Supplemental Online Content

Hawley JE, Sun T, Chism DD, et al; COVID-19 and Cancer Consortium (CCC19). Assessment of regional variability in COVID-19 outcomes among patients with cancer in the United States. *JAMA Netw Open.* 2022;5(1):e2142046. doi:10.1001/jamanetworkopen.2021.42046

eAppendix 1. Alphabetical List of Participants by Institution That Contributed at Least 1 Record to the Analysis

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Alphabetical List of Participants by Institution That Contributed at Least 1 Record to the Analysis

Bolded = site PI/co-PIs; site co-investigators are listed alphabetically by last name.

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- Keith E. Stockerl-Goldstein, MD; Omar Butt, MD, PhD; Jian L. Campian, MD, PhD; Mark A. Fiala, MSW; Jeffrey P. Henderson, MD, PhD; Ryan Monahan, MBA; Alice Y. Zhou, MD, PhD (Alvin J. Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital, St. Louis, MO, USA)
- Michael A. Thompson, MD, PhD, FASCO; Pamela Bohachek, RN; Daniel Mundt, MD; Mitrianna Streckfuss, MPH; Eyob Tadesse, MD (Aurora Cancer Care, Advocate Aurora Health, Milwaukee, WI, USA)
- 4. Philip E. Lammers, MD, MSCI (Baptist Cancer Center, Memphis, TN, USA)
- 5. **Orestis A. Panagiotou, MD, PhD**; Pamela C. Egan, MD; Dimitrios Farmakiotis, MD, FACP, FIDSA; Hina Khan, MD; Adam J. Olszewski, MD (Brown University and Lifespan Cancer Institute, Providence, RI, USA)
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- 11. Toni K. Choueiri, MD; Ziad Bakouny, MD, MSc; Gabrielle Bouchard, BS; Fiona J. Busser, BA; Jean M. Connors, MD; Catherine R. Curran, BA; George D. Demetri, MD, FASCO; Antonio Giordano, MD, PhD; Kaitlin Kelleher, BA; Anju Nohria, MD; Andrew Schmidt, MD; Grace Shaw, BA; Eli Van Allen, MD; Pier Vitale Vincent Xu, MD; Rebecca L. Zon, MD (Dana-Farber Cancer Institute, Boston, MA, USA)
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- 61. Lawrence E. Feldman, MD; Kent F. Hoskins, MD; Gerald Gantt Jr., MD; Li C. Liu, PhD; Mahir Khan, MD; Ryan H. Nguyen, DO; Mary Pasquinelli, APN, DNP; Candice Schwartz, MD; Neeta K. Venepalli, MD, MBA (University of Illinois Hospital & Health Sciences System, Chicago, IL, USA)
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- 63. Christopher R. Friese, PhD, RN, AOCN, FAAN; Leslie A. Fecher, MD (University of Michigan Rogel Cancer Center, Ann Arbor, MI, USA)
- 64. Blanche H. Mavromatis, MD; Ragneel R. Bijjula, MD; Qamar U. Zaman, MD (UPMC Western Maryland, Cumberland, MD, USA)
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- 69. Robert L. Rice, MD, PhD (WellSpan Health, York, PA, USA)
- 70. Wilhelmina D. Cabalona, MD; Christine Pilar, BS, CCRC, ACRP-PM (Wentworth-Douglass Hospital, Dover, NH, USA)
- 71. **Prakash Peddi, MD; Lane R. Rosen, MD**; Briana Barrow McCollough, BSc, CCRC (Willis-Knighton Cancer Center, Shreveport, LA, USA)
- 72. **Mehmet A. Bilen, MD**; Deepak Ravindranathan, MD, MS (Winship Cancer Institute of Emory University, Atlanta, GA, USA)
- 73. **Navid Hafez, MD, MPH**; Roy Herbst, MD, PhD; Patricia LoRusso, DO, PhD; Tyler Masters, MS; Catherine Stratton, BA (Yale Cancer Center at Yale University School of Medicine, New Haven, CT, USA)

