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Rural-Urban Differences in Survival Among People With Early Onset Colorectal Cancer

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RURAL-URBAN DIFFERENCES IN SURVIVAL AMONG PEOPLE WITH EARLY ONSET COLORECTAL CANCER

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DEDICATION

I would like to dedicate my work to the memory of my deceased mother, Mrs. Revathi Rangarajan, who died due to bladder cancer metastasis. My work is completely dedicated to my husband, Mr. Ranganathan, my loving kids, Thritha Ranganathan and Aparajit Ranganathan, without whose constant support and understanding my student tenure here was not possible.

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ABSTRACT

Colorectal cancer (CRC) is the third most common cancer and the second most among cancer deaths both in the US and globally. Early Onset Colorectal Cancer (EOCRC), occurring between the ages of 20 and 49, has continued to rise over the past decades. Several studies have reported a persistent increase in EOCRC incidence and mortality, especially in rural areas as compared to urban areas, despite decreases in rates for people over the age of 50 years. Increase in EOCRC may have played a role in lowering the age of screening recommendation to 45-49 age group. The objective of this study was to examine the association between rural-urban status and survival in an EOCRC population. The twofold objectives were, 1) to determine the rural-urban differences in 1-, 3- and 5-year survival among individuals with EOCRC and, 2) to evaluate the rural-urban differences in EOCRC survival by gender, age, race, ethnicity status, and payer types (any Medicaid, insured/no specifics, uninsured and unknown groups). Descriptive statistics for the sample were calculated and compared by rural-urban status using chi-square tests. Kaplan-Meier survival curves were constructed to examine rural-urban differences in survival among EOCRC patients. Adjusting for various characteristics, multivariable extended cox proportional hazards analyses were used to estimate hazards ratios and were reported as estimates and 95% confidence intervals. Among the included 65,716 EOCRC patients, rural patients had lower 5-year survival from EOCRC as compared to urban patients (69% vs. 71%, P<0.001). Rural EOCRC patients had greater risk of mortality from all causes [overall: HR: 1.10, 95% CI: 1.04 – 1.16, P<0.001] and

EOCRC specific [HR: 1.10, 95% CI: 1.04 – 1.17, P<0.01], as compared to urban EOCRC patients, even after adjusting for sociodemographic, individual level and clinical characteristics. Race was an effect modifier of association between rural-urban status and survival in EOCRC patients. The magnitude of the association was greatest among non-Hispanic Asians/Pacific Islanders and non-Hispanic Whites as compared to non-Hispanic Black residents or Hispanics. Rural residents with EOCRC are at greater risk for adverse survival outcomes if disparities remain. Hence, it is important to ensure rural men, and minoritized populations undergo timely screening, diagnosis, and guideline adherent treatment to avoid missed opportunities and delays in accessing needed care. Results from this study may have the potential to inform policy interventions and strategies to address rural cancer control and to overcome disparities in EOCRC survival.

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CHAPTER 1

INTRODUCTION AND SPECIFIC AIMS

1.1 Introduction

Colorectal cancer (CRC) is the third most common cancer and the second most among cancer deaths both in the United States and globally. [1,2] An estimated 106,180 new cases of colon and 44,850 cases of rectal cancer will occur in 2022.[1] Additionally, it is estimated that in 2022, over 52,580 deaths will be due to CRC.[1] More than one-tenth of the CRC cases are early in onset. i.e., occurring in individuals younger than 50 years of age.[3] Early onset colorectal cancer (EOCRC), cancer in the colon and rectum occurring between the ages of 20 and 49), has continued to rise since 1994.[4,5] This is alarming as the overall CRC incidence has been decreasing.[6,Error! Reference source not found.] The incidence rates for overall cancer among adults aged 20-49 are substantially lower among men (115.3 per 100 000) than women (203.3 per 100 000). However, CRC is the leading cause of cancer incidence for men (13.7 per 100 000) in this age-group.[7]

Studies have documented distinct geographic patterns in EOCRC survival with a greater percentage of survival disadvantage among EOCRC patients residing in the Southern parts of the US.[9,10] Figures 1.1 and 1.2, shows the results from interactive maps of CRC incidence and death rates for the latest 5-year average by US states for ages<50 years.[12] Midwest (Iowa) and southern states (Kentucky, Virginia, Oklahoma, Arkansas,

Mississippi, Alabama & Louisiana) have the highest incidence rates per 100,000 for EOCRC compared to the national average (8.4 per 100,000). Between 2015-2019, EOCRC death rates was higher in Vermont, Oklahoma, Arkansas, Mississippi, Alabama, and South Carolina (>2.2 to 2.6 per 100,000 vs 1.8 per 100,000 national average).[12]

"Primary prevention, early detection and treatment, and survivorship activities", are among the main cross-cutting priorities of the Center for Disease Control & Prevention's National Comprehensive Cancer Control Program (NCCCP)'s objectives.[Error! Reference source not found.] The US Preventive Services Taskforce (USPSTF), has recently updated its guidelines to include screening for colorectal cancer in adults aged 45 to 49 years, and this recommendation is applicable to asymptomatic adults aged 45 years or older, who are at average risk for developing CRC.[13] However, screening methods are subject to limitations and many screen-eligible populations remain unscreened.[0]

Despite the government's initiatives, significant disparities in the cancer burden exists. Several studies have reported a persistent increase in cancer incidence and mortality, especially in rural areas as compared to urban.[22-19] For example, CRC rates are higher in rural non-Hispanic White and Black men and women as compared to urban residents.[16] Also, findings suggest that rural residence is associated with increased risk for developing colon cancer.[18,20] As the rural representation comprises between ~15 – 20% of the US population,[21] cancer health disparities among rural population can have a remarkable impact on the nation's health. ***Therefore, this study aimed to investigate the association between rural-urban status and survival in EOCRC in the United States.***

The Patient Protection and Affordable Care Act (2010), reduced the number of uninsured, including those among those with cancer.[22] However, disparities in payer status remains to be a potential contributing factor influencing cancer survivorship outcomes.[23] Studies show that insurance status contributes to poorer survival in CRC especially in Medicaid and uninsured populations.[23,24] In a study by ***Tawk R et al 2015***,[25] data from Surveillance Epidemiology & End Results (SEER) Program was utilized to examine the impact of race and insurance status on CRC outcomes. They found that uninsured status was associated with an increase in CRC-related deaths even after adjusting for sociodemographic and tumor related characteristics in the population.[25] Individuals without insurance most often miss undergoing screening, may receive inadequate evaluation of symptoms and are less likely to receive chemotherapy (treatment) for advanced disease and these barriers are more pronounced in women as compared to men.[24,26] Given the evidence that insurance status, especially Medicaid payer type, race, and gender impacts survival in EOCRC, ***this study assessed the modifying role of payer status, gender, age, and race on the association between rural-urban status and survival in EOCRC.***

1.2 Aims and Research Hypotheses

The overall goal of this study was to investigate the association between rural-urban status and survival in EOCRC in the United States.

Aim 1: To determine the rural-urban differences in 1-, 3-year and 5-year survival among patients with EOCRC for sociodemographic, individual level and clinical characteristics.

Hypothesis: 1-, 3- and 5-year survival in EOCRC is lower among rural residents as compared to their urban counter parts.

Aim 2: To examine the association of rural-urban status and survival among patients with EOCRC.

Hypothesis: Survival in EOCRC is lower among rural residents as compared to their urban counterparts. after adjusting for potential confounders.

Aim 2A: To investigate the modifying impact of gender, payer type, age, and race on the association between rural-urban status and survival in patients with EOCRC.

1.3 Significance

Among the four commonly occurring cancers (female breast, prostate, lung and bronchus, colon and rectum), colorectal cancer occurs more frequently in rural areas as compared to urban areas.[27,28] Between 2000-2016, incidence of EOCRC increased to about 35% in rural areas (vs. 20% increase in urban).[29] Studies suggest that people who live in counties with persistent poverty levels are at high risk for mortality from CRC.[30,31] Also, people in rural communities often face challenges like lower rates of cancer screening (mainly CRC),[32] delayed diagnoses and survivorship related hardships (e.g., poverty, lower income levels, lack of education, lack of insurance, travel barriers), [16,1,34] which may have an adverse impact on the survival outcomes for EOCRC.

Deaths due to cancer are higher in rural areas as compared to urban.[35] More strikingly, deaths from colorectal cancer among people younger than age 55 have increased 2% per year from 2007 and 2016.[35] The 5-year relative survival for CRC is about 64% (64.5% in females vs 62.6% in males).[36] Marked racial disparities in survival for EOCRC exist. For example, non-Hispanic Black residents diagnosed with stage II CRC are 60% more likely to die of EOCRC as compared to non-Hispanic White residents.[37] It is important to note that these younger patients have more aggressive types of tumors that respond to

treatment differently than older age groups which puts them at risk for adverse survival outcomes.[37,38]

The reasons behind increases in the recent incidence of EOCRC are not completely understood.[37,39] It is also unclear whether geographic disparities contribute to an increase in incidence and poorer survival outcomes in EOCRC populations. Mortality and survival for EOCRC in rural populations are yet to be explored. Given the dearth of research on EOCRC survival, it is important to examine the association between rural-urban status and survival among EOCRC population. While geographic factors, payor status and disease staging alone cannot affect survival in EOCRC, they can impact cancer prevention, diagnosis/treatment opportunities especially in rural population, which is a major public health concern in the United States.

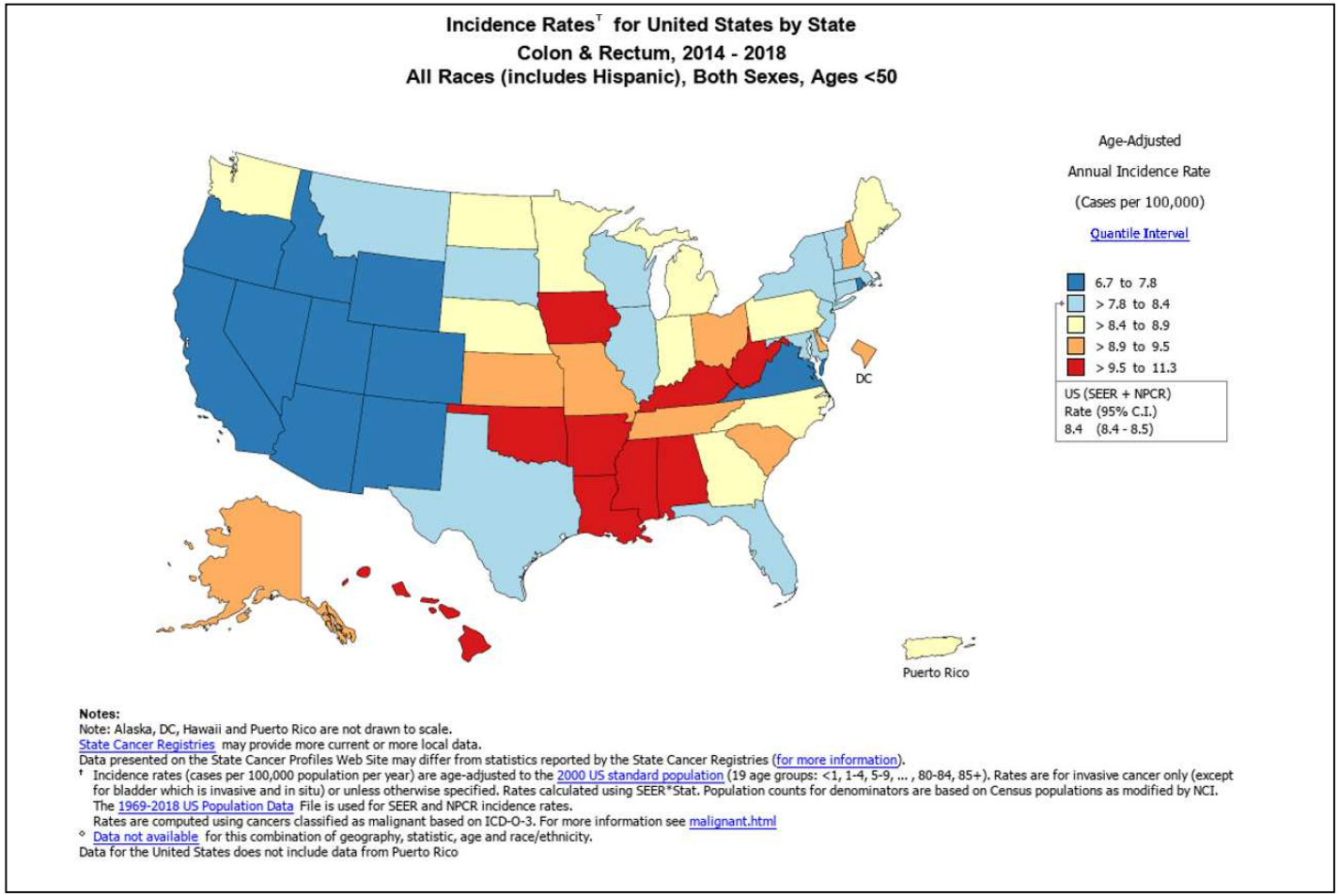

Figure 1.1: Incidence rates (2014-2018) of colorectal cancer in age group <50 years, by US states. National Cancer Institute, State Cancer Profiles. [12]

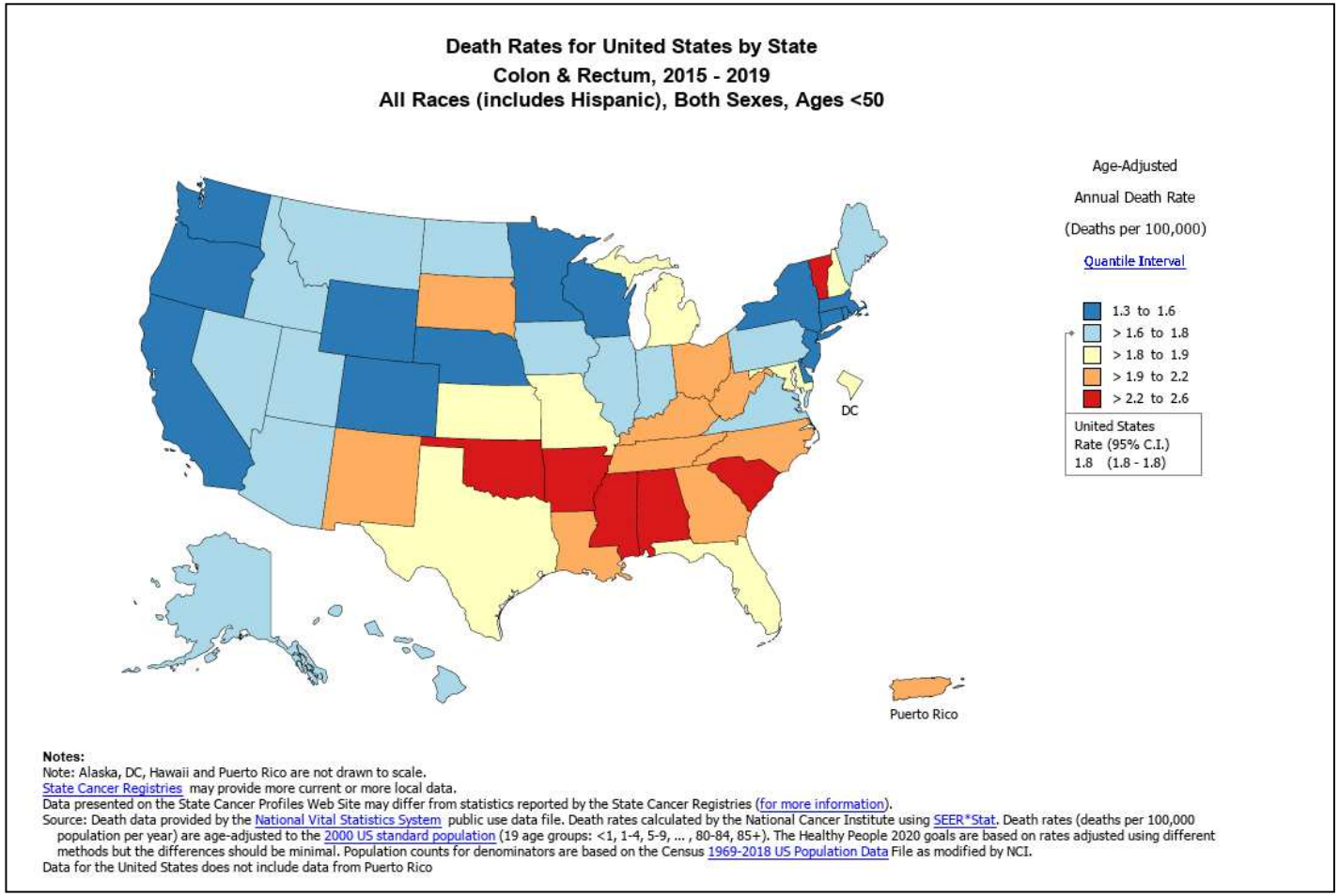

Figure 1.2: Death rates (2015-2019) of colorectal cancer in age group <50 years, by US states. National Cancer Institute, State Cancer Profiles. [12]

CHAPTER 2

BACKGROUND

2.1 EOCRC Epidemiology and Risk Factors

The incidence and mortality for CRC is decreasing in all ages above 50 years but increasing to a greater extent in the 20 – 49 years age group.[3,4] Evidence suggests that CRC will be the second leading cause for highest incidence and mortality in this age group, by the year 2040.[40,41] The trends in CRC incidence and mortality rates, as characterized by age groups among US population are shown in Figure 2.1. The incidence rates for CRC among people aged between 20-49 years was 9.3 per 100,000 in 1975 and by 2015, it increased to about 13.7 per 100,000 population.[2] On the contrary, incidence rates for age groups 50 years and above had a steady decline. Across all other age groups, mortality rates have decreased overall and is lower in elderly females aged 75+ years as compared to males (~110 per 100,000 in females vs 145 per 100,000 in males).[2] Persistent increase in both the incidence and mortality trends for EOCRC over the last decades is worrying and needs coordinated efforts to addressing disparities in the epidemiological/individual level/clinical and geographic factors influencing EOCRC survival.[42]

Risk factors relating to poorer survival outcomes in EOCRC have not been fully explored.[39] ***Hofseth L R et al, 2020***, in their review indicate potential risk factors on the incidence of CRC in patients <50 years of age.[43] They reported that the increasing incidence of EOCRC is becoming a global burden and that the individual behaviors, barriers and environment might place people at risk for developing the disease. The key exposure elements include but are not limited to westernization of diets, stress, long-term antibiotic usage, synthetic food dyes, physical inactivity and early life environmenta.[43] Evidence suggest that majority of CRC occurrence is sporadic and can be attributable to modifiable environmental risk factors, chemoprevention strategies and screening.[42] Geographic factors contributing to disparities in EOCRC survival, especially by rural-urban status has not been fully examined and, therefore, rural-urban status was a primary focus of this work.

