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Both race and insurance type independently predict the selection of oral opioids prescribed to cancer outpatients

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Abstract

Background.—Previous research suggests that racial disparities in the report of analgesic adverse effects are partially mediated by the type of opioid prescribed to African Americans despite the presence of certain comorbidities, such as renal disease.

Aims.—We aimed to identify independent predictors of the type of opioid prescribed to cancer outpatients and determine if race and chronic kidney disease (CKD) independently predict prescription type, adjusting for relevant sociodemographic and clinical confounders.

Design and Methods.—We conducted secondary analysis of a 3-month observational study. Cancer patients (N=241) were from outpatient oncology clinics within a large mid-Atlantic healthcare system. Patients were older than 18 years of age, self-identified as African Americans or Whites, and had an analgesic prescription for cancer pain.

Results.—Consistent with published literature, most patients (75.5%) were prescribed either morphine or oxycodone preparations as oral opioid therapy for cancer pain. When compared to Whites, African Americans were significantly more likely to be prescribed morphine (14% vs. 33%) and less likely to be prescribed oxycodone (64% vs. 38%, respectively, $p < 0.001$). The estimated odds for African Americans to receive morphine were 2.573 times that for Whites (95% CI = 1.077 and 6.145) after controlling for insurance type, income, and pain levels. In addition, presence of private health insurance was negatively associated with the prescription of morphine

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and positively associated with prescription of oxycodone in separate multivariable models. Presence of CKD did not predict type of analgesic prescribed.

Conclusions.—Both race and insurance type independently predict type of opioid selection for cancer outpatients. Future larger clinical studies are needed to fully understand the sources and clinical consequences of racial differences in opioid selection for cancer pain.

Keywords

Cancer pain; opioid; race; ethnicity; socioeconomic; disparities

Introduction

The National Academy of Medicine report, “Relieving Pain in America” (Simon, 2012), and other systematic reviews (Karen O Anderson, Green, & Payne, 2009; Cintron & Morrison, 2006) have found that one of the most consistent findings on pain treatment disparities pertains to African Americans. A meta-analysis of over 20 years of published studies (Meghani, Byun, & Gallagher, 2012) on analgesic disparities in pain treatment found that when compared to other racial and ethnic groups, African American patients have one of the highest risks for pain undertreatment despite lacking the linguistic barriers experienced by other minority patients (Meghani et al., 2012).

Most of the existing pain management disparities research focuses on racial and ethnic disparities in analgesic treatment of pain and have compared outcomes such as receipt of any analgesia (Meghani et al., 2012; Todd, Samaroo, & Hoffman, 1993), receipt of opioid analgesia (Chen et al., 2005; A. Heins et al., 2006; J. K. Heins et al., 2006; Pletcher, Kertesz, Kohn, & Gonzales, 2008; Singhal, Tien, & Hsia, 2016; Tamayo-Sarver et al., 2003), availability of opioids in predominantly minority neighborhoods (Green, Ndao-Brumblay, West, & Washington, 2005; Morrison, Wallenstein, Natale, Senzel, & Huang, 2000), wait time in receiving analgesia in emergency department (Epps, Ware, & Packard, 2008; Ware, Epps, Clark, & Chatterjee, 2012), and pain management index, i.e., highest reported pain levels in relation to the strength of analgesics prescribed (Cintron & Morrison, 2006; Meghani, Thompson, Chittams, Bruner, & Riegel, 2015; Minick et al., 2012).

While we know that African Americans are less likely to receive opioids for pain across care settings (Meghani et al., 2012) and more likely to have a negative pain management index (Cintron & Morrison, 2006; Meghani et al., 2015; Minick et al., 2012), it is not clear if there are also disparities in the types of strong opioids or World Health Organization Step 3 opioids (World Health Organization, 1996) (e.g. morphine, oxycodone) prescribed to African Americans with cancer pain. This understanding is important for a few reasons: Emerging literature points to poor adherence to prescribed analgesia among African Americans even with a higher burden of cancer-related pain (Meghani & Knafl, 2016; Meghani et al., 2015; Rhee, Kim, & Kim, 2012; Stout, Sexton, & Meghani, 2017; Yeager et al., 2018). These studies suggest that experience of analgesic side-effects secondary to the type of analgesia prescribed to African Americans despite clinical risks may contribute to poor adherence and lack of pain control. A study employing discrete choice experiment found that African Americans with cancer pain were more likely than Whites to make