Approved Project PIsJessica Hawley and Clara Hwang1 (a) Manuscript titleAssessment of US Regional Variability in COVID-19 Outcomes Among Patients With Cancer3 ObjectivesH0: Clinical outcomes and US census region are independent in patients with cancer and COVID-19 in adjusted models (no difference in death (30-day all-cause mortality) or composite endpoint (death, rate of ICU admission, rate of mechanical ventilation). HA: Clinical outcomes and US census region are associated in patients with cancer and COVID-19.
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1 (d) Manuscript titleAssessment of OS Regional Valuability in COVID 15Outcomes Among Patients With Cancer3 ObjectivesState specific objectives, including any prespecifiedhypothesesH0: Clinical outcomes and US census region are independent in patients with cancer and COVID-19 in adjusted models (no difference in death (30-day all-cause mortality) or composite endpoint (death, rate of ICU admission, rate of mechanical ventilation).HA: Clinical outcomes and US census region are associated in patients with cancer and COVID-19.
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4 Study design Retrospective, multi-center cohort study
5 Setting Cohort study of patients with current or past history of
cancer and lab-confirmed SARS-CoV-2 infection from >120
participating CCC19 sites. Data analyzed from March 15,
2020 – November 30, 2020. Registry built and maintained
as electronic REDCap database at VUMC.
(a) Give the eligibility criteria, Subjects included in this analysis were those with
and the sources and methods of laboratory-confirmed SARS-Cov-2 infection and past or
Describe methods of follow-up contered into the CCC19 detabase between 2/17/2020 and
11/30/2020 with follow-up data reported through
12/31/2020. We excluded records of presumptive COVID-
19 cases, patients < 18 years of age, patients with
incomplete follow-up data, cases of non-invasive cancers
and premalignant conditions or non-melanoma non-
invasive skin cancers, cases from outside the U.S., and
records with quality score >4.
(b) For matched studies, give Not a matched study.
matching criteria and number of
exposed and unexposed
7 Variables
(a) Outcomes Primary outcomes: 30-day all-cause mortality (binary)
Secondary outcomes: composite binary outcome (death at
any time, ICU admission, or mechanical ventilation), and
individual components of composite outcome to assess
Analysis of outcomes conducted overall (all time periods)
and by three prespecified time periods.
(b) Exposures 9 US Census Subregions (Defined as per list below)
(c) Potential confounders Census Region Level:

	Average daily new COVID-19 case rate per
	1,000,000 people (continuous)
	 Population density for region (continuous)
	 Center-level: SVI (continuous) RUCC code (ordinal) Type of Center – academic vs. community (binary)
	Individual-level
	• Sex
	race/ethnicity
	• smoking
	• obesity
	• specific comorbidities (CV, pulmonary, renal, DM)
	 type of malignancy (solid vs. heme)
	cancer status
	ECOG status
	 type of cancer-directed therapy or surgery
	COVID-19 treatments
	Time intervals (we are 2 months - 2 time novieds)
	• March April May
	 Sent Oct Nov
(d) Effect modifiers	None
(e) Diagnostic criteria (if	Laboratory-confirmed positive for SARS-CoV-2
applicable)	
8 Data sources/measurement For each variable of interest.	Variables of interest are defined by the CCC19 database registry and entered by each local site's data abstractor.
give sources of data and details	-race/ethnicity self-reported (5 categories)
of methods of assessment	-smoking (never v. ever v. missing)
(measurement). Describe	-obesity (y/n/missing)
comparability of assessment	-specific comorbidities (CV, pulm, renal, DM, missing)
methods if there is more than	-cancer status (active and responding, active and stable,
one group	active and progressing vs. remission/NED, unknown,
	missing) $\Gamma(0, 1, 2)$ unknown missing)
	-ECOG (U, 1, \geq 2, UNKNOWN, MISSING)
	-type of manginancy (solid vs. here)
	cytotoxic chemo, immunotherany targeted endocrine
	locoregional, other, missing/unknown)