2.2 Rural - Urban Status

A 'rural area' is defined as a small population density or size and its marked distance to a metropolitan statistical (urban) area.[44-46] Commonly used definitions for rural-urban status include (1) the Office of Management and Budget's (OMB) census designation that utilizes metropolitan and micropolitan statistical areas,[47] (2) the US Department of Agriculture (USDA) and economic research service's definition using urban influence codes that divides counties into groups based on their population size and adjacency to other county types,[48] and (3) the Rural-Urban Continuum Codes (RUCC) which are characterized by population size and adjacency to metropolitan areas based on census tracts.[49] Regardless of the complexities involved in defining 'rural' in public health

research, it is imperative to know that rural populations face several barriers (e.g. geographic, financial, behavioral, health related)[15,1,46,50] to seeking cancer care. What follows below is a review of literature (refer Table. 2.1) describing the association between rural-urban status and CRC incidence and mortality.

Rural residence is associated with increased CRC risk.[18] A population-based case-control study by ***Kinney AY et al, 2006*** [18] evaluated the effect of rural-urban residence on CRC risk and stage of disease at diagnosis for Black and White residents. They reported that rural residence was associated with increased risk of developing CRC while controlling for physical activity, cigarette smoking status, fat intake, vegetable, and fruit intake, BMI, age, race, sex, education level, poverty index (quartiles), recent CRC screening status and stage at diagnosis (OR:1.4, 95% CI, 1.1-1.8).[18]

Fowler et al, 2018,[51] utilized data from Utah SEER program (1991 – 2010) to analyze the association between CRC incidence and mortality and metropolitan status. Incidence of CRC was higher for both males (2.8 vs 1.7 per 100,000, P = .003) and females (1.6 vs 1.4 per100,000, P = .002) in non-metro counties (rural) as compared to metro counties (urban). CRC incidence between the years of 2006 to 2010 in non-metropolitan counties (rural) was significantly higher in females as compared to males (30.4 per 100,000 in metro vs 37.0 per 100,000 in non-metro, P=.002).[51]

Evidence suggests that CRC incidence in younger populations is on the rise, more predominantly in rural areas. ***Zahnd et al, 2021*** [29] analyzed SEER data on CRC

incidence in younger age groups (20-49 and ≥ 50 years). The annual percentage changes (APCs) in incidence of CRC trends between 2000-2016 years by rural-urban status and race ethnicity statuses were reported. [29] They found a 35% increase in EOCRC incidence (APC, 2.09; $P < .05$) for rural residents as compared to urban residents who had a 20% increase (APC, 1.26; $P < .05$). They also found that rural non-Hispanic Black women had the highest EOCRC incidence rates, primarily driven by colon cancer incidence which was 62% greater than urban non-Hispanic Black women.[29]

Rural residents are diagnosed with CRC at the later stages of the disease than urban residents. ***Andrilla CHA et al, 2020,***[52] examined the extent to which rural residents present at an advanced stage of CRC compared to non-rural residents in the United States. They utilized incidence data from SEER, for patients diagnosed with CRC between 2010-2014. The USDA's Urban Influence Codes (UIC) were used to categorize each US county into one of five geographic locations (metro, adjacent micropolitan, non-adjacent micropolitan, small rural and remote small rural).[52] They found that stage IV CRC at diagnosis was different across geographic designations, with patients living in remote small rural counties having the highest rate of stage IV disease. (Range: 19.2% in non-adjacent micropolitan counties to 22.7% in remote small rural counties). Also, patient characteristics, insurance status and regional practice variation were also significantly associated with late-stage CRC diagnosis especially in rural areas.[52]

2.3 Rural - Urban Differences in Survival for CRC

Rural residents face disadvantaged survival outcomes for CRC as compared to their urban counterparts. ***Raman et al,*** 2019,[53] utilized data from national cancer database (2004 – 2015) to examine the association between rural and urban CRC patients who travelled to high volume centers for treatment and CRC survival, controlling for age, sex, race, comorbidity score and stage of diagnosis. In the multivariable analysis, rural patients had worse overall survival compared to urban patients (hazard ratio [HR] 1.08; 95% confidence interval [CI] 1.04-1.12; $P < 0.001$). [53]

In a study to examine the geographic differences in adherence to national guideline on lymph node assessment for colon cancer (stage I-III), ***Short P F et al, 2016***,[54] reported that metropolitan and non-metropolitan patients differed on adherence, proximity to high-volume or accredited hospitals, and hospital type. It was estimated that roughly 100 deaths might be prevented over 5 years among each year's incident cases if the non-metropolitan disparity in hospital volume were eliminated nationally.[54]

2.4 Impact of Payer Type, Race and Sex:

Evidence suggests that cancer patients without any kind of private insurance are more susceptible to forego care and present with advanced disease and are more likely to have worse survival outcomes.[57] In addition, disparities in cancer specific mortalities are more pronounced in a Medicaid population. For example, non-Hispanic Black residents with Medicaid insurance had higher cancer specific mortality compared to non-Hispanic White residents and those who are not on Medicaid coverage.[57] Similarly, metropolitan (urban) and non-metropolitan (rural) CRC patients differ in adherence to treatment and

proximity to high-volume/accredited hospitals for care. These disparities are further aggravated by lack of health insurance status, shortage of primary care physicians and oncology specialists in non-metropolitan areas.[54]

Salem M E et al, 2021,[58] in their study to assess the impact of socioeconomic status (SES) on EOCRC survival performed a retrospective analysis of data from National Cancer Database (NCDB) between 2004 to 2016. They combined income status and education to form a representative measure of SES. Compared to patients with high SES status, EOCRC patients with lower SES were more likely to be Black residents (26.3% vs 6.1%), Hispanics (25.3% vs 10.5%) and present with stage IV disease at diagnosis (32.8% vs 27.7%).[58] They reported a 5-year survival rate of 13.9% vs 21.7% for patients with lower SES vs higher SES. They found that SES had a significant effect on survival for EOCRC adjusting for various factors (low vs high SES group, HR: 1.35, 95% CI: 1.26 – 1.46, P<.0001). Non-Private insurance vs private insurance mediated the association between SES and EOCRC survival by 31% (adj HR: 1.38, 95% CI: 1.31, 1.44). They concluded that race and insurance status were independent predictors of survival in EOCRC.[58]

Rural men have worse CRC survival than urban men. ***Rogers CR et al, 2020*** [55] utilized data from Utah cancer registry for a cohort of men diagnosed with CRC between 1997 – 2013. They assessed the differences in CRC survival between rural and urban men in Utah to investigate the potential prognostic factors impacting survival in this cohort. Rural - urban continuum area code measure (RUCA 2000) was used to define rural areas as areas with population <2,500 people, and urban areas with zip codes within an

urbanized area. Rural men faced worse 5-year survival compared to their urban counter parts (HR: 0.55, 95% CI: 0.53, 0.58 vs urban HR: 0.58, 95% CI: 0.56, 0.59). They found that race and treatment for cancer influenced survival among men in Utah.[55] For example, Black men had increased risks for both all-cause deaths (HR: 2.19, 95% CI: 1.49, 3.22) and CRC specific deaths (HR: 2.92, 95% CI: 1.94, 4.42) compared to White men. Similarly, the risk of CRC death was higher in both rural (HR: 4.28, 95% CI: 2.48, 7.38) and urban males (HR: 4.17, 95% CI: 3.33, 5.22) who did not undergo any treatment as compared to those who underwent surgery alone.

Survival after CRC diagnosis at young age is significantly worse in non-Hispanic Black individuals compared to non-Hispanic White individuals, even among those with early-stage disease. ***Holowatyj et al, 2016,***[38] in their study, utilized data from SEER 18 registry for patients (20-49 years) diagnosed with CRC between 2000-2009. The overall 5-year survival was 59% for non-Hispanic Blacks, 62.9% for Hispanics and 68.1% in non-Hispanic Whites. Also, non-Hispanic Black individuals had significantly higher hazard of cancer specific death compared to non-Hispanic White individuals, after adjusting for age, sex, stage, county level poverty estimates, for colon [HR: 1.35, 95% CI, 1.26, 1.45] and rectal cancers [HR: 1.51, 95% CI, 1.37, 1.68].[38]

In a study to assess the outcomes of late-stage diagnoses, treatment and cancer deaths as affected by race and residency status (rural vs urban), ***Hines RB et al, 2011***[56] utilized cross-sectional and follow-up data from SEER program for all incident colon and rectal tumors diagnosed between 1992 – 2007 from Atlanta and Rural Georgia Cancer Registries. The counties where the patients lived were classified as rural and urban based on USDA's RUCA designation. Urban counties were designated as those with RUCA

codes ≤ 3 and rural counties were those with RUCA codes ≥ 6. 'Survival time was calculated as the time from initial diagnosis until recorded cancer related death'. They found that compared to White residents, Black residents had 40% increased odds of late-stage cancer diagnosis (OR: 1.40, 95% CI: 1.30 – 1.51) and 50% decreased odds of having surgical treatment for colon cancer (OR: 0.50, 95% CI: 0.37 – 0.68). Also, it was reported that rural residents were at 15% increased risk of death due to colon cancer (HR: 1.15, 95% CI: 1.01 – 1.32) compared to urban residents.[56]

Evidence suggests that cancer patients without any kind of private insurance are more susceptible to forego care and present with advanced disease and are more likely to have worse survival outcomes.[57] In addition, disparities in cancer specific mortalities are more pronounced in Medicaid population. For example, non-Hispanic Black residents with Medicaid insurance had higher cancer specific mortality compared to non-Hispanic White residents and those who are not on Medicaid coverage.[57] Similarly, metropolitan (urban) and non-metropolitan (rural) CRC patients differ in adherence to treatment and proximity to high-volume/accredited hospitals for care. These disparities are further aggravated by lack of health insurance status, shortage of primary care physicians and oncology specialists in non-metropolitan areas.[54] In addition disparities by health insurance coverage type varies between colon (28.6%) and rectal cancers (19.4%) in EOCRC population, emphasizing the need for assessing access to care related issues in this population.[97]

2.5 Gaps

Rural CRC patients have adverse survival outcomes,[56] and they face, geographic, behavioral and survivorship related barriers like higher poverty, social isolation, risky behaviors/lifestyle like smoking, physical inactivity, and obesity which might contribute to poorer CRC outcomes.[46] Further, geographic factors and survival influence prevention, diagnosis/treatment opportunities for CRC, especially in rural populations.

Therefore, it is imperative to examine the association between rural-urban status and survival, especially in EOCRC population. Two-fold objectives for this study focused on (1) examining the association between rural-urban status and survival in EOCRC; (2) examining the modifying role of race, payer status and gender on the association between rural-urban status and EOCRC survival. The findings from this study will inform policy interventions and strategies to address rural cancer control and overcome disparities in EOCRC survival burden nationally.

Table 2.1: Review of results from literature examining the association between rural-urban differences in incidence and survival among patients with colorectal cancer in the United States.

Reference (Author, Year)	Study Design/type	Study duration, Follow up period (years)	Study Participants (Sample size, number, demographics)	Definition of rural-urban status, Medicaid expansion status	Methods	Confounders included in the analysis	Results and Findings
Salem M E et al, 2021	Retrospective cohort study	Data from National Cancer Database, between 2004 - 2016 was utilized to assess patients aged 18-40 years diagnosed with CRC.	Patients with appendiceal cancers were excluded. 30,903 patients were included in the study.	Rural and sub-urban categories were combined and compared with metropolitan population with population size designated in NCDB using data from USDA.	Overall survival was determined from "any cause" mortality. Survival months was defined as number of months from initial CRC diagnosis to date of death last reported to follow-up. Causal mediation analysis with counterfactual framework was performed to assess the impact of insurance status on the association between SES and EOCRC survival	Age, sex, race, ethnicity, stage of diagnosis, grade, size of tumor, surgery of the primary tumor, chemotherapy, comorbidity, area of living.	They reported a 5-year survival rate of 13.9% vs 21.7% for patients with lower SES vs higher SES. They found that SES had a significant effect on survival for EOCRC adjusting for various factors (low vs high SES group, HR: 1.35, 95% CI: 1.26 – 1.46, P<.0001). Non-Private insurance vs private insurance mediated the association between SES and EOCRC survival by 31% (adj HR: 1.38, 95% CI: 1.31, 1.44). They concluded that race and insurance status were independent predictors of survival in EOCRC.
Zahnd et al, 2021	Retrospective cohort study	Data from 2000-2016 SEER 21 registry were analyzed for early onset (age 20-49) and average onset (age>=50)	Patients diagnosed with both early onset and average onset CRC from 2000-2016 were analyzed. IRs and rate ratios were calculated for 2012-	Rural and urban populations were categorized with the USDA's Rural-Urban Continuum Codes (RUCCs), which characterizes counties based on	Rural-urban differences in EOCRC and average onset CRC incidence ratios (age adjusted) were examined across	Race/ethnicity, sex, subsite	EOCRC IRs increased 35% from 10.44 to 14.09 per 100,000 in rural populations (APC, 2.09; $P < .05$) and nearly 20% from 9.37 to 11.20 per

		CRCs.	2016 (most recent metric of cancer burden) by rural-urban status, race/ethnicity, sex, and subsite.	population size and proximity to a metropolitan area. RUCCs of 1-3 denote urban, 4-9 are considered rural.	racial/ethnic groups and by gender.		100,000 in urban populations (APC, 1.26; P <.05). AOCRC rates decreased among both rural and urban populations, but the magnitude of improvement was greater in urban populations; Between2012 and 2016, EOCRC IRs were higher among all ruralpopulations in comparison with urban populations, including NHW, NHB, and American Indian/Alaska Native populations; by gender,rural Non-Hispanic Black women had the highest EOCRC IRs across subgroup comparisons, and this was driven primarily by colon cancer IRs of 62% higher than those of their urban peers.
Rogers CR et al, 2020	Retrospective & prospective Cohort study	1997-2013 period; follow-up time was the time from CRC diagnosis to either death or the last date the patient was known to be alive/residing in	4,660 men diagnosed with CRC from Utah cancer registry	Based on census tract Zip code level, (RUCA,2000) data by US census bureau, rural areas were defined as areas with population less than 2,500 people; urban area comprises of	Study population was stratified by locality as rural and urban to determine whether there were differences in CRC survival among men living in urban and rural areas of Utah and to	Age at diagnosis, race/ethnicity, BMI, CCI, smoking status, location, area-level education, CRC stage, family history of cancer, year of diagnosis, site, and treatment	Rural men had lower 5-year CRC survival as compared to their urban counterparts. CRC survival in both rural and urban men was impacted by cancer treatment and race.

		Utah		all ZIP codes within an urbanized area (>50,000 people) plus ZIP codes from >25% population commuting to an urbanized area.	investigate the association between potential risk factors and CRC survival among men by rural-urban status		
Andrilla CHA et al, 2020	Retrospective cohort study	SEER incidence data from 2010 - 2014	132,277 patients with CRC, stratified by their county residence and urban influence codes in to five categories: metro, adjacent metro, non-adjacent micropolitan, small rural and remote small rural designations.	The county Federal Information Processing Standard (FIPS) and the USDA's urban influence codes (UIC) were used to classify each county in to 1 of the 5 mentioned geographic locations.	The independent study variable of interest was the geographic residence status of patients. Urban, rural and between intrarural category comparisons were made.	Age, sex, race/ethnicity, marital status and insurance status, patient's residence state was included to control for regional practice variation. Socioeconomic factors of the counties where the patients lived (county designations of persistent poverty, low employment, low education) were also variables of interest.	Stage IV CRC at diagnosis differed across geographic classification, with patients living in remote small rural counties having the highest rate of stage IV disease. (Range: 19.2% in non-adjacent micropolitan counties to 22.7% in remote small rural counties). Patient characteristics, insurance status and regional practice variation were also significantly associated with late-stage CRC diagnosis.