analgesic use decisions based on analgesic side effects (Meghani, Chittams, Hanlon, & Curry, 2013). In a subsequent analysis, despite a diagnosis of chronic kidney disease (CKD), African Americans were significantly more likely to receive morphine, with known toxic metabolites, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G)], which accumulate in renal disease (Meghani et al., 2014). Furthermore, authors found that racial disparities in patients' reported analgesic adverse effects was partially mediated by the type of opioid prescribed to African Americans versus Whites (Meghani et al., 2014). The authors concluded that reducing racial disparities in the type of opioid prescribed and understanding sources of disproportionate opioid-related side-effects among African-Americans may reduce the observed clinical disparities in cancer pain outcomes (Meghani et al., 2014).

Some emerging literature suggests that disparities in type of opioid prescribed may influence a number of other clinical outcomes. For instance, long-acting opioid use has been correlated with increased risk of serious infection, with patients given oxycodone demonstrating a lower rate of infection than those prescribed morphine (Wiese et al., 2018). Additionally, a large retrospective cohort study recently reported that the risk of out-of-hospital death was lower in those filling long-acting oxycodone than those filling long-acting morphine, potentially pointing to an association between type of opioid prescribed and subsequent mortality outcomes (Chung et al., 2019).

This paper extends previous published work on analgesic treatment disparities to identify independent predictors of the selection of strong opioids prescribed to cancer outpatients and determine if race and the presence of CKD independently predicts the type of opioid prescription, while adjusting for relevant sociodemographic and clinical confounders.

Methods

Study Design

This is a secondary analysis of a study to understand racial disparities in adherence to prescribed oral analgesics for cancer pain among cancer outpatients using a 3-month observational, repeated measures design (baseline and 3 months) (Meghani et al., 2014; Meghani et al., 2015). The study was approved by the Institutional Review Board of the University of Pennsylvania. Patients were recruited from two outpatient medical oncology clinics within a large mid-Atlantic healthcare system. Inclusion criteria for this study included self-identified African-Americans and Whites; at least 18 years of age; diagnosed with solid tumors or multiple myeloma with cancer-related pain requiring opioid therapy; and a prescription of an oral analgesic for cancer pain.

Measures

Race.—Study participants self-identified race based on the National Institutes of Health racial categories (Health & Health, 2015)

Prescribed Opioids.—Analgesic prescription information was gathered from patient's medical records and validated with patients during study-related home visits. We coded prescribed analgesics according to the World Health Organization analgesic steps (World

Health Organization, 1996). The majority of the patients in our study were prescribed either morphine or oxycodone preparations in immediate or extended release forms. Thus the prescribed analgesics were coded as “morphine,” “oxycodone,” or “others.” The “others” category was small and comprised of a heterogeneous mix of opioid and non-opioid analgesics.

Chronic Kidney Disease.—We used the 4-variable abbreviated Modification of Diet in Renal Disease (aMDRD) study formula to estimate glomerular filtration rate (eGFR), which takes into account gender, age, ethnicity, and serum creatinine levels (National Kidney Foundation). We extracted up to seven serum creatinine values from patients’ electronic medical records. All eGFR values for a single patient were then averaged to determine CKD status (No CKD = eGFR > 90 mL/min/1.73 m²; CKD = eGFR <89 mL/min/1.73 m²). We chose MDRD over the Cockcroft-Gault formula since the precision of the MDRD is better in patients with cancer (Kleber et al., 2007) as well as in certain populations, including older adults and obese patients (Pöge et al., 2005). The 4-variable aMDRD has also shown comparable performance as a more precise MDRD7 equation, which takes into account additional parameters (Pöge et al., 2005).

Pain Intensity.—We measured pain intensity and impact using the Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994). The psychometric properties of the BPI is well-established with cancer patients, including racial and ethnic minority patients with cancer (K. O. Anderson et al., 2000; Meghani & Keane, 2007; Meghani et al., 2015; Rhee et al., 2012; Yeager et al., 2018).