	 -COVID-19 tx (categorical: use JCO paper groupings) -Rural-urban status (center-level: ordinal – 1, 2, 3) -Neighborhood (cont: use center-level SVI) -Population density by US census subregion (continuous) -New COVID19 ave daily case over 3 time intervals by region (continuous)
9 Bias Describe any efforts to address potential sources of bias	Adjustment for covariates in multivariable models.
10 Study size Explain how the study size was arrived at	Case volume dependent on data abstracters at each site.
11 Quantitative variables Explain how quantitative variables will be handled in the analyses. If applicable, describe which groupings will be chosen and why	As per above
12 Statistical methods	
(a) Describe all statistical methods, including those to be used to control for confounding	Covariates (listed above under potential confounders) and binary outcomes will be summarized across 9 census subregions using standard descriptive statistics. Multivariable generalized linear mixed-effects models (with a logit link for binary outcomes and center-level random effects) will be used to (1) estimate adjusted covariate-outcome associations and (2) estimate adjusted subregion-level outcome rates overall and at 3-month time intervals. For secondary outcomes, the model will include an offset for (log) follow-up time. A list of potential tables and figures is provided below.
(b) Describe any methods that will be used to examine subgroups and interactions	None
(c) Explain how missing data will be addressed	Multiple imputation will be used to impute missing and unknown data for all variables included in the analysis, with some exceptions: unknown ECOG performance score and unknown cancer status will not be imputed and treated as a separate category in analyses. Imputation will be performed on the largest dataset possible (that is, after removing test cases and other manual exclusions, but before applying specific exclusion criteria). At least 10 imputations will be generated.

(d) If applicable, explain how	Excluded if no data on 30-day follow-up form. We will
loss to follow-up will be	extend follow-up time (through 12/31/2020) to ensure
addressed	that follow-up for the primary outcome, 30-day mortality,
	is complete to the best of our ability.
(e) Describe any sensitivity	None
analyses	
Date approved	January 22, 2021

US Census Regions / Division:

- Region I: Northeast
 - <u>New England:</u> Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont
 - o Middle Atlantic: New Jersey, New York, Pennsylvania
- Region II: Midwest
 - o East North Central: Indiana, Illinois, Michigan, Ohio, Wisconsin
 - <u>West North Central:</u> Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota
- Region III: South
 - <u>South Atlantic:</u> Delaware, DC, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia
 - o East South Central: Alabama, Kentucky, Mississippi, Tennessee
 - West South Central: Arkansas, Louisiana, Oklahoma, Texas
- Region IV: West
 - <u>Mountain</u>: Arizona, Colorado, Idaho, New Mexico, Montana, Utah, Nevada, Wyoming
 - o <u>Pacific:</u> Alaska, California, Hawaii, Oregon, Washington



The COVID-19 & Cancer Consortium

Approved Project Variables

Once the project design and SAP have been approved for your project, this document will be used to specify the exact outcomes and variables to be used in your analysis. Please provide as much information as you can, including the existing variable name if you know it. Use of existing variables will decrease the amount of time that it takes to get your project to the analysis phase, but we will endeavor to add any needed derived variables based on your project needs. Existing variables can be found in two places within the GitHub repo: the Data Dictionary ("CCC19_DataDictionary.csv"), which includes the native variables found in the survey, and the list of Derived Variables ("CCC19 Derived Variables Spreadsheet.xlsx").

Please fill out and return this form to Jeremy Warner (<u>jeremy.warner@vumc.org</u>), Sanjay Mishra (<u>sanjay.mishra.1@vumc.org</u>) and your assigned biostatistics lead. If you need extra rows just hit Tab when your cursor is in the bottom right cell

Outcome	Outcome variable	Outcome values	Additional Details
description	name		
Derived variable indicating whether patient has died within 30 days of COVID-19 diagnosis (default = No)	der_dead30	0 = No; 1 = Yes; 99 = Unknown	
Derived dead/alive variable	der_deadbinary	0 = No; 1 = Yes; 99 = Unknown	
Derived variable indicating whether patients required mechanical ventilation	der_mv	0 = No; 1 = Yes; 99 = Unknown	
Derived variable indicating time in ICU	der_ICU	0 = No; 1 = Yes; 99 = Unknown	
Derived variable of composite outcome	der_composite_ICU_mv_death (der_composite.3.v2 is the variable name in R script)	0 = No; 1 = Yes; 99 = Unknown	Derived with: der_deadbinary, der_mv, der_ICU
Median F/U in days	der_days_fu (der_median_fu is the variable name in R script)		

