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Using public health surveillance and electronic medical record data to examine socioeconomic factors for hepatitis C diagnosis and testing in Orange County, California

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Public Health

by

Sara Hankin Goodman

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DEDICATION

To

To my mother and father, Dr. Janet R. Hankin, Ph.D., and Dr. Allen C. Goodman, Ph.D., for continuing to push me forward and be my greatest superheroes.

To my friends I have met along the way,

And to Max Goldstein, my husband and soulmate. I love you

There is a way out of every box, a solution to every puzzle; it's just a matter of finding it.

--Captain Jean Luc Picard, "Attached," *Star Trek: The Next Generation*

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ABSTRACT OF THE DISSERTATION

Using public health surveillance and electronic medical record data to examine socioeconomic factors for hepatitis C diagnosis and testing in Orange County, California

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Doctor of Philosophy in Public Health

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Hepatitis C is the most infectious bloodborne disease in the United States. For my dissertation, I will focus on the study population in Orange County, California. This high-risk area has a significant substance use rehabilitation tourism industry (with over 400 rehabilitation facilities),.[1] and a marked increase in reported HCV cases since 2011.[2] The purpose of this dissertation was to understand why, despite effective HCV treatment, Orange County patients who test antibody-positive are not directly followed up with viral load tests and then initiated on HCV treatment. This question merits further research using routinely collected and reported public health surveillance data and electronic medical records at health care facilities.

The goals of this research were to examine socioeconomic individual and group-level correlates of the following outcomes: HCV viral load testing, undetectable HCV viral load, and HCV diagnosis in a health care setting using the University of California, Irvine Medical Center (UCIMC) medical records with chart review. This research utilized secondary data using multivariable logistic regressions and multivariable Cox Proportional Hazard regression to answer these research questions.

With an n of 27,389 individuals, that only 3.16 percent of all patients from 2010 to 2020 showed undetectable viral load. Only 37 percent of these patients were not ever viral load tested from 2010 to 2020, leaving the viremic status of these patients unknown. Those over 65 were more likely to have an undetectable HCV viral load than younger adults (HR =2.00). Residents living in census tracts in the third and fourth quartiles of percent enrollment in health insurance showed a greater likelihood of undetectable viral load. When examining 521 electronic medical records (EMRs), only 22 percent of those reported as HCV antibody-positive indicated an HCV-positive diagnosis in their EMR. Less than one percent of patients n=5 were prescribed HCV treatment. These results show an alarming loss of follow-up and an inability to link patients to care with an opportunity to improve outcomes. The findings of this study are essential for informing future HCV policies and diagnosis procedures to get individuals tested and treated for this disease.

INTRODUCTION

In their latest surveillance report in 2019, The Centers for Disease Control and Prevention reported that hepatitis C virus (HCV)infected over 123,000 individuals in the United States, with incidence rates steadily increasing since 2013 to 56.7 probable, suspect, or confirmed cases per 100,000 people in 2019.[3,4] HCV is an infectious disease caused by the HCV virus which can lead to chronic liver disease, cancer, and liver failure in patients without treatment.[3,5-7] If left untreated, the virus can lead to HCV-related cancer and mortality and increase the risk of all-cause morbidity and mortality.[3,5-7] The focus of this dissertation is to better understand HCV diagnosis and treatment-related factors in Orange County, California, to better target public health interventions, reduce the burden of disease, and improve the quality of care and health care outcomes. This chapter will give an introductory overview of HCV disease, diagnosis, treatment, and the cascade of care from the initial diagnosis to cure.

Mortality from HCV disease is challenging to assess accurately, and the actual death rates are unknown.[4,8] Deaths due to HCV are generally underreported on death certificates, so the true mortality rates are likely underestimated.[9] The Centers for Disease Control and Prevention compressed mortality file indicates a crude mortality rate of HCV in California of 2.2 deaths per 100,000 population from 1999 to 2016.[10] The HCV virus has a Reproductive Rate (R0) ranging from 1.92 to 3.96 among high-risk populations such as injection drug users indicating that every infected individual could infect at most four susceptible individuals at risk.[11] One of the most significant risks of those infected with the HCV virus is that they may have the disease without showing any symptoms.[5-7] People who do not know their viremia status may spread the HCV virus through blood or sexual fluids to others and increase the overall disease burden in the county.[5] Undiagnosed HCV is an increasing public health concern. Sequelae from untreated HCV may lead to liver cancer and liver-related mortality.[5-7] One cohort study of over 2 million patients indicated that 70 percent of HCV antibody-positive patients had moderate or worse liver fibrosis.

Challenges of HCV morbidity reporting

As stated earlier, measuring national HCV incidence and prevalence is challenging. Many researchers agree that the actual numbers of HCV infections in the United States from surveillance data and nationally representative surveys like NHANES are likely underestimated.[4,12-15] One study by Edlin et al.,[24] used HCV infection prevalence estimates from other smaller HCV research studies to create weighted averages to estimate the prevalence of HCV among special populations such as homeless people, incarcerated, and those who were hospitalized. They estimated that the total number of existing HCV infections in the United States ranges from 3.4 million to 6 million in 2015, but because these are projections, this is a conservative estimate, and the true prevalence could be much higher.[15]

HCV disease in Orange County, California

After providing the background on the disease, care cascade, and treatment, I will focus on the study population in Orange County, California, a high-risk area that has a large substance use rehabilitation tourism industry[1] and a marked increase in reported HCV cases since 2011.[2] According to title 17 of the California Health Code,[16] which requires the reporting of infectious diseases to their applicable jurisdictions to help track and prevent disease outbreaks, all antibody-positive HCV cases must be reported to the state by laboratories.

This research is based in Orange County, California, where the morbidity and mortality from HCV infection have been substantially higher than any other infectious disease in the last decade, with the exception of the current COVID-19 pandemic beginning in March 2020. [17-19] Orange County is the sixth-largest county in the United States, with approximately 3.1 million residents.[20] With over 400 substance use treatment facilities, Orange County is a rehabilitation tourism destination that brings in many out-of-state patients, some of whom have HCV related to injection drug use.[1,20] The number of cases of HCV infection in Orange County and the state of California is so high that it is not feasible to have disease intervention specialists do contact tracing by interviewing patients.[18,21] While this tracing is done for enteric diseases or sexually transmitted diseases such as HIV or syphilis, it is impractical to perform contact tracing for HCV and thus not generally done in health departments.[17,18] Despite the availability of effective treatment, we do not know how many Orange County patients who test antibody-positive are not directly followed up with viral load tests and then initiated HCV treatment. We also do not know the likelihood of those who test positive being viral load tested or treated for HCV. This question merits further research using routinely collected and reported public health surveillance data and electronic medical records at health care facilities.

HCV and at-risk populations

Those at risk for HCV include several distinct groups with different risk factors. The first group is those in the "birth cohort," individuals born between 1945 and 1965 who may have received a blood transfusion before comprehensive screening was implemented in 1992.[22,23] People who inject drugs (PWID) are also at increased risk for contracting HCV due to high-risk health behaviors.[24,25] Needle sharing directly transmits HCV between people via blood.[26,27] Several sources discuss how PWID have a self-reinforcing stigma due to low socioeconomic status, unstable housing, and poor psychological health.[28-30] These issues make them a marginalized population due to these social factors, which in turn negatively impact health, including contracting and transmitting HCV.

