after adjusting for potential confounders.
Results: A total of 504,515 patients were hospitalized for CRC. Among two groups, patients with anemia were older in age. Mortality was significantly lower among patients with nutritional anemia. Lower GI bleeding and colonoscopy during inpatient stay were significantly higher among CRC cohort with nutritional anemia. Similarly, LOS, total hospitalization charges, AKI, PE and DVT were also significantly higher among anemia cohort. However, need for abdominal surgery was significantly lower among CRC patients with nutritional anemia.
Conclusions: Nutritional anemia in CRC patients is associated with longer length of stay, increased cost, higher risk of in-patient complications. Therefore, it should be corrected to optimize outcomes among CRC patients.

Keywords: Colorectal cancer, Mortality, Nutritional anemia

INTRODUCTION

Colorectal carcinoma comprises the malignant neoplasms of the colon and rectum with multifactorial etiology. It is one of the most common leading causes of cancer related death globally. As per United States Cancer Statistics report 2020, colorectal carcinoma was the fourth most commonly diagnosed cancer with an incidence of 33 per 100000 population. In addition, colorectal cancer accounted for fourth most common cancer related death in

the United States.[1] Over past decade, despite a decreasing trend in overall CRC related mortality, the age adjusted mortality rate is increasing among younger patients and significant readmissions has been reported post Colorectal carcinoma surgeries.[2,3] This contributes to the rising overall healthcare burden due to colorectal cancer.

Disease presentations vary based on the location of tumor ranging from chronic occult blood loss in the right colonic tumor to frank bleeding in the left colonic tumor. Therefore, anemia is the most common extraintestinal symptom in patients with colorectal cancer. A retrospective study reported that 48.1% of the patients undergoing colorectal cancer surgery were found to have iron deficiency and among this iron deficient state 66.1% had anemia. Of these iron-deficient patients, 3.7% had an isolated absolute iron deficiency (AID) and 15.3% a functional iron deficiency (FID), while the rest had a combination of AID and FID.[4] Pathophysiology of anemia in colorectal cancer is multifactorial which includes disturbance in iron homeostasis, impaired proliferation of erythroid progenitor cells, and a blunted erythropoietin response to anemia. Furthermore, tumor cells can promote formation of proinflammatory cytokines and free radicals that damage erythroid progenitor cells.[5] Colorectal cancer can promote underlying inflammation and upregulation of hepcidin which altogether can cause functional iron deficiency whereas chronic blood loss from the GI tract can cause absolute iron deficiency.[5-8] In addition to iron deficiency, patients with colorectal cancer are also reported to have folate and B12 deficiency.

Advancements in the management of the colorectal cancer including primary and secondary preventive techniques have shown improvement in the survival rates, however overall disease burden continues to rise globally.[2,9] Multiple studies have been conducted assessing the preoperative prevalence and management of nutritional status including iron, folate and vitamin B12 deficiency in patients with colorectal cancer.[4,10,11] However, there is a paucity of literature assessing effects of coexisting anemia on hospitalization outcomes in patients admitted with principal diagnosis of colorectal cancer. The objective of this study was to compare the hospitalization outcomes like mortality, length of stay, discharge disposition, and other complications like AKI, sepsis, shock etc., among the cohort of patients with and without co-existing nutritional anemia in patients with colorectal cancer.