Health Insurance Type.—We collected health insurance information via self-report by study participants and validated it with information in patients’ electronic medical records. The insurance variable was coded as “private,” “Medicare,” “Medicaid,” and “other.” Managed Medicare or Medicaid plans (e.g. Bravo, HealthPartners, and Keystone Mercy) were classified as Medicare or Medicaid, respectively. Plans that were not private, Medicare, or Medicaid (such as VA, COBRA) were classified as other.

Data Analysis

A step-wise logistic model was generated by adding one variable at a time to identify the most significant to least significant variables. We ran two separate binary logistic regressions—one for the outcome of the prescription of morphine and other for prescription of oxycodone. The variables age, gender, health insurance, household income, pain levels in the past week (worst, least and average pain), duration of cancer pain, and past history of substance abuse were tested individually towards developing the final multivariable model including race and CKD status. All data were analyzed using SAS version 9.3.(SAS Institute Inc, 2012)

Results

The average age of the sample was 55 years (SD=10). There were no differences between African Americans and Whites regarding age, gender, and education (Table 1). However, African Americans were less likely to report having private health insurance when compared

to Whites ($p<0.001$) and more likely to belong to a lower income bracket ($p<0.001$). African Americans reported poor cancer pain control in all BPI pain measures, including worst pain ($p<0.001$), average pain ($p<0.001$), and least pain ($p<0.001$) scores, indicating greater pain severity and lower pain relief in the previous week as well as greater pain-related functional interference ($p=0.048$) (Table 2). There were also significant differences by race in the type of opioid prescribed (Figure 1). When compared to Whites, African Americans were significantly more likely to be prescribed morphine (14% vs. 33%, respectively) and less likely to be prescribed oxycodone (64% vs. 38%, respectively, $p<0.001$).

Independent Correlates of Morphine Prescription for Cancer Pain

Based on step-wise analyses, the final model consisted of race, income, insurance type, average pain levels, and CKD status. Of these, average pain intensity was the strongest correlate of morphine prescription ($p=0.0005$) (Table 3). The point estimate of the odds ratio for average pain in the last week was 0.716. This suggests that for a one-unit increase in average pain score, we see about a 28% decrease in the odds of receiving morphine as an index drug (95% CI, 0.594 and 0.864). Also, when compared to patients on Medicaid, patients on private insurance were 78% less likely to receive morphine (OR=0.225, 95% CI, 0.077–0.662). In addition, race was an independent predictor of morphine prescription even after controlling for insurance type, income, and pain levels. The estimated odds for African Americans to receive morphine were 2.573 times that of the estimated odds for Whites (95% CI = 1.077 and 6.145) (Table 3).

Independent Correlates of Oxycodone Prescription for Cancer Pain

The presence of private health insurance was the only significant predictor in the multivariable model for oxycodone prescription for cancer pain. The point estimate of the odds ratio for insurance type (private vs. Medicaid) was 8.437. This suggests that the estimated odds of people with private insurance type receiving oxycodone is 8.437 times that of the estimated odds for people with Medicaid insurance type (95% CI, 2.814–25.297) (Table 4).

Of note, in separate univariate logistic regression analyses, a past history of substance abuse was negatively associated with the prescription of oxycodone (likelihood estimate, - 0.4177, SE 0.172; $p=0.0154$) and positively associated with the prescription of morphine (likelihood estimate, 0.435, SE 0.180; $p=0.015$). However, the effect disappeared in multivariable analysis in each model. Also, the presence of CKD did not predict type of analgesic prescribed, while controlling for race and insurance status.

Discussion

Despite recent initiatives to spare opioids in clinical practice (Bohnert, Guy, & Losby, 2018; Dowell, Haegerich, & Chou, 2016), opioids remain important frontline treatment for the management of moderate to severe cancer pain (American Society of Clinical Oncology, 2016). Previous studies have shown that the types of opioids prescribed to patients with cancer pain relate to both their experience of analgesic adverse effects (Meghani et al., 2014) and their level of analgesic adherence for cancer pain (K. O. Anderson et al., 2000; Meghani

et al., 2015; Rhee et al., 2012). Our findings indicate that, controlling for income, health insurance, and a number of relevant clinical correlates, race is independently associated with the type of opioid prescribed to cancer outpatients.