Raman V et al, 2019	Population based cancer clinical surveillance registry, NCDB; retrospective cohort study	Data from National Cancer Database between 2004-2015 were used.	647,949 male and female CRC patients were analyzed	RUCC codes using a classification scheme that distinguishes patients' residence counties by the population size, degree of urbanization and adjacency to a metro area. Rural counties were defined as completely rural or have <2,500 urban and metropolitan counties	Two groups of patients, (1) rural patients who travelled to high volume hospitals and (2) urban patients who also travelled to high volume centers were identified and compared. Primary outcome was overall survival.	Independent predictors of survival by rural-urban status were compared with the two groups of patients (1) and (2); controlling for age, sex, race, comorbidity score, stage of disease, colectomy procedure status, and adjuvant chemotherapy status	In multivariable analysis, rural patients had worse overall survival compared to urban patients (HR, 1.08; 95% confidence interval, 1.04 – 1.12).
Fowler B et al, 2018	Retrospective cohort study	Utah SEER program involving patients diagnosed with CRC between 1991 to 2010	13,026 CRC cases of both men and women	Metro or non-metropolitan county of residence was based on where the patient lived at the time of diagnosis, defined using RUCA code definitions developed by USDA based on census tracts.	Census level demographics were characterized by metro and non-metro counties and were expressed as median, IQR, minimum and maximum percentages; CRC incidence by diagnosis year and cancer stage within gender were again stratified by metro and non-metro counties; Poisson regression models were used.	Gender, age at diagnosis, cancer stage and year of diagnosis	CRC incidence between the years of 2006 and 2010, in non-metro counties was significantly higher in females (30.4/100,000 in metro vs 37.0/100,000 in non-metro, P=0.002); non-metro counties had higher incidence of CRC for both males (2.8 vs 1.7 per 100,000, p=0.003) and females (1.6 vs 1.4 per 100,000, P=0.002) compared to metro counties; non-metro counties had better survival for females.

Holowatyj et al, 2016	Population based cohort study	SEER data on patients diagnosed with CRC (20-49 years) between 2000 and 2009	EOCRC patients, (N=28,145) diagnosed between 2000 to 2009 using SEER 18 registry	Not used	5-year survival proportions (mean and median) were calculated using Kaplan Meier analysis. Log rank tests and cox proportional hazards models were used to assess survival.	Age at diagnosis, sex, poverty index, AJCC stage, tumor location and grade	Non-Hispanic Black individuals had significantly greater hazard of cancer specific death for colon cancer, compared to non-Hispanic Whites. [HR: 1.35, 95% CI, 1.26, 1.45]; for rectal cancer [HR: 1.51, 95% CI, 1.37, 1.68] after controlling for age, sex, stage, county level poverty estimates.
Short PF et al, 2015	Retrospective cohort	Cancer registries linked to Medicare claims of patients diagnosed with I-III colon cancer between 2006 and 2008	All patients diagnosed with colon cancer in 2006, 2007, 0r 2008 who resided at diagnosis in Appalachian counties in 4 states were identified (N=15,113). Medicare claims for each Medicare patient from 2005-2009 encompassing at least 1 calendar year were obtained from CMS	Geocoded patient addresses were used to identify residents of metropolitan and non-metropolitan counties, based on Rural/Urban Continuum Codes assigned by the USDA (2003)	Metropolitan and non-metropolitan patients on guideline adherence, use of hospitals with high CRC surgical volumes or cancer accreditation and distances from each patient's residence to the nearest hospital performing CRC surgeries, nearest high-volume hospital, nearest accredited hospital and the hospital where the patient had surgery	Surgical facility, accreditation, age, sex, race/ethnicity, median county income, adherence to lymph node guideline, median distance to cancer resection hospital, etc.	Metropolitan and non-metropolitan patients differed on adherence, proximity to high-volume or accredited hospitals, and hospital type; it was estimated that roughly 100 deaths might be prevented over 5 years among each year's incident cases if the non-metropolitan disparity in hospital volume were eliminated nationally

Hines RB et al, 2011	Cross sectional and follow-up study	Follow-up data for 15 years were collected (1992 – 2007).	15,174 participants, both males and females, diagnosed with colon and rectal cancers between 1992-2007 and living in counties covered by SEER regions in Georgia were analyzed.	Counties were classified as rural or urban based on RUCA classification by the USDA	Study variables were compared according to rural/urban county level designation to access related CRC outcomes. County was treated as random effect recognizing the correlated nature of data, ie., subjects were nested with in counties and each county was given its own intercept in the model.	Anatomic locations of cancer, age, gender, race, ethnicity, mean age at diagnosis. county level SES, tumor stage and treatment.	Rural residents are at 15% increased risk of death due to colon cancer (HR: 1.15, 95% CI: 1.01 – 1.32) compared to urban residents.
Kinney AY et al, 2006	Population based case control study	Study participants were interviewed between April 1996 to December 2000	558 CRC cases and 952 controls who were enrolled in North Carolina CRC study of Black and White residents residing in 33 contiguous counties	Using 1990 Census Bureau standards, urban counties or MSA's included 1 city with 50,000 or more inhabitants and or a total metropolitan area of at least 100,000 inhabitants. Non-metropolitan counties were considered rural.	Unconditional logistic regression was used to estimate the OR as a measure of relative risk for colon cancer (assessed the association between residence and CRC risk)	Physical activity (METS/week divided in quartiles), cigarette smoking status, fat intake, vegetable, and fruit intake (servings/day divided in quartiles), age, race, sex, education level, poverty index (quartiles), recent CRC screening status and stage at diagnosis.	Rural residence is associated with increased CRC risk (OR: 1.4, 95% CI, 1.1, 1.8)

Abbreviations: NCDB: National Cancer Data Base; SES: Socio Economic Status; USDA: US Department of Agriculture; IR: Incidence Ratio; AOCRC: Average Onset Colorectal Cancer; CCI: Charleston Co-Morbidity Index; IQR: Inter Quartile Range; Stage IV CRC: The disease has spread from colon/rectum to distant organs; AJCC stage: American Joint Committee on Cancer staging system; METS: Metabolic Equivalents; MSA: Metropolitan Statistical Area designation.

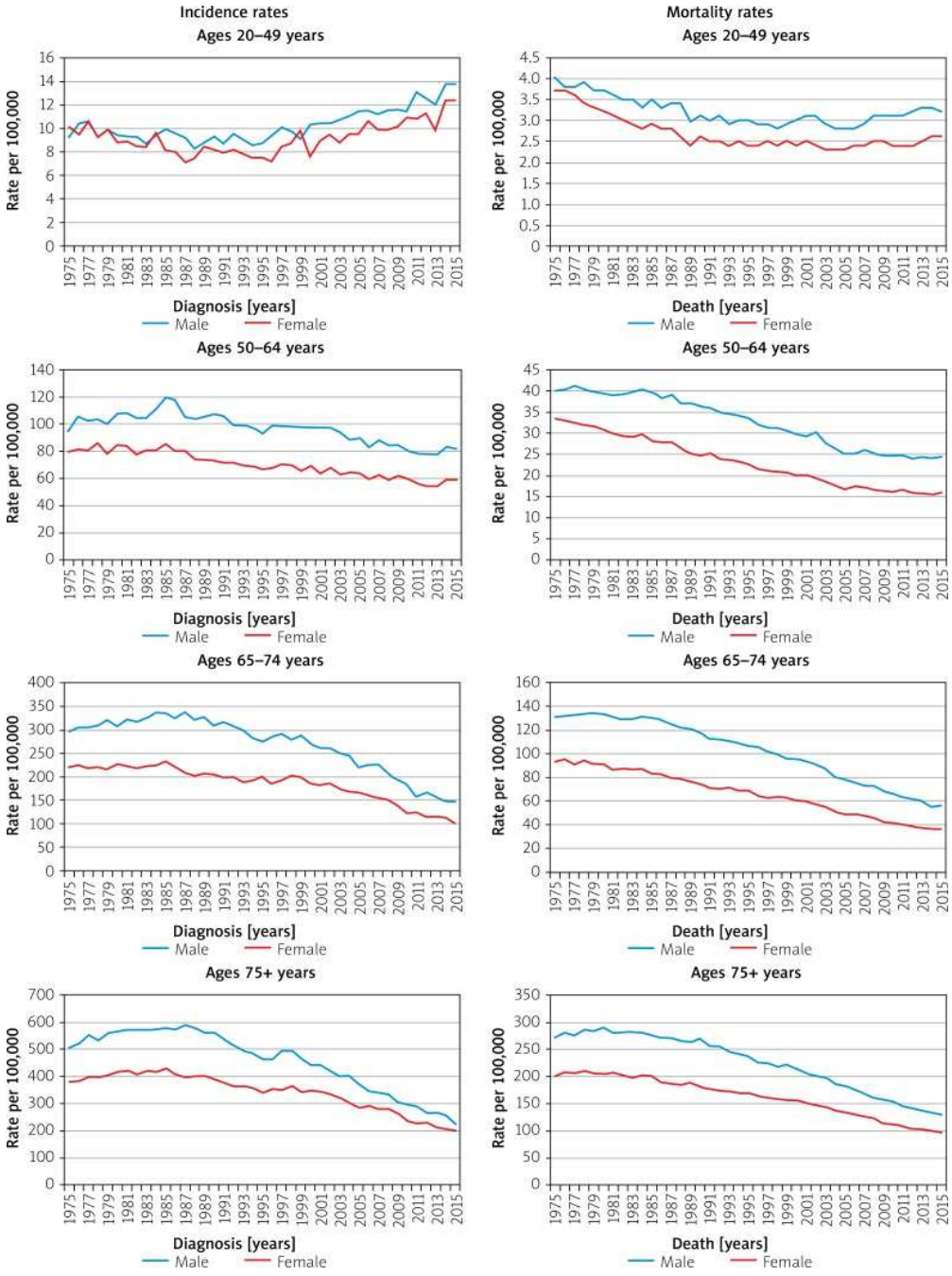

Figure 2.1: Colorectal cancer incidence and mortality trends (1975 - 2015), rates by age and gender in the US – Surveillance Epidemiology, and End Results Program (SEER) data.

CHAPTER 3: METHODS

3.1 Data Source

The National Cancer Institute's,[59] SEER's population-based cancer registries are representative of approximately 47.9 percent of the total US population, which collects data on patient demographics, tumor site, tumor morphology, stage at diagnosis and treatment. They also follow-up the patients for their vital status.[59] SEER registries have important applications in research and dissemination which enables public health researchers, health officials and surveillance experts to address cancer burden both locally and nationally.[60]

Funded by the National Cancer Institute (NCI), the SEER program has been expanded to cover multiple geographic locations across the United States, with a number representing the number of registry locations covered in each registry. List of SEER registries and their geographic locations,[61] is shown in Figure 3.1. Areas/states representing core infrastructure include ***Kentucky***, ***Greater California, Utah, Louisiana, Georgia, New York, Massachusetts, Wisconsin, and Idaho,*** where the NCI funding comes through a combination of funding from the CDC, National Program of Cancer Registries, and funding from the states.

SEER 18 registries include data from 18 cancer registries (available to researchers upon data use agreement), with cases diagnosed from 2000 through current data year. Currently, only 17 registries participate in this program, which is now known as SEER 17

registries [Detroit no longer participates].[62] Based on 2010 census, SEER 18 covers approximately 28% of the United States population from 14 states, with expanded races. Sampled population within SEER 18 represents 23.6% White residents, 25.5% Black Residents, 36.2% Hispanics, 33.9% American Indians and Alaska Natives, 47.6% Asians and 62.4% Hawaiian/Pacific Islanders.[63] The data from cancer registries are collected from medical records (hospitals, outpatient surgery centers, physician's offices, nursing homes, medical oncology offices, laboratory findings, autopsy and vital records data).[64] This study utilized data from SEER 18 registries for cases diagnosed with colon and rectal cancers between 2000 to 2016 period.

3.2 Rural-Urban Status

The definition of rural-urban status is based on USDA's Rural-Urban Continuum Codes (RUCC), which defines counties in relation to their population size and proximity to metropolitan area.[49] **Metro counties (urban)** codes ranges from '1-counties in metro-areas of 1million population or more, 2 – counties in metro areas of 250,000 to 1 million population, 3 – counties in metro areas of <250,000 population', and **non-metro counties (rural)** as '4 – urban population of 20,000 or more, adjacent to metro area, 5 – urban population of 20,000 or more, not adjacent to metro area, 6 – urban population of 2,500 to 19,999 adjacent to a metro area, 7 – urban population of 2,500 to 19,999, not adjacent to a metro area, 8 – completely rural or < 2,500 urban population, adjacent to a metro area, 9 – completely rural or <25,00 urban population, not adjacent to a metro area and unknown categories (unofficial/Alaska/Hawaii).[49] A two level Rural/Urban variable was

used as a measure of rural-urban status where, '1-3' represented most urban and '4-9' represented most rural categories.

3.3 Definition of Early Onset Colorectal Cancer

The analysis was restricted to patients with cancers of the colon and rectum, diagnosed between the ages 20 – 49 years defined as EOCRC. [3-5,29] We categorized age groups in to 20-29 years, 30-39 years and 40–49-years groups.

3.4 Survival in EOCRC

Survival is the time from EOCRC diagnosis until death or loss to followup. We utilized information from SEER 18 registries for underlying cause of death from the death certificate grouped into similar categories matching with the cancer incidence site.[65] Vital status information was obtained to determine whether a patient was alive or not, to report information on ***overall survival.*** Similarly, for ascertaining ***EOCRC specific survival,*** patients who were alive/those who died due to other causes were recoded as 'alive' and EOCRC cancer specific deaths were recoded as 'dead'. Survival months along with overall survival and EOCRC specific survival were analyzed to obtain 1-, 3- and 5-year survival for both overall and disease free) for EOCRC patients.

3.5 Potential Confounders of the Association Between Rural-Urban Status and EOCRC Survival.

The analytical framework for examining the association between rural-urban status and EOCRC survival is shown in Figure 3.2**.** Consistent with the previous literature and findings,[38,46,57] the study considered **sociodemographic factors** influencing the

association to be age, gender, census tract poverty estimate, race/ethnicity, and payer type. **Clinical factors** included were SEER stage, tumor grade, primary site, vital stats, cause of death, year of diagnosis and survival months.[28,38,46,53] Gender was coded as '1' for males and '2' for females; census tract poverty estimate categories were recoded as '≤ 5% - ≤ 10%', '>10% - ≤ 20%' and '>20% - ≤ 100% poverty levels'; race/ethnicity information were categorized as non-Hispanic Whites, non-Hispanic Blacks, non-Hispanic American Indian/Alaska Natives, Hispanics and others; year of diagnosis ranged from 2000 to 2016; payer types included, uninsured, any Medicaid (Indian public health service, Medicare with Medicaid), and insured (private, Medicare with supplement, military)/insured-no specifics and unknown groups.

Median household income status of patients was divided into quartiles (q1: ≤55,180, q2: >55,180 to <61,540, q3: >61,540 to <78,020; q4: >78,020 to <110,970 in dollars); percentage of people with < high school level education were grouped in to quartiles (q1: <9.17, q2: >9.17 to <12.46, q3: >12.46 to <17.36, q4: >17.36 to <37.02); marital status was categorized as married, single (never married), separated/divorced/widowed and unknown categories; tumor staging was categorized as localized, regional, distant and unknown/unstaged lesions; and primary site of the lesion was identified through ICD-0-3 codes for histological findings (colon, rectum).

3.6 Effect Modifiers of the Association Between Rural-Urban Status and EOCRC Survival

In the analyses it was examined whether gender, race, age, and payer types were

potential effect modifiers of the association between rural-urban status and EOCRC survival.

3.7 Inclusion Criteria

The analytical sample was restricted to CRC patients, aged 20-49 years, both males and females, cancer cases based on behavior ICD-O-3 histological coding, diagnosed between 2000 – 2016 years.

3.8 Statistical Analyses

All data used for the analyses were from SEER 18 registries, restricted to patients diagnosed with EOCRC between 2000 – 2016 period. Given the data were publicly available, this study did not require an institutional review board review/clearance. Analyses of the data were performed using SAS v9.4, SAS Institute Inc., Cary, NC.[69] Descriptive statistics for the sample characteristics were calculated and compared by rural-urban status. The statistics for each sample characteristic were expressed as either quartiles, or as frequencies and percentages for all variables (categorical). Chi-square tests were utilized to test for independence between two categorical variables. P-value less than 0.05 was considered statistically significant.

Aim1: To determine the rural-urban differences in 1-, 3- and 5-year survival among patients with EOCRC for sociodemographic, individual level and clinical characteristics.

A PROC LIFETEST procedure was used in SAS, [70] to assess the relationship between rural-urban status and risk of EOCRC. Cumulative survival statistics for

sociodemographic, individual level and clinical characteristics at 1-, 3- and 5-years of diagnosis was then determined for both overall and EOCRC specific survival respectively. Kaplan-Meier survival curves were constructed to graphically represent the survival proportions for various sample characteristics. Using Kaplan-Meier procedure the probability of each event was calculated at the exact time it occurred, which assumed that the survival probability was constant within each interval, independence between censoring and survival exist, losses occurred uniformly across study intervals and there were no secular trends.[71] Log-rank test statistic was used to assess for statistical difference between rural-urban strata, and the survival statistics were reported as percentages and 95% CI for the survival proportions. P-value less than 0.05 was considered statistically significant.

Aim 2: To examine the association of rural-urban status and survival among patients with EOCRC.

Cox proportional hazard regression models were used to examine the association between rural-urban status and survival (both overall and EOCRC specific) after adjusting for sociodemographic, individual level and clinical characteristics. Cox proportional hazard regression assumes that observations are independent, the ratio of hazards is constant or proportional over time across groups being compared (key assumption). Proportionality assumption was tested by three methods:

1. Through Kaplan-Meier curves,[72] where the graph of survival function vs. survival months and the graph of the log (-log(survival)) vs. log of survival months for each predictor yielded 'parallel like' lines (rural-urban status, race, payer status, age, census tract poverty estimates and gender).