Covariate description	Variable name	Covariate values	Additional Details
Patient-level covariate	<u>es</u>		

Region of patient residence with ex- US collapsed	der_region_v2	Non-US; Other; Undesignated US; US Midwest; US Northeast; US South; US West	
Region of patient residence with US and ex-US collapsed	der_region_v3	Non-US; Other; US	
US Census Division	der_division	East North Central; East South Central; Middle Atlantic; Mountain; New England; Pacific; South Atlantic; West North Central; West South Central	
Age with imputation for categoricals	der_age_trunc (der_age is the variable name in the R script)	Years (continuous 18-89; patients noted to be greater than 89 are set to be age = 90)	
Sex (Recode other/prefer not to say gender> missing)	der_sex	Male, Female	
Derived variable for race/ethnicity	der_race	Non-Hispanic White; Hispanic; Non-Hispanic Black; Other	
Derived variable for smoking status collapsing the current/former smoker variables	der_smoking2	Never; Current or Former; Unknown	
Binary obesity (BMI >= 30 or checkbox checked) indicator	der_obesity	0 = No; 1 = Yes; 99 = Unknown	
Cardiovascular comorbidity (CAD, CHF, Afib, arrhythmia NOS, PVD, CVA, cardiac disease NOS)	der_card	0 = No; 1 = Yes; 99 = Unknown	
Derived variable indicating whether patient has pulmonary comorbidities	der_pulm	0 = No; 1 = Yes; 99 = Unknown	
Renal comorbidities	der_renal	0 = No; 1 = Yes; 99 = Unknown	
Derived variable indicating whether patient has diabetes mellitus	der_dm2	0 = No; 1 = Yes; 99 = Unknown	

Solid tumor indicator	der_solid	0 = No; 1 = Yes;	
Hematologic malignancy indicator	der_heme	0 = No; 1 = Yes	
Derived variable indicating cancer status	der_cancer_status	0 - Remission/NED; 1 - Active, stable/responding; 2 - Active, progressing; 99 - Unknown	
Timing of cancer treatment relative to COVID-19, collapsed	der_cancer_tx_timing_v3	0 = more than 3 months; 1 = 0-3 months; 88 = never or after COVID-19 diagnosis; 99 = unknown	
Performance Status	der_ecogcat2	ECOG 0, 1, or 2+	
No cancer treatment in the 3 months prior to COVID-19	der_cancertr_none	0=No; 1=Yes; 99=Unknown	Derived with the following covariates: der_any_cyto, der_any_targeted, der_any_endo, der_any_immuno, der_any_local, der_any_other Coded as 1 if all these variables are 0; coded as 0 if any of these variables is 1; coded as 99 if any of these variables is 99; otherwise, NA
Any cytotoxic cancer treatment in the 3 months prior to COVID-19	der_any_cyto	0 = No; 1 = Yes; 99 = Unknown	
Any targeted therapy in the 3 months prior to COVID-19	der_any_targeted	0 = No; 1 = Yes; 99 = Unknown	
Any endocrine therapy in the 3 months prior to COVID-19	der_any_endo	0 = No; 1 = Yes; 99 = Unknown	
Any immunotherapy in the 3 months prior to COVID-19	der_any_immuno	0 = No; 1 = Yes; 99 = Unknown	
Any local therapy (surgery or RT) within 3 months	der_any_local	0 = No; 1 = Yes; 99 = Unknown	
Any other cancer therapy in the 3 months prior to COVID-19	der_any_other	0 = No; 1 = Yes; 99 = Unknown	
No COVID-19 treatment ever	der_covidtr_none	0 = No; 1 = Yes; 99 = Unknown	Derived with the following covariates: der_rem, der_hcq, der_steroids_c19,