This findings are important from several perspectives: About two in three patients with cancer have a creatinine clearance of <90 ml/min and, of these, 20% of patients have a creatinine clearance of <60 ml/min (Janus et al., 2010; Launay-Vacher, 2010; Launay-Vacher et al., 2007). Morphine has known toxic metabolites that can accumulate in the presence of renal insufficiency, which is highly prevalent in cancer patients (Janus et al., 2010; Launay-Vacher, 2010; Launay-Vacher et al., 2007). A relatively higher prevalence of renal impairment among African Americans in the general population (Lipworth et al., 2012) may imply that many African American patients with cancer may be subjected to hidden opioid toxicities due to the choice of opioid selection (Meghani et al., 2014). Thus, the racial difference in the choice of opioid selection and associated outcomes warrants further studies, especially in the context of clinical comorbidities, such as renal disease.

A Cochrane systematic review compared controlled release oxycodone with morphine (Schmidt-Hansen, Bennett, Arnold, Bromham, & Hilgart, 2015) and found similar levels of pain relief and adverse events for both opioids. However, most studies that informed this conclusion excluded patients with various levels of renal impairment (Bruera et al., 1998; Mercadante et al., 2010; Riley et al., 2015). Similarly, a recent study that compared the tolerability profile of morphine and oxycodone found no statistically significant difference in the tolerability of morphine or oxycodone across renal function status (Zecca et al., 2016). The authors acknowledged that the study was underpowered and the subgroup of patients with renal impairment was small (n=29) (Zecca et al., 2016). The study also excluded patients with significant renal impairment. Further investigation in larger, more resourced studies are needed, which includes serum M3G and M6G levels while testing race as a moderator of CKD and type of opioid prescribed to cancer patients.

Research is also warranted into why such systematic clinical differences exist and the extent to which they are consequential in patients' adherence to prescribed analgesia, pain control, function, and side effects. The differential opioid prescription to cancer patients (despite health insurance and income levels as demonstrated in this study) may relate to prescriber's implicit bias in the clinical treatment of cancer pain. For instance, prescribers may be more reluctant to prescribe opioids to a historically stereotyped group (Meghani et al., 2012) or prescribe an opioid with lesser street value, such as morphine (Street Rx, 2017). Dual process theory in cognitive psychology suggests that implicit biases are automatic and unconscious (Burgess, van Ryn, Crowley-Matoka, & Malat, 2006), e.g. a social construction of a phenomenon may unconsciously seep into clinical decision-making and may affect certain groups disproportionately (Ezenwa & Fleming, 2012; Meghani et al., 2012). Published studies provide support for this clinical phenomenon articulated by African Americans being treated for cancer pain: "...a lot of black people feel, especially when we're in pain, that we aren't believed, and that is the main problem with us. And we accept that, that we're not gonna be believed... And then when anything is offered to us, the first thing that's being thrown up in our face is that, well, it's got a street value. You don't need to hear that." (Meghani & Houldin, 2007). Our findings are particularly relevant in the current

context of social stigma and policy flux related to the opioid crisis (Bohnert et al., 2018; Dowell et al., 2016; Guy et al., 2017) and there may be a risk for widening pain care disparities impacting already vulnerable groups (Meghani & Vapiwala, 2018).

In addition to race, type of health insurance was an independent factor in the choice of opioid prescribed to cancer patients across our analyses. Health insurance is part of the broad socioeconomic status (SES) category, which also includes variables such as income, education, wealth, and neighborhood characteristics (Meghani & Chittams, 2015). An ongoing debate in racial disparities research is whether observed racial disparities are in effect SES disparities (Meghani & Chittams, 2015). In the studies where the effect of race on poor outcomes disappears in a statistical model controlling for SES variables (Meghani & Chittams, 2015), researchers may inadvertently conclude that SES is a confounder of race. We have previously illustrated why such an interpretation may be misguided given the intricate relationship of race and SES in the United States (Meghani & Chittams, 2015; Williams, Mohammed, Leavell, & Collins, 2010). In effect, SES disparities affect racial and ethnic subgroups disproportionately (Meghani, 2011; Meghani & Chittams, 2015). For instance, in the present study, when compared to patients on Medicaid, patients with private insurance were significantly more likely to receive an oxycodone prescription for pain. However, 89% of those who were Medicaid-insured in this study were African Americans.