Homeless individuals have an increased risk of contracting HCV and other infectious diseases. Page et al.[31] looked at correlates of HCV among homeless women in San Francisco and women with unstable housing conditions. They found that women in their sample with less than a high school education were more than 2.5 times more likely to be infected with HCV, which is statistically significant. Their unadjusted odds ratio (OR) of 2.48 95% CI (1.45–4.25) was statistically significant at $p<0.01$. When adjusted for study participants in the birth cohort, education level, current diagnosis of depression, number of psychiatric diagnoses, and injection drug use, the odds were even higher with an adjusted OR (AOR) of 2.56 (95% CI 1.36–4.82) $p<0.01$.[31]

People who are incarcerated are also a key population for HCV infection, with increased vulnerability. Prisoners are also at high-risk for hepatitis C transmission because many inmates may be asymptomatic, but they are still contagious.[32] Overcrowding in the prison system increases the proximity of inmates and further facilitates hepatitis C transmission, and multiplies risk exponentially.[33,34] Incarceration facilities place potentially infectious prisoners in close proximity to each other and to the staff, creating an incubator for infection.[34,35] [32,36-40]

Another high-risk group is United States veterans, who have an estimated three times higher prevalence of HCV compared to the general population.[41] A study found that HCV seropositivity was associated with transfusions, injection drug use, tattooing, period of military service (particularly during the Vietnam war), health care use, and lifestyle factors.[41]

Among race/ethnicities, Native Americans/Alaskan Natives have the highest rate of HCV infection with 86.7 per 100,000 per year, particularly among those between ages 30-39.[4] The next highest rates among White, non-Hispanics, (34.0 per 100,000 people per year), and Non-Hispanic African Americans with 31.0 cases per 100,000 per year.

HCV as a syndemic

Due to the large number of sociodemographic and behavioral risk factors associated with HCV infections, it is possible to examine this disease and its risk factors conceptually and theoretically using a syndemic model.[42] A Syndemic is defined as the "synergistic interaction of two or more coexistent diseases and resultant excess burden of disease."[43] It can also be a combination of "contextual and social factors"[42] with an additional sociobehavioral element, like homelessness, which leads to the clustering of diseases. Syndemic models help explain the political economy of a particular disease as syndemic risk factors are indeed social, political, and economic.[42] The contextual and social factors with HCV are homelessness, injection drug use, and opioid use, which can be seen in Figure 1 below.[44] One systematic review found that people who reported recently transitioning to injection drug use had an "HCV seroincidence of 40 per 100 person-years or higher,"[45] and that this could be a result of a substance use disorder, generally fueled by the misuse of prescription opioids or heroin.[45] A strictly biomedical approach to HCV does not typically take into context these political economy factors impacting why people do not engage in HCV treatment.

One of these political economy factors is homelessness. One study which examined homelessness among people who inject drugs found that those who reported a high number of diseases, including various types of hepatitis and HIV, were more likely to be homeless.[43] One study examining HCV prevalence in Health Care for the Homeless Programs found an average HCV prevalence of 31 percent and up to 70 percent among homeless PWID.[46] A systematic review by Arum et al. found through sensitivity analyses that studies that estimated homeless and or unstable housing had effect sizes increasing the risk of HCV infection by 1.66 (1.27-2.00) and 1.72 (1.38-1.99), respectively.[47] This study confirmed the results of previous research,[48-50] finding that those with unstable housing are also more likely to engage in high-risk behaviors such as sharing needles and drug preparation equipment or engaging in sex work to provide income.[47]

HCV Diagnosis and care cascade

After describing the general morbidity and mortality related to HCV, and those at the highest risk, we can focus on how HCV is identified and managed. Tracking patients from initial HCV diagnosis to treatment is done through a *care cascade*. This care cascade involves initial HCV infection diagnosis, treatment evaluation, treatment initiation, and treatment completion leading to sustained virologic response (SVR).[51] SVR is achieved indicated by an undetectable viral load using an RNA viral load test twelve weeks post-treatment, and they are cured.[18,52-55] The World Health Organization-(WHO)defined the care cascade as including the following: HCV testing, linkage to care, treatment, SVR, and follow-up HCV care (see Figure 1.2).[51,56] With highly effective Direct-Acting Antiviral (DAA) treatments for HCV, the greatest threat to attaining SVR is dropping out of the care cascade.[57-60] The care cascade varies by treatment facility and clinician. This cascade is important because it identifies where patients can drop out of care and assists public health practitioners in defining denominators for analysis using the number of patients in that part of the care cascade.[57-60] For example: out of those who were diagnosed with HCV infection, how many of those were linked to care and initiated treatment, and out of those who initiated treatment, who completed treatment?

The key to getting patients into treatment is diagnosing them with two separate tests confirming active HCV infection. The recommended diagnosis procedure begins with an HCV antibody enzyme-linked immune absorbed assay (ELISA) test. If positive, an RNA viral load test is required to confirm viremia (viral presence in the blood), and viremic patients are referred to treatment.[61,62] Antibody testing only indicates a past history of HCV infection, not a current infection, which must be confirmed using the RNA viral load test.[56] The diagram in Figure 1.3 explains the testing algorithm and steps for HCV diagnosis.[63] The additional testing indicated in the diagram is done if there is concern about recent HCV exposure or problems with the test specimen.[63]

HCV treatment

After active HCV infection is diagnosed with a confirmatory viral load test indicating viremia and active infection, patients are evaluated for treatment, and their virus is genotyped.[64] The American Association for the Study of Liver Diseases recommends treatment guidelines by HCV genotype and treatment history to a particular course of Direct Acting Antivirals (DAAs)to achieve the best result for each patient.[64] Patients will continue HCV infection treatment until SVR is achieved[18,53-55,64] SVR is a durable measure and appears stable after treatment, with viral loads remaining low or undetectable. Reinfection rates of HCV virus post SVR are quite rare among mono-infected low-risk patients. [65] The reinfection rate is 0.95% over five years and a pooled recurrence rate of 1.85/1000 person-years of follow-up as indicated by a meta-analysis of 7,969 patients. The results show that reinfection rates increased among high-risk patients, including those who were HIV coinfected, prisoners, and people who inject drugs. [65]

DAAs were FDA approved in 2014, and the disease has transitioned from a non-treatable chronic disorder to a disease that can be treated and cured in as little as eight weeks.[66] This medical breakthrough needs to be scaled up to the population level to eliminate the disease and improve quality of life. DAAs are over 95 percent effective and make it possible for infectious patients to be cured.[54,66-71] Unlike HIV, HCV can be treated and cured, improving overall individual and community health and quality of life. Individuals with chronic HCV infection can be treated in 8 to 24 weeks with daily DAA pills and attain sustained SVR twelve weeks post-treatment. [18,53-55,64] The Food and Drug Administration (FDA) approved the first wave of HCV medications in 2014.[66-69,71,72] Duration of treatment depends on the genotype of the virus, the patient's history of liver disease, previous HCV treatment experience, treatment cost, and drug availability.[69] health care interventions such as HCV infection care navigators and needle exchanges.

HCV and cost-effectiveness

Many studies have looked at the overall cost-effectiveness of hepatitis C testing as a whole and treatment on a larger scale.[73-76] However, individual differences between patients can make it difficult for some patients to get viral load tested and initiate treatment compared to others.[73-75] While expensive, hepatitis C testing and treatment are cost-effective, with one study estimating using Markov models that early treatment of HCV would save approximately "$27,000 per [Quality Adjusted Life Year] (QALY) gained after 30 years."[76] Early treatment not only helps prevent disease transmission and can help patients achieve SVR. Zelanev et al.[73] simulated using DAAs to help treat injection drug users using social networks and treatment chains. The researchers used computer-based modeling and found that if the baseline hepatitis C prevalence is high (estimated in this study as 85 percent among people who inject drugs), then treatment once diagnosed as viremic hepatitis C is ineffective prevention among this group.[73] If the baseline prevalence is lower than 60 percent, then treating 12 percent of individuals could help potentially eliminate hepatitis C in 10 years.[73] They found that random treatment allocation across individuals who inject drugs is more effective than simply treating all individuals.[73]

A major limitation of this cost-effectiveness model is that it assumes that everyone has equal access to and the ability to pay for treatment. It also assumes that those on treatment remain in care, finish the treatment course, and attain SVR without experiencing external barriers preventing them from completing the cascade.[73] Other studies in countries with a high burden of hepatitis C, such as Egypt, have also done cost-effectiveness models estimating costs ranging from $1,332/QALY to $9,043/QALY depending on the treatment regimen.[74,75] Although this study evaluated different treatments, the investigators did not do micro-costing to look at potential upstream barriers to hepatitis C treatment initiation suitable for a potential public health intervention.[74,75]

In general, the earlier an individual's liver disease is treated, the greater the likelihood of success, the lower the risk of liver-related complications and mortality, and the lower the costs of treatment and associated care.[77] A simulation study,[78] used 1,000 individuals receiving DAAs at different stages of liver fibrosis and found a 46 percent reduction in the cost of DAA therapy (Sofosbuvir-ledipasvir) which decreased the incremental cost-effectiveness ratio (ICER) for treating all fibrosis stages by 48 percent. This study found that the percentage of cases averted was 27 percent for hepatocellular carcinoma.[78] The researchers found that treating stage F4 of liver fibrosis (most advanced) had a higher cost compared with waiting until the disease progressed to F4. This simulation study also found that treating all patients is cost-effective in 96 percent of cases with a willingness to pay (WTP) of $150,000 per QALY.[78] This study was conducted in 2016, so it does not cover the third wave of DAAs that came out in 2017, including Mavyret (which retails for approximately $24,000 and is currently the least expensive drug on the market)[79] or Vosevi, in 2017.[78] Updated cost-effectiveness studies were not done after 2017, when the new drugs came out, and after the new United States Preventive Service Task Force screening guidelines of screening all individuals from 18 to 79 years of age.[80] These studies also do not take into account individual barriers and variability to implementing hepatitis C treatment.