			der_other_tx_c19_v2
			Coded as 1 if all these variables are 0; coded as 0 if any of these variables is 1; coded as 99 if any of these variables is 99; otherwise, NA
Remdesivir as treatment for COVID-19 ever	der_rem	0 = No; 1 = Yes; 99 = Unknown	
Hydroxychloroquine as COVID-19 treatment ever	der_hcq	0 = No; 1 = Yes; 99 = Unknown	
Steroids as COVID- 19 treatment ever	der_steroids_c19	0 = No; 1 = Yes; 99 = Unknown	
COVID-19 treatments other than HCQ, steroids, remdesivir	der_other_tx_c19_v2	0 = No; 1 = Yes; 99 = Unknown	
Trimester and year of diagnosis, using the most recent side of the interval as anchor	der_tri_rt_dx	T1 2020; T2 2020; T3 2020; T1 2021	
Derived variable indicating cancer type	der_ttype	Solid, Heme, Multiple	Derived with: der_solid, der_heme, cancer_type_2 Coded as Solid if der_solid is 1 and cancer_type_2=" "; coded as Heme if der_heme is 1 and cancer_type_2=" " Otherwise, coded as Multiple
No cancer therapy, ever	cancer_tx_never	0 = No; 1 = Yes;	Derived with der_cancer_tx_timing_v3 No recent cancer therapy; directly mapped from cancer tx_timing_v3 = 88
participating institution ID	ccc19_institution ¹		
Derived hospitalized/not hospitalized variable	der_hosp	0 = No; 1 = Yes; 99 = Unknown	Used for imputation only
Center-level covariate	<u>es</u>		
Social Vulnerability Index	svi	Continuous	
Rural-Urban Continuum Codes	rucc	1, Metro – 1 million population or more; 2, Metro – 250,000 to 1 million population; 3, Metro – fewer than 250,000 population	
Type of center	hosp_type	Academic; Community	
Number of patients at each center	volume	Integer (Patients)	Count the number of patients at each center within final dataset (with selected cohort), then link it to center-level data (using ccc19_institution from ccc19x and Center_ID from CCC19_center_level_covariates.v3_3.4.2021.xlsx)

Derived variable using state	region	US Northeast; US Midwest; US South; US West	Derived with State
Census-level covariate	es		
Average rate of SARS-CoV-2 diagnosis, per 100 cases per million population	reg_daily_avg_newCOVID_v2	Continuous	Derived with reg_T1_daily_avg_newCOVID_per_1mil, reg_T2_daily_avg_newCOVID_per_1mil, reg_T3_daily_avg_newCOVID_per_1mil der_tri_rt_dx Derived after der_tri_rt_dx imputed

¹Raw variable

Once this form has been finalized, it will be signed by:

Date: 11/17/2021 ann Approved: RENUIN Core Lead Informatics Approved: Date: 11/17/2021 Biostatistics Analyst

eMethods. Details on Social Vulnerability Index and Rural-Urban Continuum Code

The Centers for Disease Control and Prevention's Social Vulnerability Index (SVI) indicates the relative vulnerability of every U.S. Census tract (or county) according to ranks on 15 social factors in four domains: socioeconomic status, household composition and disability, minority status and language, and housing and transportation. An overall percentile rank (0-1) for the county where each center is located was used in this analysis. A SVI ranking of 0.85 indicates that 85% of tracts (or counties) in the state or nation are less vulnerable than the tract of interest and that 15% of tracts (or counties) in the state or nation are more vulnerable.

The U.S. Department of Agriculture's Economic Research Service's 2013 Rural-Urban Continuum Code (RUCC) classifies all counties in the U.S. by their official metro-nonmetro status, as defined by the Office of Management and Budget, with further breakdown by population resulting in nine RUCC codes (1-9). In this coding scheme, 1 represents counties in metropolitan areas with populations of 1 million, and 9 represents counties that are completely rural with populations of <2500, not adjacent to a metro area.

eTable 1. Average Rate of SARS-CoV-2 Diagnosis in United States Census Divisions (Cas	ses
per Million Population), Stratified by Calendar Time	

	Mar–May, 2020	Jun-Aug, 2020	Sep–Nov, 2020
New England	88	30	116
Middle Atlantic	182	134	302
East North Central	65	87	385
West North Central	33	81	351
South Atlantic	24	64	90
East South Central	40	198	312
West South Central	33	207	229
Mountain	13	58	169
Pacific	29	140	140

eTable 2. Patients' Severity of COVID-19 at Presentation by the Rural-Urban Continuum Code of the Center From Which Patients Were Reported