Finally, our study found a negative association between prescription of morphine and reported pain levels. The significance of this finding remains unclear but may suggest that patients may be receiving strong opioids from other routes, not captured in this study.

Study Limitations

The findings of this study must be interpreted in the context of the following limitations and perspectives: 1) while we are able to demonstrate that the significance of race remained after accounting for income and insurance type in the model (Table 3), it is possible that other unmeasured SES factors may relate to the effect of race on type of opioid prescription found in this study. To this end, 2) the current analyses does not allow us to assign a moral value to the sources of the observed racial differences. Our interpretation of findings is based on clinical experience and previous research on racial disparities in pain care for African Americans. Thus the observed differences may be mere differences or value-laden differences (Meghani & Gallagher, 2008) deserving further investigation. 3) Our findings may suffer from type II error due to a small sample size. For instance, certain variables, such as past history of substance abuse may become statistically significant in a larger sample. 4) We combined our analysis of immediate release and extended release preparations for the opioids due to a small clinical sample. This may explain the findings of the role of private insurance in predicting oxycodone prescription. At the time the study (Meghani et al., 2014), only extended release morphine was available in the generic forms and it was relatively inexpensive. Extended release oxycodone was available as brand name only and was significantly more expensive (ConsumerReports^(R) Health, 2012). However, the fact that we were able to identify racial differences in type of opioid prescription controlling for type of insurance and despite a small sample size indicates a clinical phenomenon of sizeable effect. 5) Consistent with published literature, most patients were prescribed morphine or

oxycodone in various forms as first line oral opioid therapy (Schmidt-Hansen et al., 2015). Thus we limited our analysis to these opioids. This excluded patients who were only prescribed opioids through non-oral routes, e.g. intravenous, subcutaneous, rectal, transdermal, and transmucosal (we do not expect this to exclude a significant number of patients as the oral route is most common in outpatient clinical practices as underscored in the National Comprehensive Cancer Network Adult Cancer Pain guidelines (National Comprehensive Cancer Network, 2015)

Conclusions

This is one of the few studies to identify differences in the selection of opioids prescribed to African Americans and Whites with cancer pain after adjusting for insurance type and relevant clinical correlates. Due to lack of consistent clinical data on morphine and its glucuronide metabolites (Smith, 2009) and research studies excluding patients with various levels of renal insufficiency status, future larger clinical studies are needed to fully understand the sources and clinical consequences of racial differences in opioid selection for cancer pain.

Additionally, there is lack of empirical evidence guiding multiple aspects of opioid prescribing practices for cancer patients (Paice et al., 2016) and a number of inconsistencies among existing national pain management guidelines (Meghani & Vapiwala, 2018) underscoring a need to further expand knowledge on opioid management for cancer pain. Careful pharmacological management of cancer pain continues to be important for optimal pain control and function, especially until there is consistent access to non-opioid, and non-pharmacological treatments for chronic pain—which still continues to remain limited in the United States (Becker et al., 2017; Meghani & Vapiwala, 2018).

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Figure 1. Type of Pain Medication by Race (%) (N=241)*

*The other group (n=59) was excluded from subsequent analysis.

Table 1.

Characteristics of Study Participants

Variable	Total (N=182)	African Americans (N=73)	Whites (N=109)	P-values ^I
<i>Mean (SD)</i>				
Age	55.1 (10.1)	54.0 (9.3)	55.8 (10.6)	0.253
<i>Frequency (%)</i>				
Gender				0.074
Male	92 (51)	31 (42)	61 (56)	
Female	90 (49)	42 (58)	48 (44)	
Marital Status				<0.001
Married	109 (60)	24 (33)	85 (78)	
Separated/Divorced/Widowed	47 (26)	33 (45)	14 (13)	
Never Married	26 (14)	16 (22)	10 (9)	
Education				0.079
Elementary	3 (2)	2 (3)	1 (1)	
High School	60 (33)	27 (37)	33 (30)	
College/Trade School	89 (49)	38 (52)	51 (47)	
More Than College	30 (16)	6 (8)	24 (22)	
Income				<0.001
<\$30, 000	57 (31)	38 (52)	19 (17)	
\$30–50,000	36 (20)	21 (29)	15 (14)	
\$50–70,000	32 (18)	10 (13)	22 (20)	
\$70–90,000	20 (11)	2 (3)	18 (17)	
>\$90,000	37 (20)	2 (3)	35 (32)	
Health Insurance				0.683
Yes	178 (98)	71 (97)	107 (98)	
No	4 (2)	2 (3)	2 (2)	
Type of Health Insurance				<0.001
Private	97 (54)	23 (31)	74 (69)	
Medicaid	18 (10)	16 (22)	2 (2)	
Medicare	42 (23)	21 (29)	21 (19)	
Other	24 (13)	13 (18)	11 (10)	

^I P-values are based on t-tests for continuous variables and chi-squared for categorical variables.