However, for some predictors it was cluttered (tumor stage, marital status, and primary site of tumor)

2. Through including time dependent covariates in the cox model, where these covariates were created by interactions with the function of survival time.[72]

3. Through testing for non-proportional hazards assumption using Schoenfeld residuals,[72,73] where the study tested whether these residuals were correlated with time or with function of time [log(time), square (time)]. It was found that tumor stage, marital status and primary site of tumor variables failed the proportionality assumption. From all the above tests, the results were similar and consistent. Rural-urban status met the proportional hazards assumption for all the tests.

A 'PROC PHREG' procedure[73] was used to estimate hazards ratios along with the 95% CI for the estimates. Covariates to be included in the model were evaluated using Kaplan-Meier estimates individually and using step wise selection. To test for hypothesis as stated in Aim 2, crude (association between rural-urban status and survival), minimally adjusted (adjusted for age and gender) and fully adjusted models (adjusted for age, gender, marital status, payer status, census tract poverty estimates, primary site of tumor, SEER summary stage and race) were run for both overall and EOCRC specific survival.

To account for non-proportionality in the variables, primary site of tumor, SEER summary stage and marital status, a STRATA statement in SAS was used for these variables along the model statement for each PROC PHREG procedure ran.[73] This allowed each stratum to have a baseline hazard of mortality from EOCRC to be same across all strata. There were two main advantages of using stratum specific models in the

cox regression. First, it is a useful diagnostic tool for assessing proportional hazards assumption. Second, it served as a way of extending cox-model to allow for non-proportionality with respect to some covariates as mentioned before (tumor stage, marital status, and primary site of tumor).

Aim2A: To investigate the modifying impact of gender, payer types and race/ethnicity on the association between rural-urban status and survival in patients with EOCRC:

Race/ethnicity, gender, age, and payer types were tested as potential effect modifiers of the association between rural-urban status and EOCRC survival. If the interaction between any of the suggested effect modifier variables and rural-urban status were statistically significant, separate statistical models were computed for each stratum of payer types, by age, by gender or race groups to elucidate the unfold associations between rural-urban status and EOCRC survival. Statistical tests were considered significant for P-value less than 0.05 across the Cox regression and a p-value of less than 0.10 for the interaction.

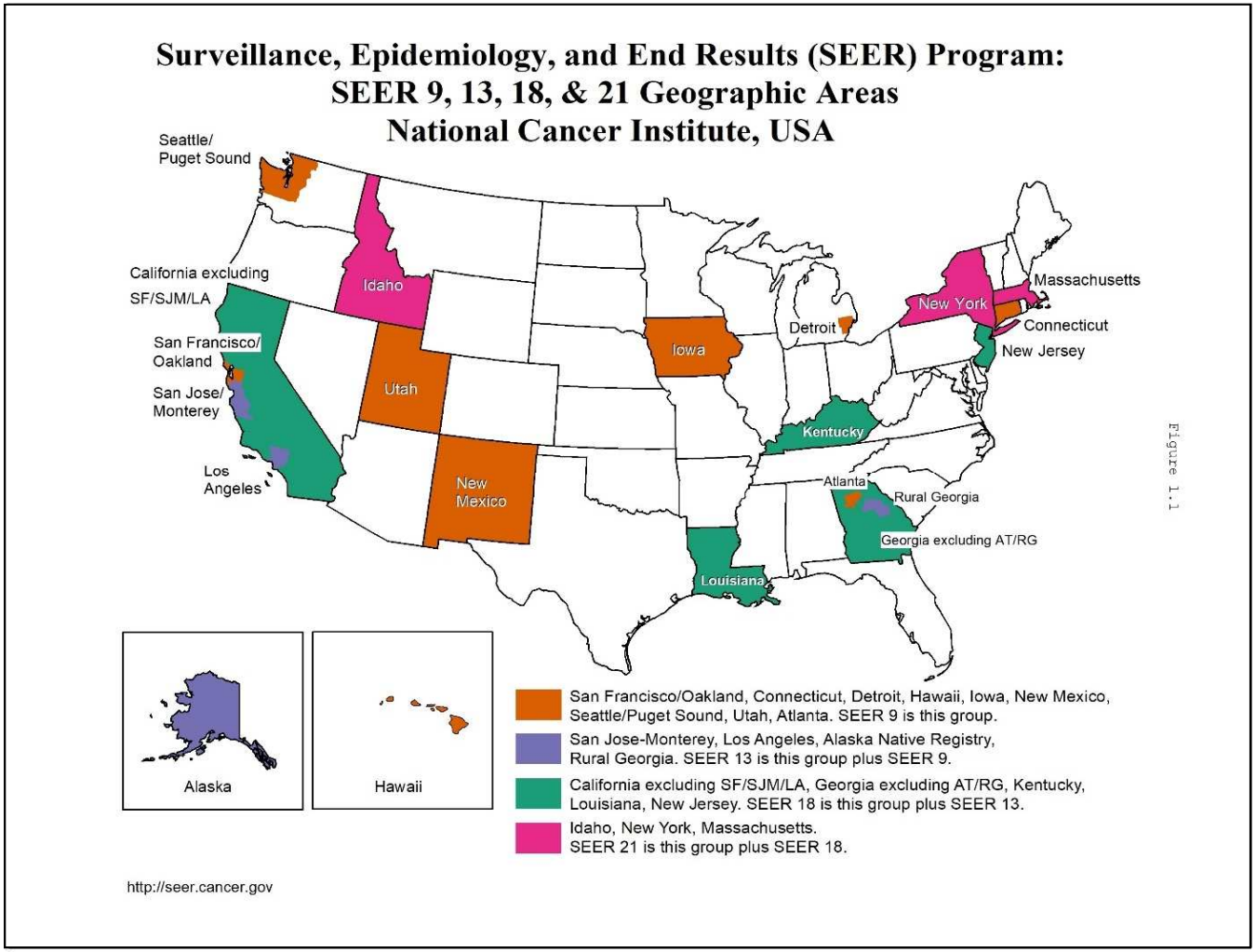

Figure 3.1: SEER Registry Locations, USA.[59]

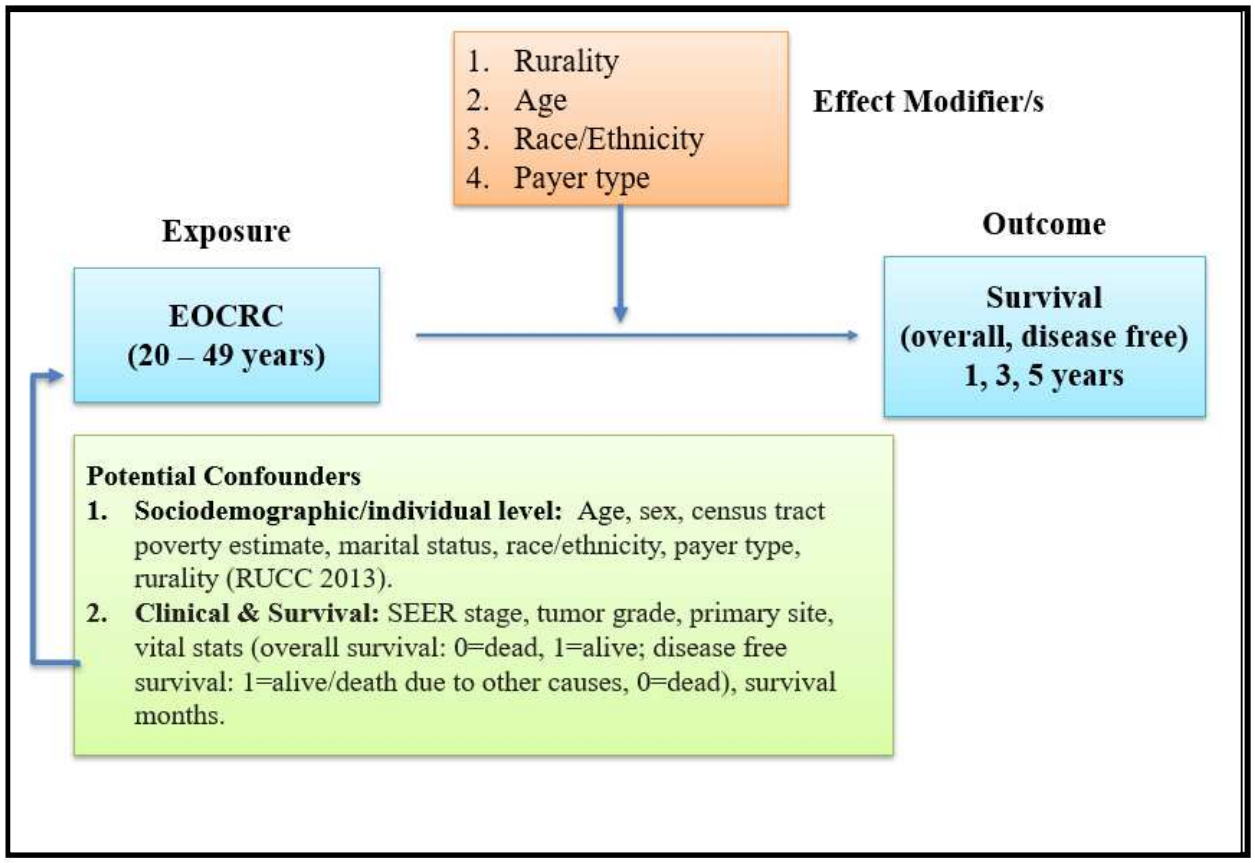

Figure 3.2: Analytical framework for association between rural-urban status and EOCRC survival, using data from SEER 18 registries.

CHAPTER 4

RESULTS

The study population comprised of (n = 65,716) those aged between 20-49 years, diagnosed with either colon or rectal cancers between 2000 – 2016 as specified in the inclusion criteria (Section: 3.7). Descriptive statistics for the sample characteristics, by rural-urban status is shown in **Table.2.** The proportion of rural EOCRC patients was 11% (n = 7,057). A higher proportion of rural EOCRC patients were aged between 40-49 years as compared to those in urban areas (76% vs. 74%, P<0.001), more likely to be any-Medicaid enrolled (13% vs. 10%, P<0.0001), were either separated / divorced / widowed (14% vs. 10%, P<0.0001), presented with distant lesion (26% vs. 25%, P=0.33) and lived in high poverty (51% vs. 11%, P<0.0001) compared to their urban counterparts. Other indicators of SES were disproportionately lower in rural residents as compared to urban residents. For example, rural residents were in the greatest quartile of having a less than high school level education as compared to urban residents. [Q4: >18.917% - ≤ 37.02%; 41% vs. 22%, P<0.0001]. Further, most of the rural residents were in the lowest quartile of median family income, ≤ $52,710, as compared to urban residents (80% vs. 19%, P<0.0001).

Kaplan Meier curves were constructed to graphically represent the survival proportions for various sample characteristics. Survival curves for rural-urban difference in overall (Figure 4.1) and EOCRC specific survival (Figure 4.2) showed, a significant

decline in survival probabilities for rural EOCRC patients (P<0.0001). Non-Hispanic Black residents had poorer survival (both overall Figure.4.3, and EOCRC specific, Figure.4.4) compared to Hispanics, non-Hispanic Whites, and other racial ethic groups. EOCRC patients with distant tumor lesion had a huge decline in survival compared to people with regional or local lesions (Figure.4.6). People who live in persistent poverty (>20% to ≤100%) encountered poorer survival due to EOCRC (Figure.4.8). Females had better survival [both overall (Figure. 4.9) and EOCRC specific (Figure.4.10)] as compared to males.

Aim1: To determine the rural-urban differences in 1-, 3- and 5-year survival among patients with EOCRC for sociodemographic, individual level and clinical characteristics.

The results of Kaplan-Meier survival analysis for 1-, 3- and 5-year survival (overall) in EOCRC patients, for sample characteristics stratified by rural-urban status are shown in Table. 4.1**.** From the sample included for the analysis, there were 19,622 (total n = 58,471) urban deaths and 2,632 (total n = 7,057) rural deaths due to all causes respectively. Significant rural-urban differences were noted in 1-, 3- and 5-year overall survival proportions with variation between 3- and 5-year survival [3- year survival, rural vs. urban: 72% vs. 74%; 5- year survival, rural vs. urban: 64% vs. 66%, P<0.0001]. Further, 1-, 3- and 5-year survival proportions were lower in rural males as compared to urban males (5- year survival, ~61% vs. ~65%, P<0.0001). Rural non-Hispanic White residents and Hispanics had lower 5-year survival as compared to their urban counter parts [non-Hispanic Whites: 66% vs. 69%, P<0.0001; Hispanics (all): 53% vs. 64%,

P<0.01]. Moreover, the 3-year overall survival proportion significantly differed among married people living in rural vs. urban areas (75% vs. 78%, P<0.0001).

The results of Kaplan-Meier survival analysis for 1-, 3- and 5-year survival (EOCRC specific), for sample characteristics stratified by rural-urban status are shown in Table. 4.2. Among the sample included for the analysis, there were 15,887 urban deaths due to EOCRC (total n = 58,471) and 2,108 rural deaths due to EOCRC (total n = 7,057) respectively. Significant rural-urban difference was noted in 1-, 3- and 5-year survival (EOCRC specific). For example, rural patients had lower 5-year survival from EOCRC as compared to urban patients (69% vs. 71%, P<0.0001). For people aged between 40-49 years, 5-year survival from EOCRC was lower in rural patients (69% vs. 71%, P<0.0001).

Rural non-Hispanic White residents (70% vs. 73%, P<0.0001) and Hispanic residents (58% vs. 69%, P<0.01) had significant decline in 5-year survival as compared to their urban counterparts. There was no significant difference in survival noted among non-Hispanic Black residents and other racial/ethnic groups. People who were single or unmarried had poorer 1-, 3- and 5- year survival from EOCRC in rural areas as compared to urban (3-year survival: 69% vs. 72%, P<0.05). Rural patients diagnosed with a distant stage lesion had poorer survival outcomes as compared to their urban counterparts (5-year survival: 21% vs. 24%, P<0.01). Further, people with an unknown/unstaged lesion in rural areas had a drastic decline in survival in rural areas vs. urban areas (5-year survival: 67% vs. 75%, P<0.05%). There were no significant rural-urban differences in EOCRC specific survival noted among all SES groups based on census tract poverty

estimates. Rural patients diagnosed with rectal cancer had lower 5-year survival as compared to their urban counterparts (70% vs. 73%, P<0.0001).

Aim 2: To examine the association of rural-urban status and survival among patients with EOCRC.

Results from the cox regression modeling of factors influencing survival (overall and EOCRC specific) in patients diagnosed with EOCRC are shown in Table. 4.4. Rural EOCRC patients had worse survival from all causes [HR: 1.17, 95% CI: 1.11-1.22, P<0.0001] and EOCRC specific [HR: 1.16, 95% CI: 1.10 – 1.22, P<0.0001] as compared to urban EOCRC patients. This association remained the same for overall but was attenuated for EOCRC specific survival after adjustment for age, gender, marital, payer status, census tract poverty estimates, primary site of tumor, SEER summary stage and race [overall: HR: 1.10, 95% CI: 1.04 – 1.16, P<0.0001; EOCRC specific: HR: 1.10, 95% CI: 1.04 – 1.17, P<0.01].

In the model stratified by gender, rural males had greater risk of overall (HR: 1.07, 95% CI: 0.99 – 1.14, P=0.071) and EOCRC specific deaths (HR: 1.08, 95% CI: 1.00 – 1.17, P=0.053) compared to urban males in the fully adjusted model. Among females, rural EOCRC patients had greater risk of overall (HR: 1.13, 95% CI: 1.05 - 1.23, P<0.01) and EOCRC specific deaths (HR: 1.13, 95% CI: 1.03 - 1.23, P<0.01), compared to urban females even after fully adjusting for all relevant factors.

For race only models, rural NH White residents had worse survival overall (HR: 1.08, 95% CI: 1.01 – 1.15, P<0.01) and EOCRC specific (HR: 1.08, 95% CI: 1.01 – 1.16, P<0.05) as compared to their urban counterparts after fully adjusting for relevant factors.

The ‘non-Hispanic Blacks only’ model did not yield any significant association between rural-urban status and risk of EOCRC survival. Among Hispanics, rural residents had greater risk of overall (HR: 1.24, 95% CI: 1.02 – 1.57, P<0.05) and EOCRC specific deaths (HR:1.20, 95% CI: 0.97 – 1.50, P=0.098), as compared to urban patients, where the association was attenuated after fully adjusting for relevant factors. Hazard of death was much higher among rural NH-Asians and Pacific Islanders [overall: HR: 1.57, 95% CI: 1.16 – 2.12, P<0.01; EOCRC specific: HR: 1.61, 95% CI: 1.15 – 2.24, P<0.01] as compared to urban NH-Asians and Pacific Islanders.

Among the people who were insured, the hazard of death overall (HR: 1.12, 95% CI: 1.03 – 1.21, P<0.01) and EOCRC specific (HR:1.13, 95% CI: 1.03 – 1.24, P<0.01) was higher in rural patients as compared to urban patients, even after adjusting for all relevant factors. There were no significant rural-urban differences noted in survival among Medicaid enrolled and uninsured groups.