Needle exchanges as a mitigating factor on HCV infection

One public health intervention that helps reduce HCV infection and increase HCV testing and diagnosis for PWID is needle exchange programs (also known as syringe services programs or SSPs).[81] Needle exchanges have shown promising results for HIV prevention.[81] Meta-analysis on needle exchanges and HCV infection are limited compared to HIV and needle exchanges. A systematic international review on the effectiveness of needle exchanges found that a "conservative interpretation of published data [on needle exchanges] fulfills six out of the nine Bradford Hill criteria [strength of association, replication findings, temporal sequence, biological plausibility, reasoning by analogy, and coherence of evidence for causation for HIV infection.]"[81] Since HCV is also transmitted through sharing needles, in addition to systematic reviews for HIV, there is also evidence from individual studies that needle exchange programs help prevent HCV infection. One of the seminal studies on needle exchanges was a case-control study in Tacoma, Washington. This study found that after adjusting for demographic characteristics, people who did not use the needle exchange were seven times more likely to contract HCV (Adjusted OR of 7.3, 95% CI =1.6-32.8).[82] Another study showed that PWID that reported using a needle exchange were statistically "significantly less likely to share needles (AOR=0.77, 95% CI=0.67–0.88)."[83] Some studies show less effectiveness with needle exchanges, but researchers note that there is selection bias that occurs in these studies where compared to non-needle exchange users, PWID who use needle exchanges "may be less socially integrated and more likely to engage in risk behaviors [such as those leading to HIV infection]."[29,83,84]

Needle exchanges are an important protective factor of HCV prevention but also are politically sensitive. When then-Governor of Indiana Mike Pence ended a needle exchange program in Indiana in 2015, it resulted in an HIV outbreak of 170 cases, with the vast majority co-infected with HCV.[85,86] This public health crisis illustrated the importance of needle exchanges and their consequences when abruptly discontinued. Needle exchange laws changed in 2015, but severe funding restrictions remain. Restrictive federal laws still prevent funding for syringes and sterile needles for needle exchanges and rely heavily on private funding to maintain them.[87] Currently, only three states (Massachusetts, New Mexico, and Washington) have laws that support full access to needle exchanges and have a permissive Medicaid treatment policy for these programs.[87,88] The effectiveness of these needle exchange programs far outweighs their cost and should be expanded and continued despite political opposition to help prevent HCV infection. A systematic review found that needle exchange programs in prisons can be effective and that few negative consequences were observed but not implementing them can be harmful.[89] Other studies have shown how mobile needle exchanges can be used to refer those who are injecting drugs into a drug treatment program between a control group (26%) and an intervention group (40%) which was statistically significant.[90] These needle exchanges could be used to refer individuals to gastroenterologists for HCV treatment, and if they are already testing for HIV in the vans, they could also collect blood for HCV testing. In Orange County, California, there was a needle exchange that operated for two years but was barred in November 2018 by a county judge due to concerns about stray syringes injuring people and the litter caused by discarded needles.[91]

Barriers to DAA Utilization

Although DAA medications are effective, their cost is a barrier to utilization. The cost of treatment with DAAs ranges from approximately $24,000 to $100,000 in the United States, which may not be covered by insurance.[79,92,93] There are currently 19 different DAA medications that are FDA approved for treating HCV infection.[92] The cost magnifies existing social inequalities in terms of who can afford these medications and who cannot.[94] Although these medications are effective, there are significant barriers to obtaining the drugs, as only people with health insurance, access to premium health care, and gastroenterology/hepatology specialists can afford them. In addition, prior authorizations for DAAs may be difficult to attain as some patients may not be as advanced in their HCV infection to receive them.[95] In one study, researchers, found that patients who scored less than an F2 (second stage) on the fibrosis scale or had insufficient clinical supporting information were denied prior authorization for treatment.[95] In addition, some insurance plans prevent prescribing DAAs unless the patient is abstaining from substance abuse or alcohol abuse, making this an additional barrier for these patients.[95]

HCV and health insurance

Due to the high cost of HCV medications, the ability to be treated and cured highly depends on insurance status. One study found that in an adjusted analysis of the National Health and Nutrition Examination Survey (NHANES) data, a large representative sample of over 35,000 individuals, the only barrier to pursuing HCV treatment was the lack of health insurance, with an OR of 2.76.[14] Those who did not have a usual source of health care were statistically significant.ly less likely to have no subsequent HCV care ($p<0.020$). This study found that many of the HCV-Positive individuals were unable to be followed up and could not be reached for further questioning. The researchers surmised that these individuals were less likely to have usual health care health insurance than those who were injecting drugs.[14]

Other studies looked at the type of insurance and found that the patient's type of insurance indeed matters. Galbraith et al.[96]examined electronic medical records in four metropolitan areas (Birmingham, AL, Oakland, CA, Baltimore, MD, and Boston, MA) and universal hepatitis C antibody screening (meaning it was offered to everyone who arrived in the emergency department unless they opted out) in emergency departments and found that across all sites across four metropolitan areas, those with commercial (non-government provided insurance) insurance had higher HCV prevalence difference of -9.3 compared to those on Medicare -4.1 and other -3.7 when Medicaid was the reference group. The only study site on the west coast, in Oakland, found that those on Medicare had a positive prevalence difference of 6.3 compared to Medicaid, where commercial had a prevalence difference of 0.2 and others had a prevalence difference of 9.8.[96]

Another study looking at NHANES data from 2013 to 2018 found that those who had health insurance, especially private health insurance, were more likely than those without health insurance to have resolved HCV infection.[97] The researchers found using age-adjusted prevalence that those who had no insurance were had a higher prevalence of 2.46, (95% CI 1.47-4.12) compared to those during the pre-DAA timeframe (2013 to 2014). (1.83, 95% CI 1.28-2.67). The prevalence among those with insurance was higher among those on Medicare and Medicaid, with 1.92, (95% CI 0.71-5.12) pre-DAAs, and 1.95, (1.11-3.40) post-DAAs. Those with private insurance had a lower prevalence overall at 0.48, (0.30-0.77) pre-DAAs, and 0.59 post-DAAs (0.31-1.13).[97]

Risk factors with respect to insurance type in the study by Ditah et al.,[97] reflected similar results. The researchers found that private insurance was an independent protective factor against HCV infection with an AOR of 0.39, 95% CI (0.18-0.82).[97] In their discussion, the researchers found that those with active HCV infection were less likely to have insurance coverage which can prevent proper linkage to care and make it difficult for them to access DAA treatment for HCV.[97]

With the Affordable Care Act passed in 2010,[98] we would expect all Americans to have health insurance and be eligible to receive HCV treatment; however, this expectation does not cover recent job loss or acute changes in insurance status. As indicated by the literature, Health insurance appears to be the main driver concerning viral load testing, undetectable viral load, and HCV diagnosis.[56,62,99,100] Nevertheless, even with the Affordable Care Act, not everyone who tests antibody-positive for hepatitis C gets follow-up viral load testing and linkage to care. Further research is needed using electronic medical record data to understand more about who is testing for viral load or not and if they are lost to follow-up.