	RUCC 1 ^a	RUCC 2 ^b	RUCC 3 ^c
	n = 3820	n = 666	n = 263
COVID-19 severity at presentation, n (%)			
Mild – no hospitalization indicated ^d	1965 (51.4)	330 (49.5)	208 (79.1)
Moderate – hospitalization indicated ^d	1407 (36.8)	254 (38.1)	47 (17.9)
Severe – ICU admission indicated ^d	443 (11.6)	80 (12.0)	7 (2.7)
Missing/unknown, n (%)	5 (0.1)	2 (0.3)	1 (0.4)

ICU, intensive care unit; RUCC, rural-urban continuum code.

^a Metro – 1 million population or more.

^b Metro – 250,000 to 1 million population.

^c Metro – fewer than 250,000 population.

^d Whether or not it occurred.

	30-day mortality	Composite outcome ^a
	OR ^b (95% CI)	OR ^c (95% CI)
Census division ^d		
New England	1.55 (0.89-2.70)	1.56 (0.74-3.28)
Middle Atlantic	1.64 (0.97-2.77)	1.32 (0.67-2.62)
East North Central	Reference	Reference
West North Central	1.16 (0.57-2.39)	1.31 (0.58-2.92)
South Atlantic	1.31 (0.73-2.35)	1.41 (0.73-2.73)
East South Central	1.58 (0.79-3.17)	1.56 (0.68-3.58)
West South Central	1.99 (0.94-4.23)	1.89 (0.72-4.92)
Mountain	1.10 (0.43-2.80)	1.35 (0.48-3.82)
Pacific	0.87 (0.43-1.76)	0.76 (0.33-1.76)

eTable 3. Associations of Census Division With 30-Day All-Cause Mortality (Primary Outcome) and the Composite Outcome (Secondary), Adjusted for Patient-Level Characteristics Only

CI, confidence interval; OR, odds ratio.

^a The composite outcome reflected the occurrence of any of the following: admission to an intensive care unit, receipt of mechanical ventilation, and total all-cause mortality. Analyses of the composite outcome were limited to 4,561 patients within non-missing data.

^b Odds ratios greater than 1 indicate higher odds of 30-day all-cause mortality.

^c Odds ratios greater than 1 indicate higher odds of admission to an intensive care unit, receipt of mechanical ventilation, or total all-cause mortality.

^d Adjusted for age, sex, race and ethnicity, smoking status, obesity, cardiovascular comorbidities, pulmonary comorbidities, renal disease, diabetes mellitus, type of malignancy, cancer status, Eastern Cooperative Oncology Group performance status, anti-COVID-19 treatments, and month of COVID-19 diagnosis. P values for evaluating the null hypothesis of equality in odds ratios across census divisions (8 degrees of freedom): 30-day mortality, 0.42; composite outcome, 0.73. **eTable 4.** Adjusted Odds Ratios Comparing the Odds of 30-Day All-Cause Mortality Between the West North Central and Mountain Census Divisions Combined vs All Other Census Divisions Combined, Stratified by Month of COVID-19 Diagnosis

	OR ^a (95% CI)
March–May, 2020	1.12 (0.55-2.27)
June–August, 2020	0.65 (0.25-1.73)
September–November, 2020	2.62 (0.86-8.01)

CI, confidence interval, OR, odds ratio.

^a P value for evaluating the null hypothesis of equality in odds ratios across month of COVID-19 diagnosis: 0.13 (2 degrees of freedom).

eFigure. Inclusion and Exclusion Criteria



^a Includes duplicate records, in situ solid malignancy, non-invasive non-melanoma skin cancer, precursor hematologic condition, benign hematologic condition, false-positive SARS-CoV-2 test, and non-CCC19 site.

^b Quality score \geq 5. Exclusions for low-quality data by census region: Northeast, 170/1734 (9.8%); Midwest, 101/1739 (5.8%); South, 80/974 (8.2%); West, 44/697 (6.3%).