In models stratified by age, rural patients aged between 30-39 years had greater hazard of death overall, as compared to their urban counterparts, but the association was attenuated after fully adjusting for relevant factors (overall: HR: 1.13, 95% CI: 1.00 – 1.28, P-value=0.057; EOCRC specific: HR: 1.11, 95% CI: 1.00 – 1.23, P-value=0.121). However, in 40–49-year age group, compared to urban patients, rural patients had greater hazard of overall (HR: 1.08, 95% CI: 1.02 – 1.15, P<0.01) and EOCRC specific (HR: 1.09, 95% CI: 1.02 – 1.17, P<0.05) deaths, even after adjusting for all relevant factors.

Aim2A: To investigate the modifying impact of gender, payer types, age and race on the association between rural-urban status and survival in patients with EOCRC:

This study did not find any significant interaction with gender (overall: P = 0.53, EOCRC specific: P = 0.75), payer types (overall: P = 0.40, EOCRC specific: P = 0.48), age (overall: P = 0.56, EOCRC specific: P = 0.58) and the association between rural-urban status and survival in EOCRC patients. Race/ethnicity was a modifier of association between rural-urban status and survival in EOCRC patients (Overall: P = 0.0016, EOCRC specific: P = 0.0271).

The association between residence (rural-urban status) and survival for each stratum of race, fully adjusted for sample characteristics, is also shown in Table 4.4**.** Rural NH-Asians/Pacific Islanders had greater hazard of both overall [HR: 1.57, 95% CI: 1.16 – 2.82, P<0.01] and EOCRC specific survival [HR: 1.61, 95% CI: 1.15 – 2.24, P<0.01] as compared to urban patients after controlling for age, gender, marital, payer status, census tract poverty estimates, primary site of tumor, SEER summary stage. Similar pattern was observed among rural Hispanic residents as compared to their urban counterparts, after fully controlling for relevant factors (overall: HR – 1.24, 95% CI: 1.01 - 1.51, P<0.05; EOCRC specific: HR: 1.20, 95% CI: 0.97 - 1.50). Rural NH White residents had greater hazard of overall deaths (HR: 1.08, 95% CI: 1.01 - 1.15, P<0.01) with a much greater risk of EOCRC specific deaths (HR: 1.08, 95% CI: 1.01 - 1.16, P<0.05) as compared to urban NH White residents, after controlling for relevant factors. The risk of deaths in rural areas was significantly higher among other races but for NH Black residents as compared to urban areas.

Table 4.1: Characteristics of adults aged 20-49 years, diagnosed with early onset colorectal cancer by rural-urban residence status, SEER 18 registries, United States.

Characteristics	**All N (%)**	**Urban/Rural status**		**P-Value**
		Urban N (%)	**Rural N (%)**	
	65,716	58,471 (89%)	7,057 (11%)	
Age at diagnosis (Years)				
20 – 29	3,479 (5%)	3,126 (5%)	353 (5%)	<0.001
30 – 39	13,748 (21%)	12,385 (21%)	1,363 (19%)	
40 - 49	48,301 (74%)	42,960 (74%)	5,341 (76%)	
Gender				
Female	31,043 (47%)	27,698 (47%)	3,345 (47%)	0.96
Male	34,485 (53%)	30,773 (53%)	3,712 (53%)	
Race/Ethnicity				
NH White	38,704 (59%)	33,206 (57%)	5,498 (78%)	<.001
NH Black	9,374 (14%)	8,543 (15%)	831 (12%)	
Hispanic (all)	10,332 (16%)	9,964 (17%)	368 (5%)	
NHA/PI	6,060 (9%)	5,905 (10%)	155 (2%)	
Other	1,058 (2%)	853 (1%)	205 (3%)	
Payer Status				
Any Medicaid	6,729 (10%)	5,843 (10%)	886 (13%)	<.001
Insured/ No specifics	29,552 (45%)	26,733 (46%)	2,819 (40%)	
Uninsured	2,745 (4%)	2,303 (4%)	442 (6%)	
Unknown	26,502 (40%)	23,592 (40%)	2,910 (41%)	
Marital Status				
Married (including common law)	37,029 (57%)	33,040 (56%)	3,989 (57%)	<.001
Single/unmarried	17,797 (27%)	16,227 (28%)	1,570 (22%)	
Separated/divorced /widowed	6,808 (10%)	5,825 (10%)	983 (14%)	
Unknown	3,894 (6%)	3,379 (6%)	515 (7%)	
Less than High School education[b]				
Quantile 1	16,573 (25%)	15,015 (26%)	1,558 (22%)	<.001
Quantile 2	17,093 (26%)	16,316 (28%)	777 (11%)	
Quantile 3	16,161 (25%)	14,301 (24%)	1,860 (26%)	
Quantile 4	15,701 (24%)	12,839 (22%)	2,862 (41%)	
Income Quantiles[c]				
Quantile 1	16,454 (25%)	10,815 (19%)	5,639 (80%)	<.001
Quantile 2	17.267 (26%)	16,252 (28%)	1,015 (14%)	
Quantile 3	15,554 (24%)	15,342 (26%)	202 (3%)	
Quantile 4	16,263 (25%)	16,062 (27%)	201 (3%)	

SEER Summary stage				
Localized	17,290 (34%)	15,442 (34%)	1,848 (34%)	0.33
Regional	19,546 (38%)	17,518 (38%)	2,028 (37%)	
Distant	13,215 (25%)	11,759 (25%)	1,456 (26%)	
Unknown/unstaged	1,738 (3%)	1,553 (3%)	185 (3%)	
Tumor grade				
Well differentiated	6,612 (10%)	5,972 (10%)	640 (9%)	<0.001
Moderately differentiated	36,129 (55%)	32,213 (55%)	3,916 (55%)	
Poorly differentiated	10,271 (16%)	9,196 (16%)	1,075 (15%)	
Undifferentiated, anaplastic	1,286 (2%)	1,109 (2%)	177 (3%)	
Unknown	11,230 (17%)	9,981 (17%)	1,249 (18%)	
Census tract poverty estimates				
≤ 5% - ≤ 10%	13,327 (20%)	12,681 (22%)	646 (9%)	<.001
>10% - ≤ 20%	42,312 (65%)	39,500 (67%)	2,812 (40%)	
>20% - ≤ 100%	9,889 (15%)	6,290 (11%)	3,599 (51%)	
Primary site				
Colon	39,631 (60%)	35,357 (60%)	4,274 (61%)	0.88
Rectum	25,897 (40%)	23,114 (40%)	2,783 (39%)	
Vital Status				
Alive	43,274 (66%)	38,849 (66%)	4,425 (63%)	<.001
Dead	22,254 (34%)	19,622 (34%)	2,632 (37%)	
Cause specific death (EOCRC)				
Alive (alive or death due to other causes)	47,533 (73%)	42,584 (73%)	4,949 (70%)	<.001
Dead (due to EOCRC)	17,995 (27%)	15,887 (27%)	2,108 (30%)	
Survival months (mean ± standard deviation)	64.69 ± 56.63	64.72 ± 56.56	64.42 ± 57.19	

NHA/PI: Non-Hispanic Asian/Pacific Islander; NH: Non-Hispanic.
Results are reported as N (column %) for all the values.
[a] Non-Hispanic American Indian/Alaska Native/Non-Hispanic Unknown Race.
[b] Less than High School education: Quantile 1: ≤ 9.7%, Quantile 2: >9.7% - ≤12.98%, Quantile 3 – >12.98% - ≤18.91%, Quantile 4: >18.917% - ≤ 37.02%.
[c] Median family income Quantiles (in dollars) : Quantile 1: ≤ 52,710, Quantile 2: >52,710 - ≤ 61,020, Quantile 3 – > 61,020 - ≤ 76,110, Quantile 4: >76,110 - ≤ 110,970.
Chi-square tests were performed to test the independence between two variables; P-value less than 0.05 was considered statistically significant.

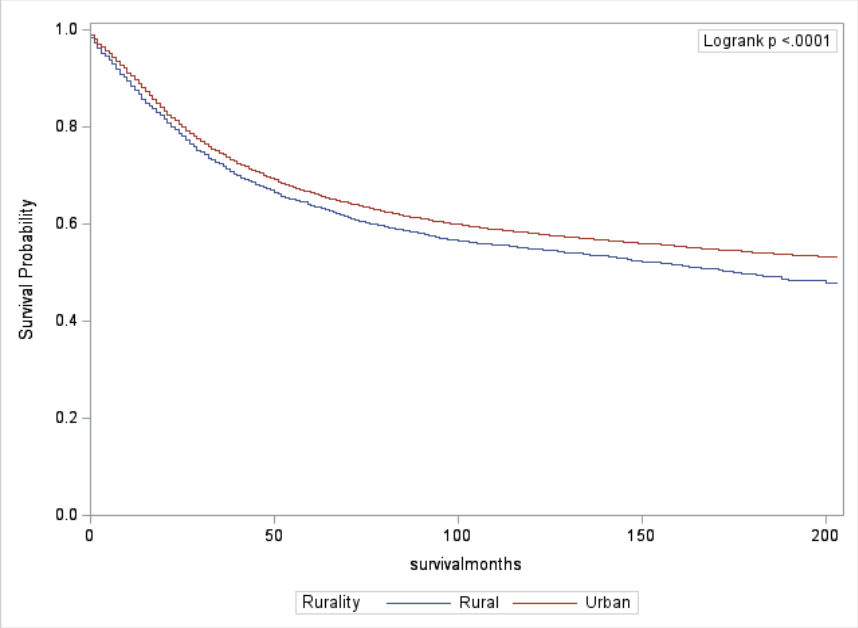

Figure: 4.1 Kaplan Meier plot of overall survival by rural – urban status

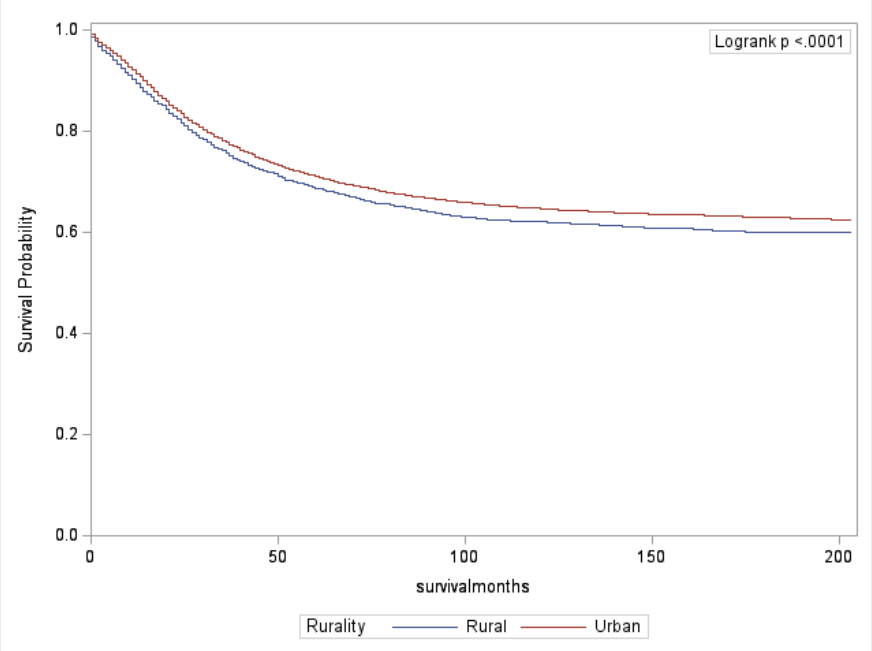

Figure: 4.2 Kaplan Meier plot of EOCRC specific survival by rural – urban status

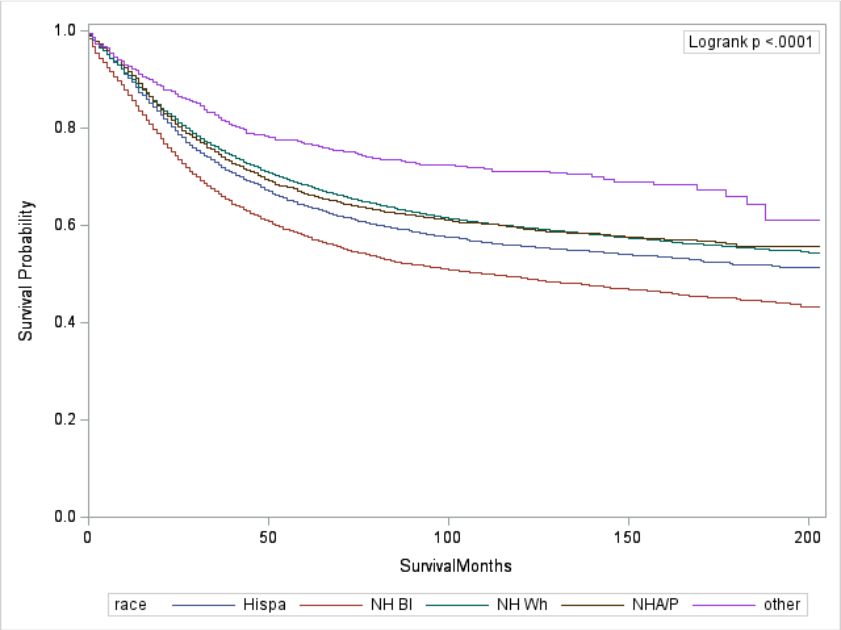

Figure: 4.3 Kaplan Meier plot of overall survival by race/ethnicity status

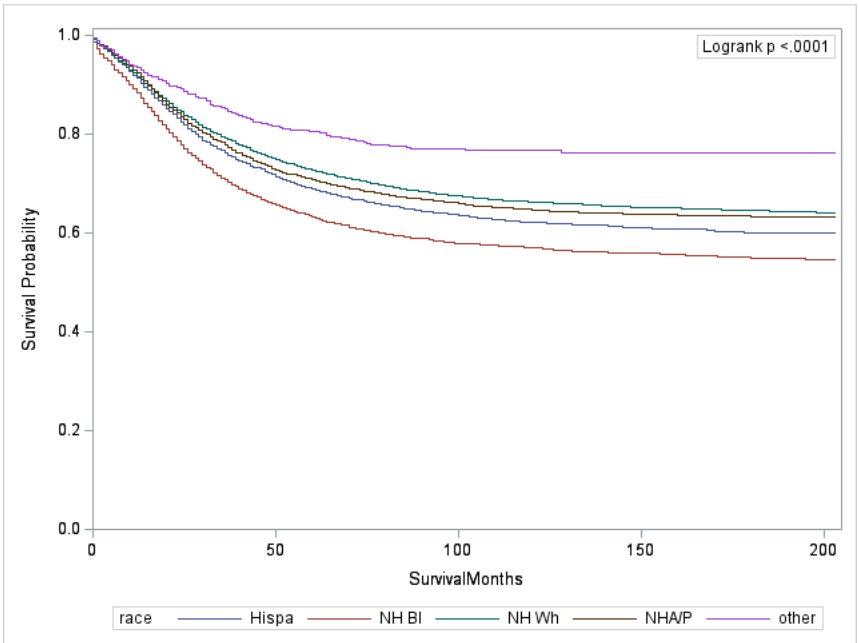

Figure: 4.4 Kaplan Meier plot of EOCRC specific survival by race/ethnicity status

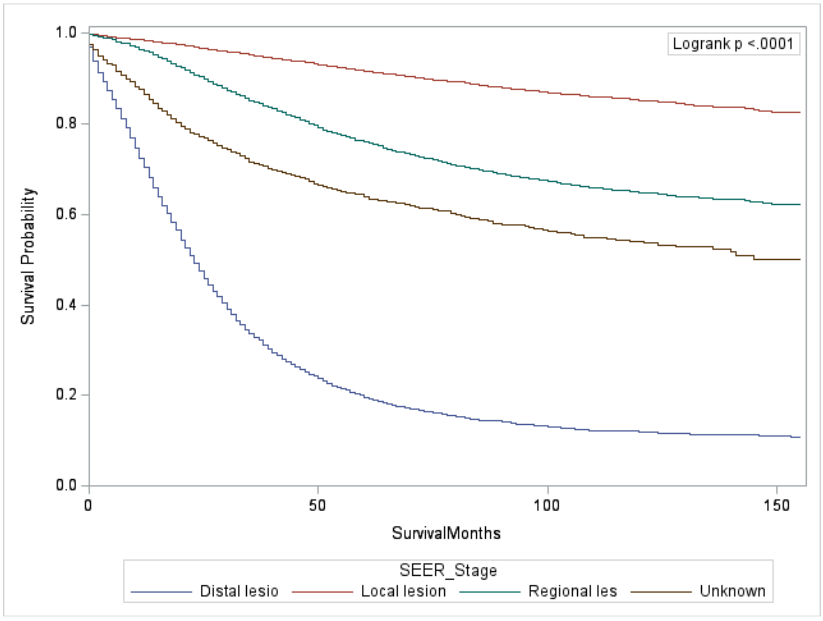

Figure: 4.5 Kaplan Meier plot of overall survival by SEER summary stage.