Routinely collected public health surveillance data, as required by the state, shows the overall morbidity of a reportable disease but does not capture individual sociodemographic information or risk factors such as insurance provider, comorbidities, drug use, and current medications. [101] The care cascade for HCV is complicated, and patients falling out of that care cascade may not receive or interrupt treatment. Electronic Medical Record (EMR) data can help show some of the nuances that surveillance data does not capture, including insurance status, comorbidities, prescriptions, and smoking and drug use.

Research Questions and Hypotheses

The goals of this research are to identify patient, provider, and institutional correlates of the following outcomes: HCV viral load testing, undetectable HCV viral load, and HCV diagnosis in a health care setting using the University of California, Irvine Medical Center (UCIMC) medical records with chart review.

The research questions examined include:

1. What are the sociodemographic and insurance correlates for patients who are getting HCV viral load testing among antibody-positive patients in Orange County, California, from 2014 to 2020? (Conceptual model 1)

Hypotheses:

a) We hypothesize that people living in areas with increased insurance coverage were more likely to be viral load-tested, as they would be able to cover the cost of treatment.

b) We hypothesize that people over the age of 65 (who are Medicare eligible) were more likely to be viral load-tested, as they would be able to cover the cost of treatment.

c) That there is a joint interaction effect on undetectable viral load between quartile of health insurance and quartile of median household income at the census tract level

2. What are the sociodemographic and insurance correlates and insurance for patients who show undetectable viral load (Published in*Health Services Research and Managerial Epidemiology)* in antibody-positive patients in Orange County, California, from 2010 to 2020? (Conceptual model 2)

Hypotheses:

a) Those who live in areas with lower median household incomes will be less likely to have an undetectable viral load

b) Those who live in areas with higher percentages of government health insurance (Medicare/Medicaid) will be less likely to have an undetectable viral load for HCV

c) Those who are older, particularly over the age of 65 (in the birth cohort born between 1945-1965 and also eligible for Medicare/Medicaid), may not be Medicaid eligible will be more likely to have an undetectable viral load for HCV

d) That there is a joint interaction effect on undetectable viral load between quartile of health insurance and quartile of median household income at the census tract level

3. In a real-world health care setting, what are the sociodemographic, comorbid, and insurance correlates for patients who are getting diagnosed with HCV among antibody-positive patients in Orange County, California, from 2010 to 2020? (Conceptual model 3)

Hypotheses:

a) Those with private insurance will be more likely to receive an HCV diagnosis

b) Those with no insurance will be more likely to receive an HCV Diagnosis

c) Those with comorbidities will be more likely to receive an HCV diagnosis

Gaps in the current research literature

The pressing concern among this population is the lack of HCV treatment indicated by undetectable viral load (as a proxy variable) that only 3.16 percent of all patients reported to the California Reportable Disease Information Exchange (CalREDIE) from 2014-show undetectable viral load and only 63 percent of all HCV antibody patients have ever been viral load tested from 2010 to 2020 leaving the viremic status of these patients unknown who could potentially infect others. There is a dearth of literature looking at HCV using county surveillance data examining facilitators to viral load testing, undetectable viral load, and cure for HCV. Many of the cohort studies looking at HCV outcomes are only done in a hospital or clinic setting with small sample sizes (<500 patients) and are not community-wide surveillance surveys at the county level.[102,103] There is a need to analyze sociodemographic variables, including race/ethnicity, age, history of incarceration, and individual-level economic and health insurance variables(whether they are on private or public insurance). These social determinants of health, including race, insurance status, and socioeconomic status,[12,104] can help identify patients with unmet needs for HCV treatment and cure.

Additionally, the evidence for sociodemographic and insurance correlates of HCV infection is not recent, with some studies that are more than ten or twenty years old, before the advent of DAA medications, widespread needle exchange programs, and increases in incidence rates over time and therefore do not reflect the latest numbers and rise in HCV infection seen nationwide. Another issue is that surveillance data that is reported to state and local health departments can be incomplete and have missing data, especially if the data is from homeless and institutionalized people. Laboratory reports are limited and may not have demographic and residence data because the report was filled out by a third party and not the patient's primary care provider.[21]

Significance

This dissertation plans to analyze public health surveillance data from CalREDIE and supplement it with electronic medical records from the University of California Irvine Medical Center (UCIMC) to better understand facilitators to viral load testing, undetectable viral load, treatment completion for HCV disease and to forecast the success of future interventions to decrease the burden of HCV in the county. The significance of this study is to better understand the barriers to HCV viral load testing, treatment initiation, treatment completion, and cost averted to improve the care cascade in a large, urban county with a bustling substance use rehabilitation tourism industry. The overall goal of these research findings is to inform the design of interventions that increase testing, initiation of care, and completion of treatment.

Despite the availability of effective HCV treatment, it remains unclear what fraction of Orange County patients who test antibody-positive are followed up with viral load tests, formally diagnosed with HCV, and then initiated HCV treatment. In addition, among those with an antibody-positive test, the sociodemographic determinants of who ultimately receives treatment are not well-characterized. This research aims to examine the relationship between individual (gender, out-of-state status, individual insurance) and area-level factors (census tract level median household income and percent of health insurance coverage) and the likelihood of undetectable viral load for HCV. This work contributes to the literature in two ways; first, it uses a large public health catchment area surveillance dataset of the nation's sixth-largest county to identify predictors of treatment. Second, this helps identify groups of patients who have unmet HCV needs for diagnosis and treatment.

Data Sources for this dissertation

The California Reportable Disease Information Exchange (CalREDIE) will be one of the data sources for this dissertation, with all HCV antibody-positive cases reported to Orange County included for analysis. The CDC and the Council of State and Territorial Epidemiologists,[105] set the case definition as the following criteria for presumptive and confirmed cases.[105] For presumptive cases, the necessary laboratory evidence is an antibody test, and for confirmed cases, the necessary laboratory evidence includes either HCV PCR RNA tests, antigen tests, or genotype testing. The case definition for HCV in the state of California is a positive antibody test.[101] As required by Title 17. of the California Code of Regulations ((CCR) §2500, §2593, §2641.5- 2643.20, and §2800-2812 Reportable Diseases and Conditions),[16] all HCV antibody-positive are reported to the state using the CalREDIE system), [18]Each participating local health department has access to their reported cases and information on testing and treatment sites from the electronic lab reports. This system is used to perform active and passive surveillance of reportable diseases in California and is confidential morbidity reports.[2,16-18] Under the current law, all HCV antibody positives are reported to CalREDIE as well as quantitative viral load tests, regardless if viral load is detected or not, including those with undetectable viral load or SVR.[2]

Additional medical information such as race/ethnicity, history of incarceration, and evidence of intravenous drug use for patients who were diagnosed with HCV infection at UCIMC will be collected by review of UCIMC medical records. OCHCA and UCIMC developed a process and a data-sharing agreement whereby OCHCA staff may access electronic medical records (EMRs) for patients who develop Title 17-defined public health reportable infectious diseases, including HCV. Using this process, UCIMC medical records that had a medical record number (MRN) in CalREDIE and did not have a "break the glass warning" were accessed, and relevant information extracted from the UCIMC electronic medical record system by OCHCA staff who received specific certification by UCI to access the UCIMC system. Researchers participating in this project who underwent OCHCA compliance and HIPAA training and who are designated by OCHCA to review this data will have access to a database with information obtained from these medical records at the OCHCA Communicable Disease Control Division office maintained by the California Department of Public Health. The unit of data collection and analysis will be at the individual level. Other studies[96,102,103] have used EMRs to look at insurance and other individual-level factors such as race, history of injection drug use, and comorbidities to help better understand how patients navigate the HCV care cascade.[96,102,103] This research received approval from the Institutional Review Boards of the University of California, Irvine protocol H.S. # 2019-548 and the O.C. Health Care Agency (OCHCA) research project 2020-03.