METHODS

Study design and database description

This was a retrospective cohort study of adult patients hospitalized with principal diagnosis of colorectal carcinoma in the US from 2016-19. Data was sourced from the Nationwide Inpatient Sample (NIS) database which is largest publicly available inpatient database in the US, developed and maintained by Healthcare Cost and Utilization Project (HCUP). NIS is largest publicly available all-payer inpatient healthcare database which estimates US regional and national inpatient utilization, access, cost, quality and outcomes from all non-federal acute care hospitals nationwide. NIS approximates a 20-percent stratified sample of all discharges from U.S. community hospitals, excluding rehabilitation and long-term acute care hospitals. It contains anonymized clinical and resource-use information including patient demographic characteristics, hospital characteristics, healthcare utilization information like total charge, length of stay, etc., that is included in a typical discharge with safeguards to protect the privacy of patients, physicians and hospitals. NIS contains unweighted data from around 7 million hospital stays and around 35 million weighted estimates of hospitalizations nationwide. Databases from 2016 onwards are coded using the International Classification of Diseases, tenth revision, clinical modification/procedure coding system (ICD-10-CM/PCM). In the NIS, diagnoses are divided into two separate categories: principal diagnosis and secondary diagnoses. A principal admission diagnosis represents the chief medical ailment responsible for admission of the patient to the hospital for care during this hospitalization and Secondary diagnoses includes additional medical conditions other than principal admission diagnosis including other past medical histories.[12,13]

Study population

A total of 504515 patients aged 18 years or more, admitted from 2016 to 2019 with principal admission diagnosis of Colorectal cancer (CRC) were identified using ICD-10-CM coding system from NIS database. ICD-10 codes C18.X, C19, C20 and others were used to query the NIS database 2016-2019 to identify patients admitted with principal diagnosis of CRC.[14] Patients admitted with principal admission diagnosis of CRC were then stratified into two groups: patients with (study group) and without (control group) secondary diagnosis of nutritional anemia. Nutritional anemia was defined as those having either of the four conditions: iron deficiency (D50.X), vitamin B12 deficiency (D51.X), folate deficiency (D52.X) or other nutritional deficiency (D53.X). Flow diagram depicting the distribution of study participants is presented in Figure 1.

Study variables and outcomes

Study variables include patient's demographic variables, hospital characteristics and Charlson Comorbidity Index (CCI). Information about age, sex, race, insurance provider, median income in patient's zip code and hospital characteristics including hospital region, teaching status, bed size and location were collected from NIS database directly. Patient's comorbid status was categorized using Deyo adaption of CCI for research relying on ICD diagnosis and procedure codes. Deyo adaption of CCI consists of total of 19 categories of clinical comorbid conditions which are assigned prespecified scores.[15] CCI

predicts the 10-year mortality of the patient based on the CCI scores.

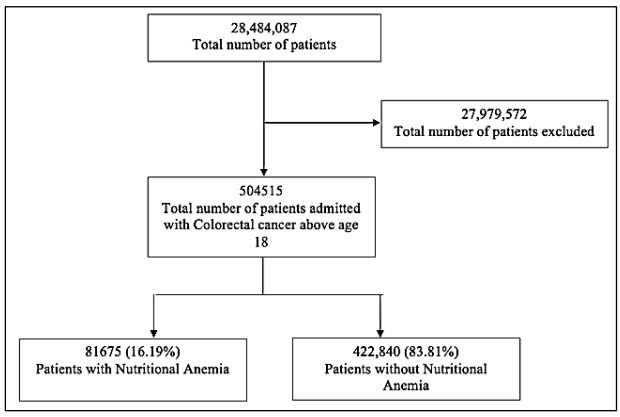

Figure 1: Patient inclusion and exclusion flow diagram.

The primary outcome of the study was mortality where secondary outcomes included length of stay, total parenteral nutrition (TPN), acute kidney injury (AKI), sepsis, shock, lower GI bleeding, pulmonary embolism, deep vein thrombosis (DVT), cardiac arrest, stroke, colonoscopy/sigmoidoscopy (with biopsy), abdominal surgery and total hospitalization charge. Mortality, length of stay and total hospitalization charge were directly coded within the NIS for each hospitalization. Procedures like colonoscopy, abdominal surgery and total parenteral nutrition were defined using appropriate ICD-10 PCM codes. Rest of the secondary outcomes were coded using appropriate ICD-10 DCM codes (available in supplementary file 1). Potential confounders addressed in the study included age, sex, race, median income in patient's zip code, CCI, hospital bed size, hospital region, hospital teaching status, and hospital location.