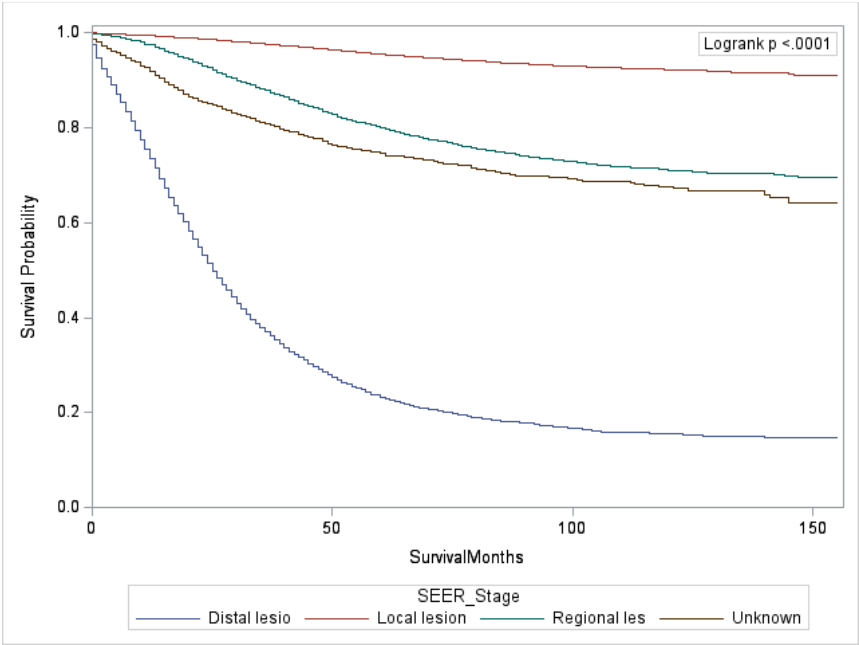

Figure: 4.6 Kaplan Meier plot of EOCRC specific survival by SEER summary stage.

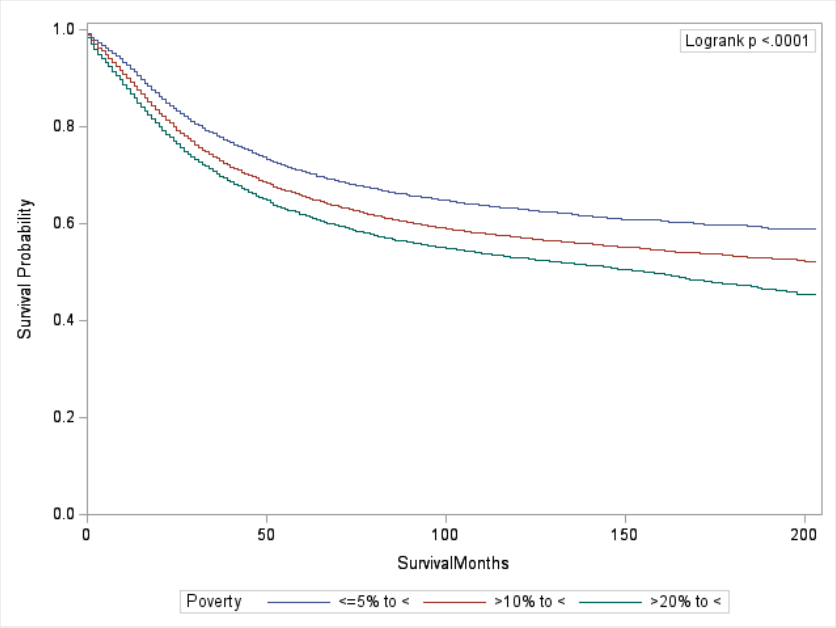

Figure: 4.7 Kaplan Meier plot of overall survival by census tract poverty estimates.

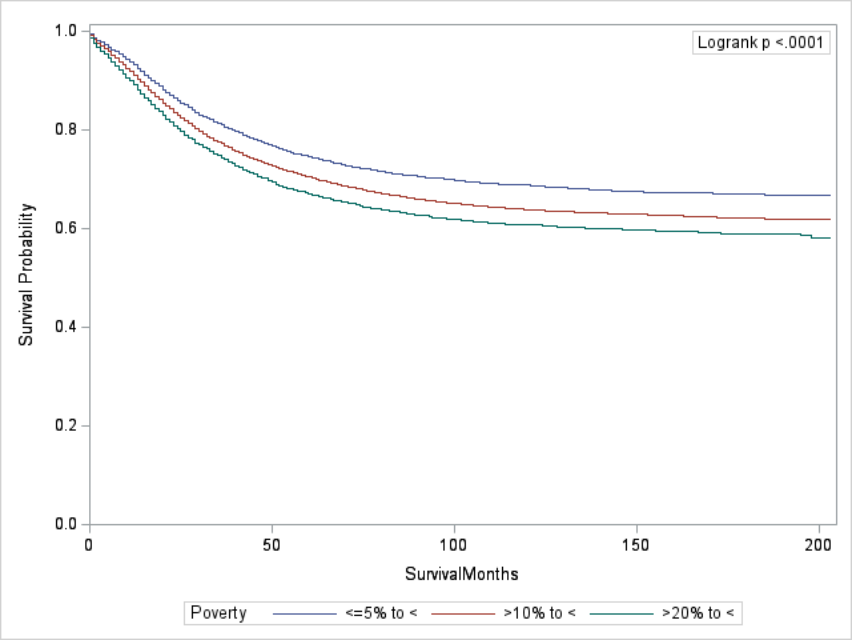

Figure: 4.8 Kaplan Meier plot of EOCRC specific survival by census tract poverty estimates.

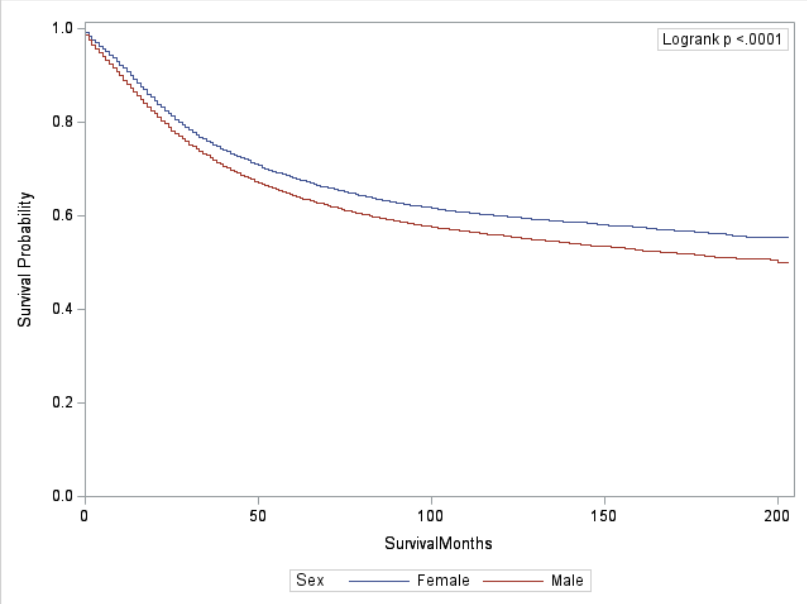

Figure: 4.9 Kaplan Meier plot of overall survival by gender.

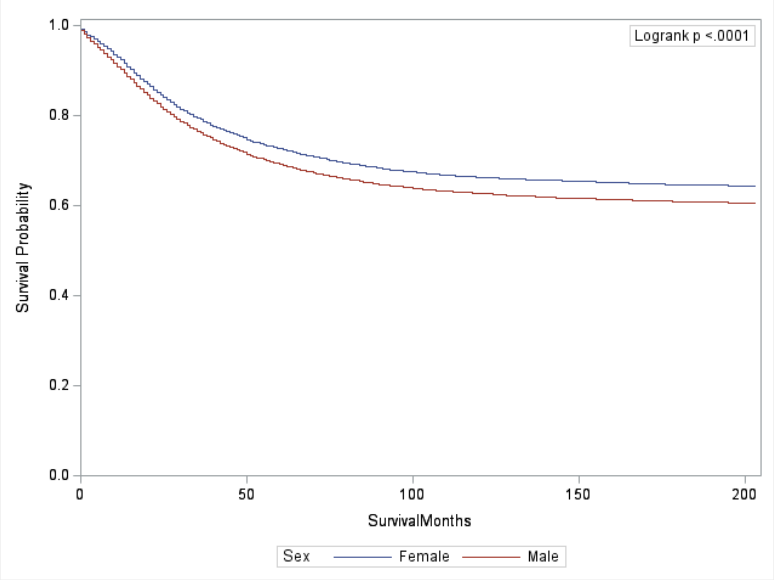

Figure: 4.10 Kaplan Meier plot of EOCRC specific survival by gender.

Table 4.2**:** 1-year, 3-year and 5-year survival (Overall) for adults with Early Onset Colorectal Cancer by rural-urban status for each sample characteristics, SEER-18 registries, United States.

Characteristics	Urban Residence					Rural Residence				
	Total	**No of deaths (All causes)**	**1-year survival (95% CI)**	**3-year survival (95% CI)**	**5-year survival (95% CI)**	**Total**	**No of deaths (All causes)**	**1-year survival (95% CI)**	**3-year survival (95% CI)**	**5-year survival (95% CI)**
Overall ***	58,471	19,622	90% (89% –90%)	74% (74% - 75%)	66% (66% - 67%)	7,057	2,632	88% (87% - 88%)	72% (71% - 73%)	64% (63% - 65%)
Age at diagnosis (Years)										
20 – 29	3,126	921	90% (88% - 91%)	73% (71% - 75%)	66% (64% - 68%)	353	118	87% (83% - 90%)	72% (67% - 77%)	67% (61% - 72%)
30 - 39 **	12,385	3,929	90% (89% - 90%)	74% (74% - 75%)	67% (66% - 68%)	1,363	472	88% (86% - 89%)	71% (68% - 73%)	63% (60% - 66%)
40 - 49 ***	42,960	14,772	90% (89% - 90%)	74% (74% - 75%)	63% (66% - 67%)	5,341	2,042	88% (87% - 89%)	72% (71% - 73%)	64% (62% - 65%)
Gender										
Female ***	27,698	8,688	91% (90% - 91%)	76% (75% - 76%)	68% (68% - 69%)	3,345	1,168	89% (88% - 90%)	73% (72% - 75%)	66% (65% - 68%)
Male ***	30,773	10,934	88% (88% - 89%)	73% (72% - 73%)	65% (64% - 65%)	3,712	1,464	87% (85% - 88%)	70% (69% - 72%)	61% (60% - 63%)
Race/Ethnicity										
NH White ***	33,206	10,863	90% (90% - 91%)	76% (76% - 77%)	69% (68% - 69%)	5,498	1,983	88% (87% - 89%)	73% (72% - 75%)	66% (64% - 67%)
NH Black	8,543	3,581	86% (85% - 87%)	67% (66% - 68%)	58% (57% - 59%)	831	366	85% (82% - 87%)	65% (61% - 68%)	57% (53% - 60%)
Hispanic (all) *	9,964	3,190	89% (89% - 90%)	73% (72% - 74%)	64% (63% - 66%)	368	145	86% (82% - 90%)	68% (62% - 73%)	53% (47% - 59%)
NHA/PI	5,905	1,867	91% (90% - 92%)	75% (73% - 76%)	67% (65% - 68%)	155	62	87% (80% - 91%)	69% (61% - 76%)	59% (50% - 67%)
Other ***	853	121	95% (93% - 96%)	88% (85% - 90%)	83% (80% - 86%)	205	76	86% (80% - 90%)	70% (63% - 76%)	63% (56% - 70%)

Payer Status										
Any Medicaid	5,843	2,216	83% (82% - 84%)	60% (58% - 61%)	50% (49% - 52%)	886	370	84% (81% - 86%)	59% (56% - 63%)	49% (45% - 53%)
Insured/No Specifics *	26,733	6,484	92% (92% - 93%)	79% (78% - 79%)	71% (70% - 71%)	2,819	761	91% (89% - 92%)	76% (75% - 78%)	68% (66% - 70%)
Uninsured	2,303	881	84% (82% - 85%)	65% (63% - 67%)	54% (52% - 57%)	442	179	83% (79% - 86%)	63% (58% - 68%)	54% (49% - 60%)
Unknown *	23.592	10,041	89% (88% - 89%)	73% (73% - 74%)	66% (65% - 67%)	2,910	1,588	87% (86% - 88%)	72% (70% - 74%)	65% (63% - 67%)
Marital Status										
Married *** (Including common law)	33,040	10,164	92% (91% - 92%)	78% (77% - 78%)	70% (69% - 71%)	3,989	1,367	90% (89% - 91%)	75% (74% - 76%)	68% (66% - 69%)
Single / unmarried *	16,227	6,315	86% (85% - 86%)	67% (66% - 68%)	59% (58% - 60%)	1,570	678	83% (81% - 85%)	65% (62% - 68%)	56% (54% - 59%)
Separated / divorced / widowed **	5,825	2,357	88% (87% - 88%)	70% (69% - 72%)	62% (60% - 63%)	983	415	85% (82% - 87%)	67% (64% - 70%)	57% (54% - 61%)
Unknown ***	3,379	786	92% (91% - 93%)	80% (79% - 82%)	75% (73% - 77%)	515	172	88% (85% - 91%)	76% (72% - 80%)	67% (62% - 72%)
SEER summary Stage										
Localized ***	15,442	1,350	98% (98% - 99%)	95% (94% - 95%)	92% (91% - 92%)	1,848	219	98% (97% - 99%)	94% (92% - 95%)	89% (87% - 91%)
Regional ***	17,518	4,000	96% (96% - 96%)	85% (84% - 86%)	76% (75% - 77%)	2,028	537	96% (95% - 96%)	84% (81% - 85%)	73% (71% - 76%)
Distant ***	11,759	8,193	70% (70% - 72%)	33% (32% - 34%)	20% (19% - 21%)	1,456	1,063	66% (64% - 69%)	29% (27% - 32%)	17% (15% - 20%)
Unknown/ Unstaged	1,553	498	87% (85% - 89%)	72% (69% - 74%)	64% (62% - 67%)	185	73	83% (76% - 88%)	67% (59% - 74%)	58% (50% - 66%)
Census tract poverty estimates										
≤ 5% - ≤ 10%	12,681	3,737	92%	78%	71%	646	206	90%	75%	69%

			(91% - 92%)	(78% - 79%)	(70% - 72%)			(88% - 92%)	(72% - 79%)	(65% - 72%)
>10% - ≤ 20%	39,500	13,493	89% (89% - 90%)	73% (73% - 74%)	66% (65% - 66%)	2,812	988	89% (87% - 90%)	73% (72% - 75%)	66% (64% - 68%)
>20% - ≤ 100%	6,290	2,392	87% (86% - 88%)	71% (69% - 72%)	62% (61% - 64%)	3,599	1,438	87% (85% - 88%)	70% (68% - 72%)	61% (59% - 63%)
Primary Site										
Colon ***	35,357	12,344	88% (88% - 89%)	72% (72% - 73%)	65% (64% - 65%)	4,274	1,636	86% (85% - 87%)	71% (69% - 72%)	63% (61% - 65%)
Rectum ***	23,114	7,278	92% (91% - 92%)	77% (77% - 78%)	69% (69% - 70%)	2,783	996	90% (89% - 91%)	74% (72% - 76%)	65% (63% -67%)

NHA/PI: Non-Hispanic Asian/Pacific Islander; NH: Non-Hispanic.
P-value less than 0.05 was considered statistically significant; *P<0.01, **P<0.05, ***P<0.0001.

Table 4.3**:** 1-year, 3-year and 5-year survival (EOCRC specific) for adults with Early Onset Colorectal Cancer by rural-urban status for each sample characteristics, SEER-18 registries, United States.