All cases reported to CalREDIE will be matched at the census tract level will be joined with data from the 2017 American Community Survey (ACS) (n=91,165). The 2017 ACS was used as it was the most recent ACS 5-year estimate conducted at the time of analysis. This matching allowed us to examine the role of median household income and percent of residents with health insurance on sustained HCV treatment. Health insurance was further divided into percent with private health insurance, percent with no health insurance, and government health insurance (state or federal, Medicaid or Medicare).[106] These data were aggregated into quartiles to be consistent with the literature.[107]

Implications of this research

The implications of this research may help medical and public health professionals identify people at risk of complications from HCV and propose policy and structural changes that can improve the quality of care and health outcomes. We can also look at the costs averted to help convince policymakers and governmental agencies to fund testing and treatment of HCV and connect those infected to care. Finally, this project has the potential to help enhance existing public health surveillance and strengthen the capability of local public health departments, primary care providers, and facilities (public vs. private hospitals, incarceration facilities, and substance use treatment centers) to better identify patients who need follow-up HCV viral load testing and treatment and initiate the care cascade to help them attain SVR and be cured.

RESEARCH CHAPTER 1: SOCIODEMOGRAPHIC PREDICTORS OF VIRAL LOAD TESTING AMONG HEPATITIS C ANTIBODY-POSITIVE PATIENTS

Abstract

In Orange County, California, from 2010 to 2020, only 64 percent of hepatitis C (HCV) antibody-positive individuals were tested for viral load.[17]

Objective: To compare the characteristics of HCV antibody-positive individuals and ever tested for viral load compared to those who are not viral load tested.

Study Design: This was a retrospective cohort study.

Data Sources: Secondary data was reported to the California Reportable Disease Information Exchange (CalREDIE [2]) in Orange County, California, from 2010 to 2020.

Data Collection/Abstraction Methods: Participants in this dataset included 33,300 patients in the CalREDIE database in Orange County, California, from January 1, 2014, to March 1, 2020. These were individual records extracted from the CalREDIE data warehouse.

Findings

The results show that the following HCV antibody-positive adults were more likely to ever test for viral load than their counterparts: 1) Individuals over 65 years old showed increased relative to younger adults (OR=1.10), 2) Males, compared to females (OR 1.13), 3) those out-of-state vs. Californians (OR 1.27), 4) residents of census tracts with higher levels of percent health insurance enrollment vs. residents of other lots with the lowest quartile of percent health insurance enrollment (OR=1.36).

Conclusions: In this large urban county sample, HCV antibody-positive males, older than 65, from out-of-state, and those living in census tracts with higher insurance coverage are more likely to be tested for HCV and may have health insurance to cover expensive HCV DAAs.

These results suggest that those who are viral load tested are more likely to afford HCV treatment. More research is needed to follow people through the HCV care cascade to help diagnose patients and connect them to treatment.

Introduction

Hepatitis C (HCV) is an infectious disease caused by the hepatitis C virus, leading to chronic liver disease and mortality in patients without treatment.[3,5-7] The Centers for Disease Control and Prevention (CDC) reported that in 2017, the HCV virus infected over 143,000 individuals in the United States, and incidence rates steadily increased since 2013.[3] Those at increased risk for HCV include those over the age of 65, veterans, people who inject drugs (PWID), veterans, and those living with HIV.[3,5,14,63,108] The focus of this study is to better understand factors related to HCV diagnosis using ever testing for viral load testing in Orange County, California,

The HCV virus has a Reproductive Rate (R0) ranging from 1.92 to 3.96 among high-risk populations such as injection drug users, indicating that every infected individual could infect up to 4 susceptible individuals at risk.[11] HCV is transmitted via infected blood through needle sharing, needle sticks or other blood exposures, sexual fluids, or from mother to child.[5] One of the most significant risks of those infected with the HCV virus is that they may have the disease without showing any symptoms and could potentially infect other individuals causing a threat to public health.[5-7] Complications from HCV, when left untreated, may lead to liver fibrosis, liver cancer, and liver-related mortality.[5-7] One cohort study of over 2 million patients indicated that 70 percent of HCV antibody-positive patients had moderate or worse liver fibrosis.[9]

HCV Diagnosis and care cascade

Tracking patients from initial HCV diagnosis to treatment is done through a care cascade. Initial diagnosis is essential to get patients connected to care. This care cascade involves initial HCV infection diagnosis, treatment evaluation, treatment initiation, and completion, leading to sustained virologic response (SVR).[51] SVR is achieved by an undetectable viral load using an

RNA viral load test twelve weeks post-treatment and cured.[18,51,53-56,109] With highly effective Direct-Acting Antiviral (DAA) treatments for HCV, the greatest threat to attaining SVR is dropping out of the care cascade. The care cascade varies by treatment facility and clinician. This cascade is important because it identifies where patients can drop out of care because their viral load is not being monitored, and they cannot further be evaluated for treatment. This care cascade assists public health practitioners in defining denominators for analysis using the number of patients in that part of the process.

The key to getting patients into treatment is diagnosing them with two separate tests confirming active HCV infection. The recommended diagnosis procedure begins with an HCV antibody enzyme-linked immune absorbed assay (ELISA) test. If positive, an RNA viral load test is required to confirm viremia (viral presence in the blood), and viremic patients are referred to treatment.[61,62] Antibody testing alone cannot determine current infection, which must be confirmed using the RNA viral load test.[56]

Importance of viral load testing

HCV antibody tests are only one part of the diagnosis process. An antibody test will be positive if a patient has ever been infected with HCV and will remain positive throughout the patient's life. An antibody test does not indicate viremia, and a person can remain antibody-positive with an undetectable viral load.[63,64,110]. However, not all positive patients are tested for viral load, and it is unclear why. Clinical guidelines recommend that every patient with a positive HCV antibody test should be tested for the viral load to determine if they had an active infection.[63,64,110] After active HCV infection is diagnosed with a confirmatory viral load test indicating viremia and active infection, patients are evaluated for treatment, and their virus is genotyped.[109]

In Orange County, California, only 64 percent of antibody-positive individuals are tested for viral load.[17] Based on previous analysis (in press) on an undetectable viral load among the same study population, we hypothesize that with increased insurance coverage, those over 65 were more likely to be viral load-tested, as they would be able to cover the cost of treatment.[111] The objective of this research is to compare the characteristics of individuals who are HCV antibody-positive and ever tested for viral load compared to those who are not viral load tested.

Methods

This study was a retrospective cohort looking at disease incidents from January 1, 2010, to March 1, 2020. All cases reported to CalREDIE that could be matched with a census tract were joined with data from the 2017 American Community Survey (ACS) (n=27,389) to add information on median tract income and percent of residents with health insurance to help understand the role of neighborhood socioeconomic status facilitators to ever testing for viral load. The 2017 ACS ~~was used as it~~ was the most recent ACS 5-year estimate conducted at the time of analysis. A flow chart of inclusion and exclusion for this analysis can be found in figure 3.1. All cases included in this analysis were diagnosed as HCV antibody-positive using an ELISA test and were reported to CalREDIE. Those cases excluded were 5,763 people who were unable to join census tract data and those with missing variables (n=148).[18] Sensitivity analysis did not indicate a significant difference in odds ratios of ever HCV viral load testing between those that were joined and those that were not joined.

This research was approved by the Institutional Review Boards of the University of California, Irvine protocol HS# 2019-548 and the Orange County Health Care Agency. The dependent variable in this analysis was ever having a viral load test versus never having a viral load test which was coded as binary.

We measured individual patient evidence of HCV infection by extracting data from the CalREDIE database for patients assigned to the Orange County Health Care Agency who tested positive using an HCV antibody test. If the home address for the case was ever recorded outside of the state of California, the case was designated as ever-living out-of-state.

Independent variables at the individual level included age, gender, and ever-living out-of-state status. The coding for gender was categorical as collected (male, female, or unknown) and recoded into binary, male or female. Those with unknown gender or male-to-female transgender were coded as missing. Age was divided into 10-year age groups after the age of 19. Approximately 80 percent of data on race/ethnicity were missing and were not included in this analysis.