Statistical analysis

Stata® _Version 18 software (StataCorp, Texas, USA) was used for data analysis. All analyses were conducted using the weighted samples for national estimates in adjunct with HCUP regulations for using the NIS database. HCUP rules and regulations were thoroughly followed in utilizing the NIS database. Hospitalization characteristics such as mean age and distribution of variables like race, gender, hospital location, hospital teaching status, and hospital bed capacity were obtained from the database. Continuous variables were expressed as mean ± standard deviation and was assessed by Student's t-test whereas categorical variables were expressed as frequencies and percentages and assessed by Pearson chi-square method. To identify all possible confounders, we performed thorough review of existing literature on colorectal carcinoma and anemia, obtained expert opinion from the experts in the respective fields, and performed a univariate screening. Following the univariate screening, all the variables with p value less than 0.2 were included in Multivariate regression model to adjust for confounders while calculating the primary and secondary outcomes. Outcomes that were adjusted for included age, race, Charlson comorbidity groups, hospital location, hospital region, hospital bed size, hospital teaching status, insurance status, quartile of household income. Multivariate linear regression analysis was used for continuous variables whereas multivariate logistic regression analysis was used for binary/dichotomous variables to compare the outcomes among different groups. All p values <0.05 were considered statistically significant.

RESULTS

Demographic characteristics

A total of 504515 patients were hospitalized with principal diagnosis of CRC of which 16.19% had Nutritional anemia. The patients with nutritional anemia were more likely to be females (51.16% vs 46.66% with p<0.001) and older in age (69.06 vs 65.77 years with p<0.001) compared to the patients without nutritional anemia. Among the entire study population, patients in both the groups were more likely to have Medicare as insurance provider and predominant race was White. Patients with nutritional anemia were more likely to have higher CCI score compared to control group. A majority of the CRC hospitalizations occurred in urban located teaching hospitals. Figure 1 depicts the distribution of study population into those two groups. Table 1 demonstrates the patient and hospital characteristics.

Primary outcome

The rate of in-hospital mortality for patients with nutritional anemia was lower compared to those without it (2.05% vs 2.64% with p<0.001 respectively). Patients with nutritional anemia had 38% lower odds of in-hospital mortality compared to patients without nutritional anemia on multivariate analysis.

Secondary outcomes

Measures of healthcare utilization

Hospital length of stay and total hospitalization charges were used as surrogate measures of healthcare utilization. Among all the patients hospitalized for CRC, patients with nutritional anemia were found to have higher mean length of stay [3.73 vs 2.53 days, p<0.001] and higher total hospitalization charges [$46895 vs $39546, p<0.001] compared to control group. This was further supported by higher adjusted coefficient for Length of stay [1.17(1.03-1.30), p<0.001] and total hospitalization charges [$7313 (5553-9072) p<0.001] on multivariate regression model.

Table 1: Patient demographic characteristics.

Variable	Total patients with Colorectal cancer: 504515		
	Nutritional anemia: 16.19(%)	No nutritional anemia: 83.81(%)	P value
Gender			
Female	(51.16)	(46.66)	<0.001
Male	(48.84)	(53.34)	<0.001
Mean age in years	69.06	65.77	<0.001
Insurance provider			
Medicare	(62.13)	(53.75)	< 0.001
Medicaid	(10.24)	(9.71)	
Private	(23.99)	(34.03)	
Uninsured	(3.65)	(2.5)	
Charlson comorbidity index			
0	(0.067)	(0.2)	< 0.001
1	(0.067)	(0.13)	
2	(23.2)	(34.19)	
3 or more	(76.67)	(65.49)	
Median income in patient zip code			
$1 - 51,999	(28.87)	(26.89)	<0.0001
$52,000 - 65,999	(26.02)	(26.33)	
$66,000 - 87,999	(24.52)	(24.63)	
$88,000+	(20.59)	(22.15)	
Hospital region			
Northwest	(16.92)	(19.09)	<0.001
Midwest	(23.82)	(21.92)	
South	(38.89)	(39.25)	
West	(20.37)	(19.74)	
Hospital teaching status			
Non teaching	(31.78)	(27.44)	< 0.001
Teaching	(68.22)	(72.56)	
Hospital bed size			
Small	(18.9)	(17.54)	<0.001
Medium	(29.97)	(28.43)	
Large	(51.13)	(54.03)	
Race			
White	(67.56)	(72.52)	< 0.001
Black	(16.05)	(11.3)	
Hispanic	(9.83)	(8.97)	
Asian or Pacific Islander	(3.47)	(3.78)	
Native American	(0.47)	(0.51)	
Other	(2.62)	(2.91)	
Hospital location			
Rural	(8.08)	(8.19)	0.6535
Urban	(91.92)	(91.81)	