Table 2.

Clinical Variables

Variable	Total (N=182)	African Americans (N=73)	Whites (N=109)	P-values ^I
<i>Mean (SD)</i>				
Worst pain (0–10)	6.8 (2.3)	7.6 (2.0)	6.2 (2.5)	<0.001
Least pain (0–10)	3.3 (2.0)	4.1 (2.0)	2.7 (1.8)	<0.001
Average pain (0–10)	4.7 (2.0)	5.4 (1.9)	4.2 (2.0)	<0.001
Pain interference (0–10)	35.4 (16.0)	38.3 (16.5)	33.5 (15.4)	0.048
<i>Frequency (%)</i>				
Type of Opioid Prescribed				<0.001
Oxycodone	128 (70)	39 (53)	89 (82)	
Morphine	54 (30)	34 (47)	20 (18)	
Presence of metastatic disease				.030
Yes	142 (78)	51 (70)	91 (83)	
No	40 (22)	22 (30)	18 (17)	
Past History of Substance Abuse				.040
Yes	32 (18)	18 (25)	14 (13)	
No	150 (82)	55 (75)	95 (87)	
Estimated Glomerular Filtration Rate (eGFR)				0.054
90	100 (55)	46 (63)	54 (49)	
60–89	53 (29)	14 (19)	39 (36)	
<60	29 (16)	13 (18)	16 (15)	

^IP-values are based on t-tests for continuous variables and chi-squared for categorical variables. CKD=Chronic Kidney Disease (estimated using eGFR; No CKD = eGFR >90 mL/min/1.73 m²; CKD= eGFR <89 mL/min/1.73 m²)

Table 3.

Independent Correlates of Morphine Prescription for Cancer Pain

<i>Variable (reference)</i>	<i>Levels</i>	<i>OR</i>	<i>95% CI</i>		<i>Wald Chi-Square</i>	<i>Pr > ChiSq</i>
<i>Average pain</i>	(0–10)	0.716	0.594	0.864	12.2101	0.0005
<i>Race (ref: Whites)</i>	African Americans	2.570	1.077	6.134	4.5261	0.0334
<i>Insurance Type (ref: Medicaid)</i>	Private	0.225	0.077	0.662	4.0304	0.0447
	Other	0.199	0.021	1.909	1.0047	0.3162
	Multiple	0.731	0.216	2.480	0.8559	0.3549
	Medicare	0.805	0.288	2.249	1.9787	0.1595
<i>Income (ref: <50K)</i>	>=\$50, 000	0.565	0.241	1.327	1.7184	0.1899
<i>Chronic Kidney Disease (ref: No)</i>	Yes	1.855	0.910	3.781	2.8883	0.0892

Table 4.

Independent Correlates of Oxycodone Prescription for Cancer Pain

<i>Variable (reference)</i>		<i>OR</i>	<i>95% CI</i>		<i>Wald Chi-Square</i>	<i>Pr > ChiSq</i>
<i>Race (ref: Whites)</i>	African Americans	0.700	0.366	1.337	1.1682	0.2798
<i>Income (ref: <\$50,000)</i>	>=\$50,000	1.510	0.805	2.834	1.6483	0.1992
<i>Insurance Type (ref: Medicaid)</i>	Private	8.437	2.814	25.297	9.9166	0.0016
	Other	3.252	0.574	18.438	0.0093	0.9231
	Multiple	3.738	1.066	13.102	0.0455	0.8311
	Medicare	4.765	1.540	14.739	1.1211	0.2897
<i>Chronic Kidney Disease (ref: No)</i>	Yes	0.683	0.383	1.216	1.6778	0.1952