Variables from the 2017 ACS at the census tract level for all census tracts able to be joined with the surveillance data included median household income and percent with health insurance. Health insurance was further divided into percent with private health insurance, percent with no health insurance, and government health insurance (state or federal, Medicaid or Medicare.)[106]. These data were aggregated into quartiles because entering these measures as continuous is consistent with the literature.[107] When percentages are continuous, it makes it more challenging to interpret and less meaningful. When broken up into quartiles, there are clear delineations of income and or health care insurance coverage in those census tracts, making the coefficients easier to understand.[107]

The data were analyzed using Stata version 13 (StataCorp, College Station, TX). Analysis of the data included descriptive statistics, bivariate and multivariable stratified, and interaction term logistic regression to analyze the likelihood of ever having viral load testing for HCV. Multivariable survival analysis was used to examine the effects of combined risk factors and adjusted for confounding variables such as age (among those older than 65 and those 65 and younger). This binary definition of age was chosen as individuals age 65 and older are eligible for government health insurance through Medicare who may be able to receive treatment at this age when they could not previously afford HCV treatment.[112]

Results

A description of the sample analyzed is in table 1.1. The mean age was 51.36, and the median age was 54.50. The sample was mostly male, 58.45 percent, and the vast majority of patients were classified as California residents.

In a multivariable logistic regression with ever testing for HCV viral load as the outcome (Table 2), gender, age, and being ever out-of-state were more likely to get tested. For males compared to females, the OR=1.12 (95% CI=1.06-1.17). Those who were ever out-of-state had odds that were 1.55 times of ever being tested for viral load compared to California residents (95% CI=1.35-1.78).

Percent health insurance at the census tract level was statistically significant for all quartiles when compared to quartile 1. Quartile 2 83.6%-89.3% coverage compared to quartile 1 71.3%-83.6% had odds that were 1.2 times higher (1.12-1.30). Those in quartile 3, 89.3%-94.2%, had odds that were 1.32 times higher than quartile 1 (1.22-1.43). Those in quartile 4 4.2%-100% had an odds ratio of 1.33 (1.20-1.47) higher to get viral load tested than those in quartile 1. In this multivariable logistic regression, only the second quartile of estimated median household income at the census tract level was statistically significant, with odds that were 1.09 higher (1.00-1.18) than quartile 1. All other quartiles were not statistically significant. None of the quartiles of percent government health insurance at the census tract were statistically significant when compared to the first quartile.

Multivariable regression results

A multivariable regression (table 1.2) was conducted to control for age, census tract level of insurance coverage, census tract level of government health insurance, and ever testing with an out-of-state address. When income was initially added to the model without adding the health insurance variables, it was statistically significant; however, income was highly correlated with Spearman's Rho of 0.70 between median household income and percent health insurance and -0.78 between median estimated household income and government insurance, which is consistent with the literature.[113] When examining the effect of ever viral load testing between quartiles of median household income after controlling for percent health insurance and percent government health insurance, it was no longer significant. In general, those who were 65 and older had an odds ratio that was 1.1 times higher of ever viral load testing compared to their younger counterparts. A positive association of ever testing for viral load with the higher quartiles of insurance coverage at the census tract level indicated an increase in adjusted odds when comparing the higher quartiles to the lowest quartile of insurance coverage (less than 83.6 percent). Compared to the first quartile: the second quartile (AOR=1.23), the third quartile (AOR=1.35), and the fourth quartile (AOR=1.36) all had higher odds of ever testing for viral load compared to the first quartile and were statistically significant.

Percentage of government health insurance at the census tract level had a positive association with ever testing for viral load. Generally, lower coverage of government health insurance coverage was associated with higher viral load testing; however, only the third quartile, when compared to the first quartile, has odds that are 1.09 times higher than the first quartile, with all the other quartiles not having significant changes in odds of viral load testing.

Stratified logistic regression

This sample skewed younger ages, those 65 and younger comprising over 82 percent of the sample, which necessitated stratification; in a stratified logistic regression (table 1.3), those who were age 65 and younger had higher odds of ever viral load testing compared to those over 65. The highest quartile of percent health insurance had an OR of 1.38 compared to 1.23 among those over 65. Those who were out-of-state had 1.28 higher adjusted odds compared to 1.06 among those who were over 65. Males 65 and younger had adjusted odds that were 1.19 times higher compared to females 65 and younger.

Discussion

There are several interesting findings in this paper. First, those who were ever tested out-of-state were 1.55 times more likely to have viral load testing. Among those that were out-of-state residents, they were more likely to have viral load testing compared to their in-state counterparts. This is concerning because these findings imply that those who are out of state may be receiving better care compared to California residents. To the best of our knowledge, the only study looking at out of state status and HCV in the United States is the second chapter of this dissertation.[114]

The second finding is that all quartiles of the percentage of health insurance coverage at the census tract level were statistically significant compared to the lowest quartile. This means that those who live in a census tract with more health insurance coverage were more likely to have viral load testing. This may mean that those who are living in areas with lower health insurance coverage are not getting viral load-tested, evaluated for treatment, and cured. It reinforces the idea of the relationship between place and health and that those living in well-covered census tracts are generally more likely to receive better health care.[115,116] The third finding was that those who were over the age of 65 were more likely to get viral load tested. This makes sense as those who are over the age of 65 have Medicare coverage, which would cover screening and treatment. These findings were contrary to the previous screening recommendations,[117] those who were over the age of 65 were more likely to get viral load tested compared to those 65 and younger. Only 64 percent of all antibody positives that could be joined to census tracts were viral load tested at all. This means that many asymptomatic individuals may not be tested for viral load and not even know if they were viremic. The finding that those deemed out-of-state are more likely to be tested for viral load is striking because Orange County is a rehabilitation tourism destination.[17,18] Orange County is the sixth-largest county in the United States, with approximately 3.1 million residents.[20] With over 400 substance use treatment facilities, Orange County is a rehabilitation tourism destination that brings in many out-of-state patients, some of whom have HCV related to injection drug use.[1,20] With the Affordable Care Act being passed in 2010,[98], we would expect all people to be insured and able to pay for treatment; however, this does not cover recent job loss or acute changes in insurance status. This is the first time using census tract level data that correlates HCV ever viral load testing for HCV using public health surveillance.

The presence of health insurance appears to be the main driver concerning viral load testing. Yet, even with the Affordable Care Act, not everyone who tests antibody-positive for HCV gets viral load testing. As indicated by other studies,[95] current substance use and having a high enough fibrosis score of 2 or higher were used by some insurance companies to exclude patients from treatment coverage, creating another barrier to treatment evaluation and initiation. Further research is needed using electronic medical record data to understand more about who is testing for viral load or not. There is a dearth in the literature examining who among those who are antibody tested indeed get viral load testing. Some researchers have looked at predictors of antibody testing for opt-out screening of HCV in emergency rooms. Galbraith et al.,[96] examined electronic medical records and universal HCV antibody screening (meaning it was offered to everyone unless they opted out) in emergency departments and found that across all sites across four metropolitan areas, those with commercial insurance had a higher prevalence difference of -9.3 compared to those on Medicare -4.1 and other -3.7 when Medicaid was the reference group. The only participating study site in the state of California, located in Oakland, found that those on Medicare had a positive prevalence difference of 6.3 compared to Medicaid, where commercial had a prevalence difference of 0.2 and others had a prevalence difference of 9.8.

Limitations

This dataset relies on county-wide surveillance data, which have incomplete and/or missing values on individual covariates such as race/ethnicity. Certain patients (n=5,763) could not be joined to census tracts, and we were unable to use these cases in the analysis because they could not be geocoded by CalREDIE or did not have an address associated with their surveillance record. Due to the lack of information in electronic lab reporting, we are unable to ascertain some of the risk factors for HCV, such as incarcerations status, injection drug use, or homelessness. We are not excluding these individuals from the analysis; however, there is insufficient information in this dataset to ascertain those risk factors. Infectious disease risk factors like these are generally incomplete and not consistently collected in CalREDIE. This is especially true ascertainment of the homeless population who are at increased risk of contracting HCV and could not be geocoded.[3,14] Those with less access to health care and lower incomes are less likely to receive viral load testing, widening the gap of those who are unable to pay for expensive DAA medications should they become diagnosed. Nevertheless, the lack of ascertainment of this population likely leads to an underestimate of the role of tract-level private insurance coverage on the likelihood of treatment.

In addition, census tract-level information does not necessarily reflect the status of individuals living in that tract. One other limitation is that viremic patients who were out of state may have returned to their home state for treatment, and that may not be captured in this data.