Characteristics	**Urban Residence**					**Rural Residence**				
	Total	**No of deaths (All causes)**	**1-year survival (95% CI)**	**3-year survival (95% CI)**	**5-year survival (95% CI)**	**Total**	**No of deaths (All causes)**	**1-year survival (95% CI)**	**3-year survival (95% CI)**	**5-year survival (95% CI)**
Overall ***	58,471	15,887	91% (91% -92%)	78% (77% - 78%)	71% (70% - 71%)	7,057	2,108	90% (89% - 90%)	76% (75% - 77%)	69% (68% - 70%)
Age at diagnosis (Years)										
20 – 29	3,126	790	91% (90% - 92%)	76% (74% - 78%)	69% (67% - 71%)	353	101	88% (84% - 91%)	75% (70% - 79%)	70% (64% - 75%)
30 - 39	12,385	3,280	91% (91% - 92%)	78% (77% - 78%)	71% (70% - 72%)	1,363	391	90% (88% - 91%)	75% (72% - 77%)	68% (65% - 70%)
40 - 49 ***	42,960	11,817	91% (91% - 92%)	78% (77% - 78%)	71% (71% - 72%)	5,341	1,616	90% (89% - 91%)	76% (75% - 77%)	69% (67% - 70%)
Gender										
Female *	27,698	7,046	93% (92% - 93%)	79% (79% - 80%)	73% (72% - 73%)	3,345	939	91% (90% - 92%)	77% (76% - 79%)	71% (69% - 73%)
Male ***	30,773	8,841	90% (90% - 91%)	76% (76% - 77%)	69% (69% - 70%)	3,712	1,169	89% (88% - 90%)	74% (73% - 76%)	67% (65% - 68%)
Race/Ethnicity										
NH White ***	33,206	8,711	92% (91% - 92%)	80% (79% - 80%)	73% (72% - 74%)	5,498	1,588	90% (89% - 91%)	77% (76% - 78%)	70% (69% - 72%)
NH Black	8,543	2889	88% (88% - 89%)	71% (70% - 72%)	63% (62% - 65%)	831	297	87% (85% - 90%)	69% (65% - 72%)	62% (58% - 65%)
Hispanic (all) *	9,964	2,620	91% (91% - 92%)	76% (75% - 77%)	69% (68% - 70%)	368	119	89% (85% - 92%)	72% (67% - 77%)	58% (52% - 64%)
NHA/PI	5,905	1,566	92% (92% - 93%)	78% (77% - 79%)	71% (69% - 72%)	155	49	89% (82% - 93%)	73% (65% - 78%)	66% (57% - 73%)
Other ***	853	101	96% (94% - 97%)	90% (87% - 92%)	85% (82% - 88%)	205	55	89% (83% - 92%)	76% (69% - 81%)	70% (62% - 76%)

Payer Status										
Any Medicaid	5,843	1,793	87% (86% - 88%)	65% (64% - 67%)	57% (55% - 58%)	886	301	86% (83% - 88%)	65% (61% - 68%)	55% (51% - 59%)
Insured/No Specifics **	26,733	5,356	99% (93% - 94%)	82% (81% - 82%)	75% (74% - 75%)	2,819	619	89% (86% - 91%)	80% (78% - 82%)	73% (71% - 75%)
Uninsured	2,303	737	86% (85% - 88%)	69% (67% - 71%)	60% (57% - 62%)	442	149	86% (82% - 89%)	67% (62% - 72%)	61% (55% - 66%)
Unknown **	23,592	8,001	90% (90% - 91%)	77% (76% - 78%)	71% (70% - 71%)	2,910	1,039	89% (88% - 90%)	76% (74% - 77%)	69% (67% - 71%)
Marital Status										
Married *** (Including common law)	33,040	8,384	93% (92% - 93%)	81% (80% - 81%)	74% (73% - 74%)	3,989	1,122	91% (91% - 92%)	78% (77% - 80%)	72% (70% - 73%)
Single / Unmarried **	16,227	5,065	88% (88% - 89%)	72% (71% - 72%)	64% (63% - 65%)	1,570	538	86% (83% - 87%)	69% (67% - 72%)	62% (59% - 65%)
Separated / divorced / widowed	5,825	1,852	90% (89% - 90%)	75% (73% - 76%)	67% (66% - 69%)	983	317	90% (89% - 90%)	75% (73% - 76%)	64% (61% - 68%)
Unknown ***	3,379	586	94% (93% - 95%)	84% (83% - 86%)	80% (78% - 81%)	515	131	90% (87% - 92%)	80% (76% - 83%)	72% (68% - 77%)
SEER summary Stage										
Localized ***	15,442	685	99% (98% - 99%)	98% (97% - 98%)	96% (95% - 96%)	1,848	118	99% (98% - 99%)	97% (96% - 98%)	94% (92% - 95%)
Regional **	17,518	3,181	97% (97% - 98%)	88% (87% - 88%)	80% (79% - 81%)	2,028	412	97% (96% - 97%)	87% (85% - 88%)	78% (76% - 80%)
Distant *	11,759	7,293	74% (73% - 75%)	37% (36% - 38%)	24% (23% - 25%)	1,456	946	70% (67% - 72%)	33% (31% - 36%)	21% (18% - 23%)
Unknown/ Unstaged **	1,553	313	92% (91% - 94%)	81% (79% - 84%)	75% (72% - 78%)	185	51	87% (81% - 92%)	75% (67% - 81%)	67% (58% - 74%)
Census tract poverty estimates										
≤5% - ≤ 10%	12,681	3,078	93% (93% - 94%)	81% (80% - 82%)	75% (74% - 75%)	646	167	92% (89% - 94%)	79% (75% - 82%)	73% (69% - 76%)

>10% - ≤ 20%	39,500	10,909	91% (91% - 92%)	77% (77% - 78%)	70% (70% - 71%)	2,812	801	90% (89% - 91%)	77% (75% - 79%)	71% (69% - 72%)
>20% - ≤ 100%	6,290	1,900	89% (89% - 90%)	75% (73% - 76%)	67% (66% - 69%)	3,599	1,140	89% (88% - 90%)	74% (72% - 76%)	66% (65% - 68%)
Primary Site										
Colon *	35,357	9,977	90% (90% - 91%)	76% (75% - 76%)	69% (69% - 70%)	4,274	1,299	88% (87% - 89%)	75% (73% - 76%)	68% (67% - 70%)
Rectum ***	23,114	5,910	93% (93% - 94%)	81% (80% - 81%)	73% (73% - 74%)	2,783	809	91% (90% - 92%)	78% (76% - 79%)	70% (68% - 71%)

NHA/PI: Non-Hispanic Asian/Pacific Islander; NH: Non-Hispanic.
P-value less than 0.05 was considered statistically significant; *P<0.01, **P<0.05, ***P<0.0001.

Table 4.4: Cox proportional hazards modeling of factors modifying the association between rural-urban status and survival in adults diagnosed with EOCRC, SEER 18 registries, United States.

Overall Survival			**Disease specific survival**		
Crude [a] HR (95% CI)	Minimally adjusted [b] HR (95% CI)	Fully adjusted [c] HR (95% CI)	Crude [a] HR (95% CI)	Minimally adjusted [b] HR (95% CI)	Fully adjusted [c] HR (95% CI)
Reference = urban					
All Participants					
1.17 (1.11 – 1.22) ***	1.16 (1.11 – 1.22) ***	1.10 (1.04 – 1.16) ***	1.16 (1.10 – 1.22) ***	1.15 (1.09 – 1.22) ***	1.10 (1.04 – 1.17) *
Males only					
1.13 (1.06 – 1.20) ***	1.13 (1.05 – 1.20) ***	1.07 (0.99 – 1.14)	1.13 (1.05 – 1.21) *	1.12 (1.05 – 1.19) ***	1.08 (1.00 – 1.17)
Females only					
1.20 (1.12 – 1.29) ***	1.20 (1.11 – 1.29) ***	1.13 (1.05 – 1.23) *	1.18 (1.09 – 1.28) ***	1.10 (1.03 – 1.18) *	1.13 (1.03 – 1.23) *
Non-Hispanic Whites only					
1.20 (1.14 – 1.27) ***	1.20 (1.13 – 1.27) ***	1.08 (1.01 – 1.15) *	1.20 (1.12 – 1.28) ***	1.14 (1.08 – 1.21) ***	1.08 (1.01 – 1.16) **
Non-Hispanic Blacks only					
1.02 (0.89 – 1.16)	1.01 (0.89 – 1.15)	0.97 (0.85 – 1.12)	1.01 (0.88 – 1.17)	1.06 (0.94 – 1.19)	1.00 (0.86 – 1.17)
Hispanics (all)					
1.30 (1.07 – 1.57) *	1.29 (1.06 – 1.57) *	1.24 (1.01 – 1.51) **	1.27 (1.02 – 1.57) **	1.30 (1.08 – 1.56) *	1.20 (0.97 – 1.50)
Non-Hispanic Asians/Pacific Islanders only					
1.60 (1.19 – 2.16) *	1.61 (1.19 – 2.17) *	1.57 (1.16 – 2.12) *	1.64 (1.18 – 2.28) *	1.20 (0.90 – 1.59)	1.61 (1.15 – 2.24) *
Other Races					
1.86 (1.30 – 2.68) ***	1.91 (1.33 – 2.75) ***	1.74 (1.15 – 2.64) *	1.79 (1.20 – 2.68) *	2.27 (1.63 – 3.15) ***	1.69 (1.06 – 2.66) *
Any Medicaid only					

1.10 (0.98 – 1.23)	1.11 (0.99 – 1.24)	1.09 (0.96 – 1.24)	1.13 (1.00 – 1.28)	1.06 (0.94 – 1.20)	1.13 (0.98 – 1.29)
Insured/No specifics group only					
1.15 (1.07 – 1.24) ***	1.14 (1.06 – 1.23) ***	1.12 (1.03 – 1.21) *	1.13 (1.04 – 1.23) *	1.10 (1.01 – 1.20) **	1.13 (1.03 – 1.24) *
Uninsured only					
0.99 (0.84 – 1.16)	0.98 (0.83 – 1.16)	0.94 (0.78 – 1.13)	0.97 (0.81 – 1.16)	1.02 (0.86 – 1.22)	0.94 (0.76 – 1.15)
Insurance Status – Unknown group					
1.17 (1.08 – 1.28) ***	1.17 (1.07 – 1.28) ***	1.12 (1.02– 1.23) *	1.17 (1.06 – 1.29) *	1.07 (1.00 – 1.14) **	1.11 (1.00 – 1.24) **
Age at diagnosis = 20 – 29 years only					
1.25 (1.00 – 1.57)	1.26 (1.00 – 1.58) **	1.23 (0.96 – 1.58)	1.26 (0.98 – 1.61)	1.07 (0.87 – 1.32)	1.24 (0.95 – 1.63)
Age at diagnosis = 30 – 39 years only					
1.21 (1.08 – 1.36) ***	1.21 (1.08 – 1.35) *	1.13 (1.00 – 1.28)	1.19 (1.05 – 1.35) *	1.11 (1.00 – 1.23)	1.12 (0.97 – 1.28)
Age at diagnosis = 40 – 49 years only					
1.15 (1.09 – 1.21) ***	1.15 (1.08 – 1.21) ***	1.08 (1.02 – 1.15) *	1.14 (1.07 – 1.21) ***	1.11 (1.06 – 1.17) ***	1.09 (1.02 – 1.17) **

Strata statement was used in all PHREG models to account for non-proportionality for covariates (prime site, stage and marital status)

[a] Association between residence (exposure) and survival in early onset colorectal cancer (outcome).

[b] Association between residence and survival in early onset colorectal cancer, adjusted for age and gender; adjusted for age in gender specific models. adjusted for gender in age specific models.

[c] Association between residence and survival in early onset colorectal cancer, adjusted for age, gender, marital status, payer status, census tract poverty estimates, Primary site of tumor, SEER summary stage and race.

P-value less than 0.05 was considered statistically significant for all cox proportional hazard models.

* P<0.01, ** P<0.05, *** P<0.0001.

CHAPTER 5

DISCUSSION AND CONCLUSION

This study investigated the association between rural-urban status and survival in EOCRC in the United States, using data from population-based SEER 18 registries. Rural patients had significantly worse 5-year survival from EOCRC with the greatest disparities among males, those aged between 40-49 years, those with rectal cancers, those who are single/unmarried, those with distant lesion, and Hispanics as compared to urban EOCRC patients. There were significant rural-urban differences in EOCRC mortality even after adjusting for various sociodemographic, individual level, area level and clinical characteristics. The study results are consistent with the findings from previous studies which reported worse CRC survival outcomes in rural residents compared to urban residents [53,55,55,81]. Race/ethnicity was an effect modifier of association between rural-urban status and survival in EOCRC patients with the greatest magnitude of association among

non-Hispanic Asians/Pacific Islanders and non-Hispanic Whites as compared to non-Hispanic Black residents or Hispanic residents. However, these findings are not reflective of the evidence from previous literature where non-Hispanic black residents are reported to be at greater risk of adverse survival outcomes from EOCRC.[9,29,58]

Rural men have worse 5-year, EOCRC specific survival compared to women. This is

consistent with the findings from existing literature. ***Holowatyj et al, 2016,*** reported that men experience worse overall and cancer specific survival from CRC at young age (<50 years) compared with women.[38]Also, evidence suggest that CRC mortality rates are 40% higher in men than women.[55] Clinical stage of the disease and race/ethnicity are reported to be influencing the huge variation in CRC survival by gender, especially in younger people.[55] Moreover, the biological differences in hormones and genes (sexual dimorphism) has been proven to contribute to better EOCRC survival outcomes in women than men.[90] The key proliferative pathways in CRC tumorgenesis have a protective mechanism through estrogen regulated genes and cell signaling.[90] Increasing trends in mortality for EOCRC is alarming, especially when there is inequitable distribution of the disease burden across rural-urban locations.[2] Health behaviors, access to cancer care and perceived needs may be explored in the future to clearly understand this huge variation in EOCRC survival among gender subgroups.

Single/unmarried rural EOCRC patients have worse 1-, 3- and 5-year survival from EOCRC. This finding is consistent with the findings reported by ***Aizer et al, 2013***, where they examined the association between marital status and cancer survival.[81] They reported that married people were more likely to seek definitive care, less likely to present with more advanced disease or die from cancer compared to unmarried people.[81] Similarly, rural patients diagnosed with a distant stage lesion had poorer survival (5-year) as compared to their urban counterparts. Evidence supports that rural patients with CRC are diagnosed at later stages as compared to their urban counterparts.[18,52,53,56,58]

Degree of rurality can alter the risk of late-stage cancer diagnosis up to 10%, [82] and can inform disparities in rural cancer control across the continuum.

Rural patients diagnosed with rectal cancer had worse 5-year survival as compared to their urban counterparts. These findings corroborate with that of ***Shankaranarayanan et al***, ***2014,*** where rural patients with rectal cancers were reported to have shorter survival as compared to urban or other micropolitan patients.[87] Aggressive treatment prognosis and survival benefits are unclear in EOCRC patients indicating that these patients respond differently to treatment regimens.[37,38,91] Findings from a military based health system linked to cancer registry showed that EOCRC patients received 2-8 times greater courses of postoperative systemic chemotherapy on an average compared to older CRC patients (65 – 75years), across all cancer stages of the disease.[91] Evidence suggests that the median time to treatment from the onset of symptom in early onset rectal cancer is 217 days vs. 29.5 days in patients older than 50 years.[94] Delays in presentation to physician, [94] specialist referral, access to care have been long reported. In addition, the time to diagnosis and treatment for CRC in rural areas are prolonged compared to urban.[79,94-96] Further, rural CRC patients reported to have prolonged time interval from first symptom or screening test to treatment contributing to geographic disparities in CRC survival.[79] Given the increasing rates of EOCRC, especially in rural areas, [29,83,86] future exploration of trends in segmental mortality rates of EOCRC can better explain rural-urban disparities in disease burden and survival. Patient cohort group aged 40-49 years in rural areas had worse 5-year survival compared to urban. Studies reported that majority of CRC occurrence is sporadic and can be attributable to modifiable environmental risk factors, chemoprevention strategies and screening.[42] With the new era of updated

screening guidelines for CRC from USPSTF,[13] these findings can help identify needy populations and encourage timely diagnosis and treatment strategies.

Rural dwelling EOCRC patients are at significantly greater risk of dying from EOCRC as compared to urban EOCRC patients after adjusting for relevant sociodemographic, individual level, area level and clinical characteristics. Many factors might be responsible for the disproportionate burden of mortality in EOCRC by residence status. Studies show that prognosis related factors affect survival in rural patients as compared to urban.[55,56,74] ***Rogers CR et al, 2020,*** [55] reported that patients who received chemotherapy, surgery and radiation for CRC had reduced risk of all-cause mortality. However, this reduction was not stable in rural patients due to lack of comprehensive treatment options or availability. ***Hashibe M et al, 2018,*** [74] in their study reported that differences in treatment were observed between rural and metropolitan (urban) cancer patients where, rural patients remained without receiving surgery or radiation. They explained that this difference could be due to lack of adherence to treatment guidelines.[74] Further, studies indicate disparities in less invasive procedures for colon cancer treatment among rural residents as compared to their urban counterparts.[75,76] Treatment options and selection vary across geographic locations and accounting for structural, location level, neighborhood access to healthier foods/physical activity, access to care and utilization of services may decrease SES related survival disparities in EOCRC patients.

Among males, the age adjusted hazard of EOCRC mortality was 13% higher in rural patients compared to urban. However, the association was attenuated when fully adjusted for all relevant factors. Evidence suggest that rural men had poorer survival from CRC as compared to urban men.[55] It was reported that rural males with CRC were more likely to

report social and behavioral issues, were diagnosed at older ages, with diagnosis pertaining to different anatomic subsites which lead to differences in stage at diagnosis impacting treatment and thereby survival in rural males comparatively.[55] Current study did not find any modifying role of gender on the association between rural-urban status and EOCRC survival. Given the evidence that men are more susceptible to colon cancer than women,[78] it is important to ensure rural men undergo USPSTF recommended [13] screening for colon cancer to avoid any missed opportunities. Also, gender specific social, biological, behavioral, and environmental conditions influencing survival outcomes in EOCRC needs further evaluation to understand geographic disparities in cancer burden especially among rural residents.

Risk of death was 20% (overall) and 14% (EOCRC specific) statistically significantly higher in non-Hispanic White rural patients compared to non-Hispanic White urban EOCRC patients after adjusting for age and gender. However, the association was attenuated when fully adjusted for age, gender, marital status, payer status, census tract poverty estimates, primary site of tumor, SEER summary stage. Similarly, among Hispanics and non-Hispanic Asians/Pacific Islanders, rural residents had significantly greater hazard of mortality both overall and EOCRC specific, as compared to urban patients, after adjusting for relevant factors. Education status, health literacy and access to care have been reported to influence survival disparities among rural and urban residents.[80] Also these disparities in survival trends among racial ethnic minority groups has been persistent over the last three decades.[77,80] Need for policy interventions focusing on improving access to care and utilization especially in rural areas are warranted.

Race was an effect modifier of association between rural-urban status and survival in EOCRC patients. The strength of the association between urban/rural status and overall and disease-free survival was greatest among non-Hispanic Whites and non-Hispanic Asians/Pacific Islanders as compared to non-Hispanic Black residents. Several studies have reported that rural NH Black residents are at greater risk of being diagnosed with CRC and they tend to have poorer survival outcomes.[18,23,24,29,46,56,58] However, this study found no significant association between rural-urban status and survival among NH Blacks. Evidence from previous literature suggest that the trends in CRC mortality gap between NH Whites and Hispanics is narrowing indicating that Hispanic population may face greater disparities in CRC mortality as compared to NH Whites over the time.[88] Disparities in SES, education level, access to care and utilization may influence survival outcomes especially in rural population. It is important to make sure rural and minoritized populations undergo timely screening, diagnosis, and guideline adherent treatment to avoid missed opportunities and delays in accessing needed care. On the contrary, evidence suggest that non-Hispanic Asians and other racial subgroups are less influenced by SES or other treatment disparities in CRC survival, in view of biological factors associated with improved survival in this population.[89] Hence, exploration of familial, genetic factors impacting EOCRC survival in non-Hispanic Asians/Pacific Islander population is encouraged.