Other outcomes

During CRC hospitalization, patients with nutritional anemia were associated with higher odds of development of complications like AKI [aOR-1.24(1.17-1.31), p<0.001], sepsis [aOR=1.49 (1.28-1.73), p<0.001], pulmonary embolism [aOR-1.91 (1.67-2.19), p<0.001] and deep vein thrombosis [aOR=1.59(1.42-1.78), p<0.001] compared to patients without it. Among procedural interventions, patients with nutritional anemia were associated with higher odds of undergoing colonoscopy [aOR=2.49 (2.40-2.59), p<0.001] and lower odds of requiring abdominal surgery [aOR=0.87 (0.84-0.90), p<0.001] compared to patients without nutritional anemia. Odds of lower GI bleeding was noted higher among nutritional anemia group compared to those

without it [aOR=2.39 (2.25-2.54), p<0.001]. Requirement of total parenteral nutrition was reported higher among nutritional anemia group compared to no nutritional anemia group [2.49% vs 2.03% p<0.001 respectively] with showing increasing trend of adjusted OR 1.12, p=0.054. Development of shock was noted lower among patients with nutritional anemia [aOR=0.78 (0.67-0.89), p=0.001] compared to those without it.

Table 2: Clinical outcomes in patients hospitalized with colorectal cancer.

Outcomes	Anemia	No anemia	P value
Mortality (%)	2.05	2.64	<0.001
Adjusted OR	0.62 (0.54-0.70)[a]		<0.001
Unadjusted OR	0.77 (0.68-0.87)[a]		<0.001
LOS (days)	3.73	2.56	<0.001
Adjusted coeff	1.17 (1.03-1.30)[a]		<0.001
Unadjusted coeff	1.58 (1.45-1.70)[a]		<0.001
Total charge ($)	46895	39546	<0.001
Adjusted coeff	7313 (5553-9072)[a]		<0.001
Unadjusted coeff	9500 (7760-11239)[a]		<0.001
AKI	15.23%	10.36%	<0.001
Adjusted OR	1.24 (1.17-1.31)[a]		<0.001
Unadjusted OR	1.56 (1.48-1.63)[a]		<0.001
Shock (%)	1.63	1.81	0.1333
Adjusted OR	0.78 (0.67-0.89)[a]		0.001
Unadjusted OR	0.90 (0.79-1.03)[a]		0.133
Sepsis (%)	1.63	0.97	<0.001
Adjusted OR	1.49 (1.28-1.73)[a]		<0.001
Unadjusted OR	1.68 (1.48-1.93)[a]		<0.001
TPN (%)	2.49	2.03	0.002
Adjusted OR	1.12 (0.99-1.25)[a]		0.054
Unadjusted OR	1.22 (1.10-1.37)[a]		0.000
Pulmonary embolism (%)	2.06	0.98	<0.001
Adjusted OR	1.91 (1.67-2.19)[a]		<0.001
Unadjusted OR	2.13 (1.87-2.42)[a]		<0.001
DVT (%)	3.04	1.62	<0.001
Adjusted OR	1.59 (1.42-1.78)[a]		<0.001
Unadjusted OR	1.90 (1.70-2.11)[a]		<0.001
Colonoscopy (%)	43.97	23.05	<0.001
Adjusted OR	2.49 (2.40-2.59)[a]		<0.001
Unadjusted OR	2.61 (2.52-2.71)[a]		<0.001
Abdominal surgery	51.91%	56.85%	<0.001
Adjusted OR	0.87 (0.84-0.90)[a]		<0.001
Unadjusted OR	0.81 (0.79-0.84)[a]		<0.001
Lower GI bleed (%)	12.24	4.77%	<0.001
Adjusted OR	2.39 (2.25-2.54)[a]		<0.001
Unadjusted OR	2.78 (2.62-2.94)[a]		<0.001