Finally, Orange County is a substance use rehabilitation tourism destination.[1] Our results only reflect evidence of HCV treatment from one county. These results may not be generalizable to other locations in California or in the United States as a whole. Despite this limitation, the size of Orange County's population (> 3 million) indicates that results hold valuable public health implications for similar demographic populations.

Implications

This research has policy implications for identifying groups at risk for not getting viral load tested for HCV, failing to enter the care cascade, and initiating care. These policies would help ensure that everyone with a positive HCV antibody test has a follow-up viral load test. Health care facilities could implement this using pop-up alerts in electronic medical records to help improve compliance. The second is Universal HCV screening of all patients ages 18 to 79 as recommended by the United States Preventive Services Taskforce.[80] This screening would include both antibody tests and follow-up viral load testing. Those with positive antibody tests could help identify more asymptomatic viremic individuals and get them into care. Outside this dataset, vulnerable groups such as the homeless, those who are incarcerated, and those without health insurance should be targeted for viral load testing. Future research should identify additional risk factors for HCV testing and treatment with retrospective reviews of electronic medical records of HCV antibody-positive patients with potentially more detailed information about insurance providers, smoking status, risk factors such as intravenous drug use, and comorbidities.

Table 1.1: Descriptive characteristics of HCV antibody-positive patients ever testing for HCV viral load in Orange County, California

Table 1.1: Descriptive characteristics of HCV antibody-positive patients ever testing for HCV viral load in Orange County, California(n=27,389)		
Gender (coded as binary)	N	Percent
Female	11,388	41.55
Male	16,001	58.45
Total	27,389	100
Ever tested with an out-of-state address	N	Percent
Never tested with an out-of-state address (California)	26,259	95.87
Ever tested with an out-of-state address	1,130	4.13
Total	27,389	100.00
Ever tested for HCV Viral load	N	Percent
Never Tested for Hepatitis C Viral load	9,906	36.17
Ever tested for Hepatitis C viral load	17,483	63.83
Total	27,389	100
Age group 10 years	N	Percent
<18	277	1.01
18-19	201	0.74
20-29	3409	12.45
30-39	2960	10.81
40-49	3589	13.11
50-59	7433	27.13
60-69	6677	24.38
70-79	2082	7.60
80+	761	2.78
Total	27,389	100
Year a person was first tested	N	Percent
2010	5	0.02
2011	237	0.87
2012	390	1.42
2013	550	2.01
2014	3377	12.33

2015	5640	20.60
2016	4154	15.17
2017	4560	16.65
2018	4271	15.60
2019	3649	13.33
2020[1]	547	2.00
missing	5	0.02
Total	27,389	100

Table 1.2: Multivariable logistic regression with age coded as binary of HCV antibody-positive patients ever testing for HCV viral load

Table 1.2: Multivariable logistic regression with age coded as binary of HCV antibody-positive patients ever testing for HCV viral load (n=27,389)	
	Adjusted OR (AOR), (95% CI)
Gender (coded as binary)	
Female	Reference
Male	1.13 (1.08-1.19)
Ever tested with an out-of-state address	
Never tested with an out-of-state address (California)	Reference
Ever tested with an out-of-state address	1.27 (1.12-1.45)
Age Group	
Younger than 65	Reference
65 and older	1.10 (1.03-1.18)
Estimated Median Income by quartile	
Q1=$31,029-$54,330	Reference
Q2=$54,331-$70,250	1.12 (1.03-1.21)
Q3=$70,251$92,861	1.01 (0.92-1.11)
Q4=$92,862-$250,000+	1.03 (0.91-1.15)
Percent Health insurance at the census tract level by quartile	
Q1=71.3%-83.6%	Reference
Q2=83.7%-89.3%	1.23 (1.14-1.33)
Q3=89.4%-94.2%	1.35 (1.24-1.46)
Q4=94.3%-100%	1.36 (1.23-1.51)
Percent Government Health insurance at the census tract level by quartile	

[1] Data up to March 1, 2020

Q1=11.1%-25.7%	Reference
Q2=25.8%- 33.2%	1.03 (0.95-1.10)
Q3=33.3%-42.2%	1.09 (1.00-1.19)
Q4=42.3%-60.6%	1.09 (0.99-1.21)
Constant	1.20 (1.07-1.33)
Observations	27,389

Table 1.3: Stratified multivariable logistic regression on ever testing for HCV viral load

Table 1.3: Stratified multivariable logistic regression of HCV antibody-positive patients ever testing for HCV viral load (n=27,389)

	65 and Younger AOR (95% CI)	Over 65 AOR (95% CI)
Gender (coded as binary)		
Female	Reference	Reference
Male	1.19 (1.12-1.25)	0.93 (0.83-1.05)
Ever tested with an out-of-state address		
Never tested with an out-of-state address (California)	Reference	Reference
Ever tested with an out-of-state address	1.28 (1.12-1.46)	1.06 (0.51-2.20)
Estimated Median Income by quartile		
Q1=$31,029-$54,330	Reference	Reference
Q2=$54,331-$70,250	1.14 (1.05-1.24)	1.01 (0.83-1.23)
Q3=$70,251$92,861	1.05 (0.94-1.17)	0.86 (0.68-1.10)
Q4=$92,862-$250,000+	1.04 (0.91-1.18)	1.00 (0.76-1.32)
Percent Health insurance at the census tract level by quartile		
Q1=71.3%-83.6%	Reference	Reference
Q2=83.7%-89.3%	1.23 (1.13-1.33)	1.19 (0.98-1.43)
Q3=89.4%-94.2%	1.36 (1.24-1.49)	1.22 (1.00-1.49)
Q4=94.3%-100%	1.38 (1.23-1.54)	1.23 (0.98-1.54)
Percent Government Health insurance at the census tract level by quartile		
Q1=11.1%-25.7%	Reference	Reference
Q2=25.8%- 33.2%	1.03 (0.95-1.12)	1.00 (0.84-1.20)
Q3=33.3%-42.2%	1.08 (0.99-1.19)	1.13 (0.92-1.39)
Q4=42.3%-60.6%	1.07 (0.96-1.19)	1.22 (0.95-1.56)
Constant	1.15 (1.02-1.29)	1.63 (1.24-2.14)
Observations (n)	22,598	4,791

RESEARCH CHAPTER 2: MEASURING HAZARDS OF UNDETECTABLE VIRAL LOAD AMONG HEPATITIS C ANTIBODY-POSITIVE RESIDENTS OF A LARGE SOUTHERN CALIFORNIA COUNTY. (CURRENTLY PUBLISHED IN *HEALTH SERVICES RESEARCH AND MANAGERIAL EPIDEMIOLOGY, 2021)*

ABSTRACT

¶¶

Background Hepatitis C virus (HCV) infection is the most common bloodborne infection in the U.S. However, only a small proportion of persons are treated and cured. Previous research has not characterized sociodemographic characteristics of who receives treatment. We examined predictors of undetectable viral load for HCV in Orange County, the sixth-largest county in the United States, where HCV is the most commonly reported infection.

Methods: From 2014 to 2020, we acquired public health surveillance data from 91,165 HCV antibody-positive care encounters from the California Reportable Disease Information Exchange (CalREDIE). We used a time-to-event proportional hazards framework to estimate individual and area-level correlates of time-to-HCV undetectable viral load among HCV + individuals.

Results: Older adults (>65 years) showed an increased hazard of an undetectable viral load relative to younger adults (HR =2.00). In addition, residents of census tracts with greater enrollment in

health insurance showed a greater likelihood of undetectable viral load (HR=1.36). The moderating effect of higher tract median household income and higher tract levels of health insurance were more likely to have undetectable viral load and was statistically significant.

Conclusion: In a large urban county, HCV antibody-positive older adults appear much more likely to show undetectable viral load compared to younger adults. Residents in areas with higher quartiles of health insurance enrollment have an increased likelihood of undetectable viral load. The extent to which constraints impede HCV care requires further investigation, including

follow-up studies on health insurance type to test the relationship of health insurance type to undetectable viral load.