Among the people who were insured, the hazard of mortality overall (12%) and EOCRC specific (12%) was significantly higher in rural patients as compared to urban patients, even after adjusting for all relevant factors. Access to care and utilization may greatly be impacted in rural areas despite being eligible for needed care. Rural and

urban CRC patients differ in adherence to treatment and proximity to high-volume/accredited hospitals for care. These disparities are further aggravated by inadequate health insurance status, shortage of primary care physicians and oncology specialists in rural.[54] Given the evidence that insurance status influences survival, [25-27, 54] more specific assessment of active insurance status/enrollment may inform barriers to health care utilization among rural residents.

Among 40–49-year age group, rural patients had significantly greater hazard of overall (8%) and EOCRC specific (9%) mortality, compared to urban patients, even after adjusting for all relevant factors. Studies reported persistent increase in CRC incidence and mortality especially among younger age groups.[16-20] However, this study did not find any significant interaction between age and rural-urban status in EOCRC survival. Younger patients are being diagnosed with more aggressive type of tumors that respond to treatment regimen differently than older age groups[37,38]**.** Rural residents with EOCRC may be at greater risk for adverse survival outcomes if age related disparities remain.

A major strength of this study is that SEER data are population based, publicly available and are representative of 28% of US population. SEER registry uses standard county level RUCC definitions for rural and urban status and it represents more than 1/3rd of US general population.[46] Also, the sampled population in SEER represents expanded racial ethnic groups which enabled us to make better comparisons. Different geographic locations in SEER ensures high quality reporting system which includes epidemiologically significant population subgroups for consideration.[84] However, this study has some limitations. SEER does not report information on risk factors [smoking, drinking, tobacco use etc.,], comorbid conditions, family history of cancers or any

medical conditions, environmental exposure to carcinogens, tumor/molecular phenotypes, and chemotherapy use.[77,85] Also, this study was restricted to patients diagnosed with EOCRC within the 20-to-49-year age group. Hence comparisons across other CRC age groups were not performed. This study included the most compelling factors influencing survival in EOCRC population based on previous literature and reported findings that were available through SEER. However, confounding due to any unmeasurable factors were not accounted for in the analyses. Finally, cox proportional hazards model was extended to stratum specific models to account for non-proportionality in covariates (marital status, stage of disease and primary site) which reduced statistical power.

In conclusion, this study investigated the association between rural-urban status and survival in EOCRC and found that rural patients had poorer 5-year survival from EOCRC as compared to urban patients. Disproportionate burden of EOCRC mortality by rural-urban status exist. Men, those who are insured, those who were single/unmarried, those diagnosed with distant lesion, those aged between 40-49 years, and those with rectal cancers from rural areas have worse survival outcomes compared to urban counterparts. Race is an effect modifier of association between rural-urban status and survival in EOCRC patients. Rural non-Hispanic Whites and NH Asians/Pacific Islanders have greater hazard of both overall and disease-free survival as compared to urban non-Hispanic Black residents even after controlling for sociodemographic, individual level and clinical factors.

Rural residents with EOCRC may be at greater risk for adverse survival outcomes if disparities remain. Hence, it is important to ensure rural men, and minoritized populations undergo timely screening, diagnosis, and guideline adherent treatment to

avoid missed opportunities and delays in accessing needed care. Need for policy interventions focusing on improving access to care and utilization, especially in rural areas are warranted. Also, future exploration of trends in segmental incidence and mortality rates of EOCRC can better explain disease burden in rural and urban areas.

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APPENDIX A: 10-YEAR SURVIVAL AND COX TABLES

Table A.1: 10-year survival (Overall) for adults with Early Onset Colorectal Cancer by rurality, SEER-18 registries, United States.

Characteristics	**Urban Residence**			**Rural Residence**		
	Total	**No of deaths (all causes)**	**10-year survival (95% CI)**	**Total**	**No of deaths (all causes)**	**10-year survival (95% CI)**
Overall ***	58,471	19,622	58.12% (57.63% - 58.60%)	7,057	2,632	54.97% (53.57% - 56.35%)
Age at diagnosis (Years)						
20 - 29	3,126	921	59.07% (56.79% - 61.26%)	353	118	56.00% (49.02% - 62.40%)
30 - 39	12,385	3,929	59.66% (58.60% - 60.70%)	1,363	472	57.11% (53.92% - 60.16%)
40 - 49	42,960	14,772	57.64% (57.08% - 58.20%)	5,341	2,042	54.27% (52.66% - 55.85%)
Gender						
Female	27,698	8,688	60.19% (59.48% - 60.89%)	3,345	1,168	57.91% (55.90% - 59.87%)
Male	30,773	10,934	56.27% (55.61% -56.94%)	3,712	1,464	52.24% (50.28% - 54.15%)
Race						
NH White	33,206	10,863	60.15% (59.52% - 60.78%)	5,498	1,983	56.58% (55.01% - 58.13%)
NH Black	8,543	3,581	49.49% (48.21% - 50.75%)	831	366	47.26% (43.13% - 51.27%)
Hispanic (all)	9,964	3,190	56.10% (54.82% - 57.36%)	368	145	45.57% (38.71% - 52.16%)
NHA/PI	5,905	1,867	59.62% (58.07% - 61.13%)	155	62	50.81% (40.83% - 59.94%)
Other	853	121	78.48% (74.27% - 82.07%)	205	76	55.35% (46.60% - 63.25%)
Payer Status						
Any Medicaid	5,843	2,216	39.53% (36.98% - 42.06%)	886	370	35.28% (29.31% - 41.30%)
Insured/No specifics	26,733	6,484	62.85% (61.79% - 63.89%)	2,819	761	58.84% (55.82% - 61.72%)

Uninsured	2,303	881	45.03% (41.16% - 48.81%)	442	179	42.54% (35.11% - 49.76%)
Unknown	23.592	10,041	57.90% (57.25% - 58.54%)	2,910	1,588	56.32% (54.46% - 58.14%)
Marital Status						
Married (including common law)	33,040	10,164	62.06% (61.43% - 62.68%)	3,989	1,367	59.26% (57.45% - 61.02%)
Single/unmarried	16,227	6,315	50.11% (49.14% - 51.07%)	1,570	678	45.83% (42.70% - 48.89%)
Separated /divorced /Widowed	5,825	2,357	51.63% (50.09% - 53.15%)	983	415	48.59% (44.75% - 52.31%)
Unknown	3,379	786	68.53% (66.45% - 70.50%)	515	172	57.63% (51.99% - 62.84%)
SEER summary Stage						
Localized	15,442	1,350	85.52% (84.69% - 86.31%)	1,848	219	81.68% (79.11% - 83.96%)
Regional	17,518	4,000	65.29% (64.30% - 66.27%)	2,028	537	60.60% (57.56% - 63.49%)
Distant	11,759	8,193	12.25% (11.40% - 13.13%)	1,456	1,063	9.06% (7.36% - 11.88%)
Unknown/ Unstaged	1,553	498	54.74% (51.30% - 58.04%)	185	73	45.78% (35.97% - 55.05%)
Census tract poverty estimates						
≤5% - ≤ 10%	12,681	3,737	63.17% (62.15% - 64.18%)	646	206	60.31% (55.63% - 64.66%)
>10% - ≤ 20%	39,500	13,493	57.22% (56.62% - 57.81%)	2,812	988	57.29% (55.07% - 59.45%)
>20% - ≤ 100%	6,290	2,392	53.50% (52.00% - 54.98%)	3,599	1,438	52.04% (50.07% - 53.97%)
Primary Site						
Colon	35,357	12,344	56.73% (56.11% - 57.35%)	4,274	1,636	53.45% (51.63% - 55.24%)
Rectum	23,114	7,278	60.22% (59.44% - 60.98%)	2,783	996	57.20% (55.00% - 59.33%)

Table A.2: 10-year survival (EOCRC specific) for adults with Early Onset Colorectal Cancer by rurality, SEER-18 registries, United States.

Characteristics	**Urban Residence**			**Rural Residence**		
	Total	**No of EOCRC deaths**	**10-year survival (95% CI)**	**Total**	**No of EOCRC deaths**	**10-year survival (95% CI)**
Overall	58,471	15,887	64.71% (64.23% - 65.18%)	7,057	2,108	62.07% (60.68% - 63.42%)
Age at diagnosis (Years)						
20 - 29	3,126	790	63.87% (61.63% - 66.02%)	353	101	61.48% (54.65% - 67.60%)
30 - 39	12,385	3,280	65.20% (64.15% - 66.22%)	1,363	391	62.75% (59.55% - 65.77%)
40 - 49	42,960	11,817	64.63% (64.07% - 65.17%)	5,341	1,616	61.86% (60.27% - 63.41%)
Gender						
Female	27,698	7,046	66.49% (65.80% - 67.17%)	3,345	939	64.49% (62.50% - 66.41%)
Male	30,773	8,841	63.11% (62.45% - 63.77%)	3,712	1,169	59.78% (57.84% - 61.67%)
Race						
NH White	33,206	8,711	66.76% (66.15% - 67.36%)	5,498	1,588	63.43% (61.87% - 64.94%)
NH Black	8,543	2,889	57.21% (55.92% - 58.47%)	831	297	55.19% (50.96% - 59.21%)
Hispanic (all)	9,964	2,620	62.47% (61.20% - 63.71%)	368	119	52.83% (45.66% - 59.49%)
NHA/PI	5,905	1,566	64.85% (63.31% - 66.33%)	155	49	59.35% (49.44% - 67.94%)
Other	853	101	82.48% (78.93% - 85.49%)	205	55	64.95% (56.16% - 72.41%)
Payer Status						
Any Medicaid	5,843	1,793	49.44% (47.14% - 51.70%)	886	301	44.68% (37.81% - 51.30%)
Insured/No specifics	26,733	5,356	68.90% (68.00% - 69.77%)	2,819	619	66.02% (63.27% - 68.62%)
Uninsured	2,303	737	54.20% (51.20% - 57.09%)	442	149	50.44% (42.64% - 57.73%)
Unknown	23,592	8,001	64.32% (63.68% - 64.96%)	2,910	1,039	62.81% (60.94% - 64.61%)
Marital Status						

Married (including common law)	33,040	8,384	67.55% (66.94% - 68.15%)	3,989	1,122	64.71% (62.91% - 66.44%)
Single/unmarried	16,227	5,065	58.27% (57.30% - 59.22%)	1,570	538	55.34% (52.19% - 58.36%)
Separated /divorced /widowed	5,825	1,852	60.00% (58.46% - 61.49%)	983	317	58.46% (54.53% - 62.18%)
Unknown	3,379	586	75.37% (73.42% - 77.20%)	515	131	65.99% (60.43% - 70.96%)
SEER summary Stage						
Localized	15,442	685	92.41% (91.78% - 93.00%)	1,848	118	89.00% (86.60% - 91.00%)
Regional	17,518	3,181	71.23% (70.27% - 72.16%)	2,028	412	68.99% (66.13% - 71.66%)
Distant	11,759	7,293	15.89% (14.89% - 16.93%)	1,456	946	12.14% (9.65% - 14.93%)
Unknown/ Unstaged	1,553	313	68.16% (64.66% - 71.40%)	185	51	60.10% (50.00% - 68.80%)
Census tract poverty estimates						
≤5% - ≤ 10%	12,681	3,078	68.87% (67.89% - 69.84%)	646	167	67.13% (62.63% - 71.22%)
>10% - ≤ 20%	39,500	10,909	63.88% (63.30% - 64.46%)	2,812	801	63.69% (61.48% - 65.81%)
>20% - ≤ 100%	6,290	1,900	61.26% (59.78% - 62.71%)	3,599	1,140	59.79% (57.82% - 61.69%)
Primary Site						
Colon	35,357	9,977	63.61% (62.99% - 64.21%)	4,274	1,299	61.26% (59.45% - 63.01%)
Rectum	23,114	5,910	63.38% (65.62% - 67.13%)	2,783	809	63.19% (61.00% – 65.30%)

Table A.3 Cox proportional hazards modeling of factors influencing survival in adults diagnosed with EOCRC, SEER 18 registries, United States. §

Characteristics	Overall Survival				Disease specific survival			
	Colon (n = 31, 204)		Rectum (n = 20,585)		Colon (n = 31, 204)		Rectum (n = 20,585)	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Residence								
Urban	*reference*							
Rural	1.11 (1.04 – 1.19)	0.0023	1.10 (1.01 – 1.19)	0.0366	1.10 (1.02 – 1.19)	0.0097	1.11 (1.01 – 1.22)	0.0271
Race								
NH White	*reference*							
NH Black	1.26 (1.19 – 1.33)	<0.0001	1.22 (1.13 – 1.32)	<0.0001	1.30 (1.23 – 1.38)	<0.0001	1.18 (1.08 – 1.29)	0.0002
Hispanic (all)	1.01 (0.95 – 1.07)	0.1214	1.08 (1.01 – 1.16)	0.0346	1.03 (0.97 – 1.10)	0.3537	1.09 (1.00 – 1.17)	0.0515
NHA/PI	1.08 (1.01 – 1.16)	0.0373	1.10 (1.00 – 1.20)	0.0445	1.31 (1.05 – 1.22)	0.0021	1.09 (0.99 – 1.20)	0.0980
Other	0.65 (0.52 – 0.81)	0.0001	0.76 (0.60 – 0.96)	0.0209	0.73 (0.57 – 0.92)	0.0090	0.76 (0.58 – 0.99)	0.0396
Gender								
Male	*reference*							
Female	0.84 (0.80 – 0.87)	<0.0001	0.81 (0.77 – 0.85)	<0.0001	0.84 (0.81 – 0.88)	<0.0001	0.79 (0.74 – 0.83)	<0.0001
Age at diagnosis (years)								
20 - 29	*reference*							
30 - 39	1.01 (0.91 – 1.11)	0.9111	0.97 (0.86 – 1.10)	0.6546	0.96 (0.87 – 1.08)	0.5130	0.93 (0.81 – 1.06)	0.2702
40 - 49	1.10 (1.00 – 1.21)	0.0428	1.02 (0.91 – 1.14)	0.7819	1.01 (0.91 - 1.12)	0.8557	0.95 (0.84 – 1.08)	0.4356
Marital Status								
Married (Including common law)	*reference*							
Single/unmarried	1.29 (1.23 – 1.35)	<0.0001	1.37 (1.29 – 1.46)	<0.0001	1.25 (1.18 – 1.31)	<0.0001	1.33 (1.25 – 1.43)	<0.0001
Separated /divorced /widowed	1.20 (1.12 – 1.28)	<0.0001	1.24 (1.14 – 1.34)	<0.0001	1.14 (1.06 – 1.22)	0.0005	1.17 (1.07 – 1.28)	0.0006
Unknown	1.05 (0.95 – 1.17)	0.3005	0.89 (0.78 – 1.02)	0.0852	1.03 (0.92 – 1.15)	0.6529	0.83 (0.71 – 0.97)	0.0160

Payer Status								
Insured/no specifics	***reference***							
Any Medicaid	1.45 (1.37 – 1.54)	<0.0001	1.67 (1.55 – 1.80)	<0.0001	1.38 (1.29 – 1.47)	<0.0001	1.70 (1.56 – 1.84)	<0.0001
Uninsured	1.35 (1.24 – 1.46)	<0.0001	1.56 (1.40 – 1.74)	<0.0001	1.36 (1.24 – 1.48)	<0.0001	1.60 (1.42 – 1.81)	<0.0001
Unknown	1.23 (1.17 – 1.28)	<0.0001	1.22 (1.15 – 1.30)	<0.0001	1.24 (1.18 – 1.31)	<0.0001	1.27 (1.19 – 1.36)	<0.0001
Census tract poverty estimates								
≤5% - ≤ 10%	***reference***							
>10% - ≤ 20%	1.18 (1.12 – 1.25)	<0.0001	1.16 (1.08 – 1.24)	<0.0001	1.17 (1.10 – 1.24)	<0.0001	1.14 (1.06 – 1.23)	0.0008
>20% - ≤ 100%	1.28 (1.20 – 1.38)	<0.0001	1.25 (1.14 – 1.37)	<0.0001	1.26 (1.16 – 1.37)	<0.0001	1.21 (1.09 – 1.34)	0.0004
SEER summary Stage								
Localized	***reference***							
Regional	2.99 (2.76 – 3.24)	<0.0001	2.54 (2.33 – 2.76)	<0.0001	5.18 (4.62 – 5.81)	<0.0001	3.59 (3.23 – 3.99)	<0.0001
Distant	18.03 (16.71 – 19.45)	<0.0001	14.17 (13.08 – 15.36)	<0.0001	35.64 (31.94 - 39.77)	<0.0001	22.04 (19.92 – 24.39)	<0.0001
Unknown /unstaged	6.15 (5.39 – 7.02)	<0.0001	3.41 (2.96 – 3.93)	<0.0001	8.79 (7.38 – 10.47)	<0.0001	3.78 (3.16 – 4.53)	<0.0001

§ Association between residence and survival in early onset colorectal cancer, adjusted for rural-urban status, age and gender, marital status, payer status, census tract poverty estimates, SEER summary stage and race.

P-value less than 0.05 was considered statistically significant for all cox proportional hazard models.