a=95% Confidence Interval

DISCUSSION

We analyzed the outcomes of CRC hospitalization among two groups of patients with and without nutritional anemia with underlying CRC in this study. Major differences were seen among two groups in terms of in-hospital mortality, measures of healthcare utilization and development of other complications. Although, nutritional anemia among CRC patients was found to be associated with lower in-hospital mortality, measures of healthcare utilization (LOS and total hospitalization charges) were found to be higher among patients with nutritional anemia. Significantly higher odds of development of complications like AKI, sepsis, deep vein thrombosis, pulmonary embolism, and lower GI bleeding was seen among CRC patients with nutritional anemia compared to non-anemia group. However, there was a lower odd of development of shock among colorectal cancer patients with nutritional anemia compared to those without it. Our study reported higher odds of undergoing colonoscopy and lower odds of abdominal surgery among patients with nutritional anemia compared to those without nutritional anemia. Although not statistically significant, there were was a positive trend of requirement of TPN among nutritional anemia group compared to those without it.

Over the past decade, studies have shown that despite of uptrend in colorectal cancer admissions, there is overall decrease in all cause inpatient mortality due to colorectal cancer (4.5% in 2010 to 4.16% in 2019, P=.033).[16] Interestingly, our study reported significantly reduced inpatient mortality among patients with nutritional anemia as compared to those without it which can be attributed to different factors. In a Swedish based single center retrospective study evaluating the effects of preoperative anemia in colorectal cancer patients undergoing surgery, presence of anemia was associated with increased risk for overall mortality (HR 2.1, 95% CI 1.4-3.2, p<0.001).[17] The difference in the trends in the mortality compared to our study may be attributed to the elective nature of admissions for surgical procedure whereas our study participants had non elective admissions presenting with varied symptomatology. Also, our study lacks the data on severity of anemia which can further affect the study results. While a National inpatient sample database study (1999-2014) claimed that inpatient mortality was higher in colorectal cancer patients with Iron deficiency anemia compared to those without it (4.5% vs. 2.3%, p<0.001) our study results are unique as it takes into account the B12 and folate deficiency anemia in the study group in addition to iron deficiency anemia. More research literature like effects of B12 and folate deficiency on the mortality among colorectal cancer patients are required to further solidify the findings of this study.[18]

Our study reported that colorectal cancer patients with nutritional anemia were found to have higher odds of increased length of stay and increased total hospitalization charges compared to those without it. As per our study findings patients with nutritional anemia were likely to have higher comorbidity burden and higher odds of in-patient complications like DVT, pulmonary embolism, AKI sepsis and lower GI bleeding. This can contribute to complicated hospital course which can increase length of

stay and total hospitalization charges. Higher CCI index is associated with increased length of hospitalizations in colorectal cancer and other diseases states as well.[19-21] This finding can be further supported by an NIS based study where lower GI bleeding was associated with increased odds of LOS (adjusted coefficient: 0.61 days, p<0.01) and total hospitalization charges (adjusted coefficients: $3334.64, p = 0.001) in patients with colorectal cancer.[22]

The pathophysiology of lower GI bleeding in colorectal cancer involves tumor growth, invasion and eventual infiltration of the colon or rectum which can compromise the integrity of the blood vessels, leading to bleeding.[22] In advanced stages, the necrosis and ulceration of the tumor surface can contribute to development of haemorrhage.[23] Chronic GI blood loss along with functional iron deficiency can contribute to development of anemia in patients with colorectal cancer and this is supported by the higher association of lower GI bleeding in patients with nutritional anemia compared to those without anemia in our study. As per the American College of Gastroenterology guidelines, Colonoscopy is the first choice for diagnostic and therapeutic intervention in management of lower GI bleeding with the diagnostic yield of 48 to 90% in this patient population.[23-25] Higher odds of lower GI bleeding the nutritional anemia cohort further necessitates the colonoscopic intervention in this group which is supported by the statistically significant higher odds of performance of colonoscopy in this cohort in our study.

Studies showing correlation between development of DVT and pulmonary embolism among anemia patients particularly in colorectal cancer patients have been lacking. Exact pathophysiology for development in thrombosis in anemic patients remains elusive. However, some mechanisms have been postulated to support these findings. In anemia, hypoxia induced changes in gene expression may affect the interaction between erythrocytes and endothelium, increasing the risk for thrombosis.[26] Also, iron deficiency has been linked to thrombosis secondary to reduced inhibition of thrombopoiesis and subsequent reactive thrombocytosis.[27] There are some studies where anemia was found to be an independent predictor for DVT and pulmonary embolism. In a retrospective analysis of patients undergoing bone trauma surgery, patients with preoperative anemia were highly correlated with perioperative DVT after adjusting for confounding factors and propensity score matching.[17] In a retrospective study conducted by Can et al it was found that the mean blood hemoglobin level was lower in the pulmonary embolism group compared to age and gender matched control group [11.6±2.0 g/dl vs 13.0±1.7 g /dl (p<0.001].[28] These results further correlate with the findings of our study where DVT and PE were found to be higher among nutritional anemia group compared to control group.

Pathophysiology for development of kidney injury in anemic patients is multifactorial ranging from renal hypoxia and oxidative stress to development of subclinical renal insults.[29,30] In a retrospective study evaluating the relationship between anemia and AKI in critically ill patients, it was noticed that patients with anemia were associated with higher odds of development of AKI. This finding can be correlated with our study findings where there was a higher associated odds of development of AKI in anemic patients compared to the control group. As per our study findings, colorectal patients with nutritional anemia were associated with higher odds of sepsis compared to those without it. This can be correlated with a systemic review and meta-analysis evaluating the prognostic value of hemoglobin level in patient with sepsis where the mortality of sepsis patients increased with decreasing hemoglobin levels.[31]

There are some inherent limitations of our study. Firstly, given the administrative nature of the NIS database, it is vulnerable to potential misclassification of subjects and variables. To reduce the sampling bias, we used previously validated codes to define the study sample. While quality control measures are in place to monitor the data abstraction process, the possibility of human coding errors cannot be excluded. Secondly, our analysis relies exclusively on claimed data rather than clinical details, hence it is not possible to take into account the multiple comorbidities associated with principal diagnosis. Thirdly, we were not able to differentiate the patients based on the severity of the anemia which can affect the outcomes. Also, newly diagnosed cancer patients and those who received the anticancer therapy treatment were not able to be separated which can be a potential confounder affecting the outcomes of hospitalization. Fourthly, NIS specifically lacks intra-procedural details, specific procedural techniques utilized during the procedure, operator preferences which can be significantly related with the outcomes. Lastly, using the National Inpatient Sample we are unable to correlate the exact cause of death in any given cohort.

CONCLUSION

Despite the limitations of the study, this is one of the first population-based studies done using the largest publicly available national database which evaluated the outcomes of the colorectal hospitalizations. Our study reported higher odds of inpatient complications like AKI, sepsis, DVT, pulmonary embolism and lower GI bleeding. Therefore, early identification and management of such complications can help improve overall healthcare outcomes among colorectal cancer patients. Also, there was a higher likelihood of inpatient colonoscopy and lower odds of intra-abdominal surgery among patients with nutritional anemia cohorts. This study reported some unique findings like lower odds of association in hospital mortality, development of shock and performance of abdominal surgery among nutritional anemia patients which warrants further research to support the results. Overall, this study has paved a way for new possibilities like nutritional supplementation in improving the

outcomes of colorectal hospitalizations in patients with nutritional anemia, for which further research and clinical trials would be appreciated.

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