Background

According to the Centers for Disease Control and Prevention (CDC), the incidence of hepatitis C (HCV) in the United States has steadily increased since 2013, with an estimated 2.4 million individuals living with the virus.[3,8,118] Hepatitis C is an infectious virus and the most common bloodborne pathogen in the U.S. If left untreated, the HCV virus can cause cancer and liver-related death, increased liver fibrosis, and a higher risk of all-cause morbidity and mortality.[3,5-7,9] In California, the CDC estimates a crude mortality rate of HCV with 4.98 deaths per 100,000 people in 2018

HCV Diagnosis and care cascade

Tracking patients from initial HCV diagnosis to treatment is done through a care cascade. This care cascade involves initial HCV infection diagnosis, treatment evaluation, treatment initiation, and treatment completion[18,51,53-55,109] With successful treatment leading to a sustained virologic response (SVR), with the virus remaining undetectable 12 weeks post-treatment completion.[18,51,53-55,109] Although generally accepted as the standard of care, the care cascade may vary by treatment facility and clinician. This cascade is crucial because it identifies where patients can drop out of HCV care and assists public health practitioners in defining denominators for analysis using the number of patients in that part of the care cascade.
Diagnosis of HCV is imperative for patients to receive care. To diagnose HCV infection, patients must complete antibody testing and a subsequent viral load test to confirm viremia or chronic infection. Active infection of HCV is only confirmed using a viral load test.[56] The recommended diagnosis procedure begins with an HCV antibody enzyme-linked immune absorbed assay

(ELISA) test with a follow-up RNA viral load test with viremic patients referred to treatment.[61,62]

A viable cure for HCV is available. In 2014, the Food and Drug Administration (FDA) approved the first wave of DAAs, curing the disease in as few as eight weeks with a likelihood of reinfection post-SVR.[51,64-68,71,72,119] Numerous studies have shown that these DAAs are over 95 percent effective.[54,66-71]

Although DAA medications are effective, their cost (ranging from $24,000 to $100,000) is a barrier to utilization, preventing infected individuals from seeking treatment.[79,92-94] Insurance coverage of these medications should be examined to understand their independent and multiplicative effect on attaining an undetectable viral load.

Orange County, California, is the 6th most populous county in the U.S., with a population of 3.3 million.[20] The morbidity and mortality from hepatitis C infection in Orange County have been substantially greater than any other infectious disease in the last decade (excluding the recent COVID-19 pandemic.)[17,18]

Despite the availability of effective treatment, it remains unclear what fraction of Orange County, California (O.C.) with an antibody-positive test, the sociodemographic determinants of who ultimately receives treatment are not well-characterized due to gaps in surveillance data. To better understand the infection rates in O.C. and how it relates to HCV testing, we examine the relationship between the individual (age, gender, out-of-state status) and area-level factors (census-tract level median income and insurance coverage) and the likelihood of an undetectable viral load for HCV.

Methods and Data Sources

Participants

Participants in this dataset included 23,950 HCV antibody-positive patients (and 91,165 patient encounters) in the (California Reportable Disease Information Exchange) CalREDIE infectious disease report database for cases assigned to O.C., California, from January 1st, 2014, to March 1st, 2020. [18] All HCV viral load tests, regardless of the result, are reported to CalREDIE.[2] This research received approval from the Institutional Review Boards of the University of California, Irvine protocol H.S. # 2019-548 and the O.C. Health Care Agency (OCHCA)

Measures

The dependent or time-to-event variable is an undetectable viral load. An undetectable viral load was classified as having less than 20 copies/ml on a PCR RNA viral load test.[120] A sensitivity analysis was conducted with different viral load cut-offs to determine an undetectable viral load that could lead to sustained virologic response or natural clearing of HCV infection.[120] We measured a previous history of HCV infection by extracting data from the CalREDIE database for patients assigned to the OCHCA who tested positive using an HCV antibody test; cases with addresses outside of California were designated out-of-state.

We specified a Cox proportional hazard model, and the time period for evidence of undetectable viral load was by year. This regression uses time over multiple individual encounters per person to control for it in analysis and helps to see what the hazard of an event (in this case, whether an undetectable viral load) will happen.[121] The hazard function, in this case, is the "risk" of having an undetectable viral load at time t.[120,121] In this dataset, there were 23,950 people with 91,165 total encounters as panel data. The unit of analysis is by person.

Independent variables at the individual level included age, gender, and in/out-of-state status. The coding for gender was categorical as collected (male, female, or unknown) and recoded into binary, male, or female. Age was divided into 10-year age groups after the age of 19 also as binary (65 and younger and over 65 years of age).[119] Due to 80 percent of missing race/ethnicity data in this dataset, we did not examine this covariate in these analyses.

Observations with census tract information were joined with data from the 2017 American Community Survey (ACS) (n=23,950 or 73 percent). The 2017 ACS was used as it was the most recent ACS 5-year estimate conducted at the time of analysis. This matching allowed us to examine the role of median household income and percent of residents with health insurance with an undetectable HCV viral load. Health insurance was further divided into percent with private health insurance, percent with no health insurance, and government health insurance (state or federal, Medicaid or Medicare.)[106] These data were aggregated into quartiles to be consistent with the literature and to better understand the wealth as distributed.[107] Data were analyzed using Stata version 13 (StataCorp, College Station, TX).

Results

The mean age was 51.83 years (Table 2.1). Participants were mostly male (58.66 percent), and 20.47 percent of participants were over 65 years. California residents comprised 98.25 percent of the and 1.83 percent were out-of-state. A total of 259 individual patients (1.08 percent) showed an undetectable viral load at any time between 2014 and 2020.

Adults over 65 were more likely to have an undetectable viral load relative to younger adults (HR=1.60 (1.47-1.76)) (table 2.2). In addition, in/out-of-state residence does affect an undetectable viral load making the hazard lower (HR=0.65 95% Confidence Interval (0.45-0.95). Residents of census tracts with the highest percentage of any health insurance coverage were more likely to have an undetectable viral load (HR=1.36, 95% CI (1.09-1.70)). Patients in tracts with higher quartiles of government health insurance were less likely to have an undetectable viral load. The fourth quartile of percent health insurance (over 92 percent coverage compared to quartile 1) HR=1.36 (1.19-1.57), and all quartiles of percent on government health insurance compared to quartile 1 were less likely to have an undetectable viral load. In general, persons residing in census tracts with a higher percentage of public health insurance showed reduced HRs of receiving treatment.

An interaction term between median income and health insurance was significant (table 2.3) When holding the quartile of income constant, increasing the quartile of insurance increased the HR of an undetectable viral load. Quartile 4, compared to quartile 1, had the highest HR of 9.75.

Multivariable Cox Proportional Hazard Models stratified by patients over 65.

Given the discovered difference in treatment rates by those over 65 compared to younger patients and the strong relationship between retirement age and health insurance type, we conducted a stratified *post hoc* analysis for those aged 65 and younger (n=74,136) and those over 65 (n=17,029 in table 2.4). Among older adults, a greater proportion of public health insurance at the census tract corresponds with an increased probability of that patient having an undetectable viral load

Discussion

This study examined over a seven-year period with 91,165 care encounters of 23,950 patients in the sixth-largest county in the U.S. approximately 97 percent of patients who have HCV virus antibodies do not indicate undetectable viral load indicating a lack of HCV treatment or spontaneous clearance. Those who lived in census tracts with higher quartiles of private health insurance, and those over the age of 65, had higher odds of an undetectable viral load, with 34 percent of patients not being tested at all for viral load. These findings, taken together, indicate an alarming level of potential under-diagnosis and linkage to care for detected HCV antibody-positive cases. These results indicate financial and health insurance barriers to diagnosis that impede patients' ability to be linked to care.

These results imply inadequate screening for those 65 and younger compared to their older counterparts[80]. This confirmed results from a study that found that universal screening identified that those younger than the 1945-1965 birth cohort comprised nearly 48 percent of all HCV cases in four large metropolitan emergency departments.[96]

Those in census tracts with lower insurance coverage are less likely to have an undetectable viral load. In a study of 38,025 persons in sites across the United States, Ditah and colleagues found that those who did not continue HCV follow-up care were less likely to have health care insurance.[14] Our work builds upon that of Ditah and colleagues and covers a period after DAA approval. If others replicate our work using individual-level data on health insurance type, this financial barrier to treatment requires significant policy attention and amelioration.[60]. Our study, with a large sample size, in a widespread geographical area, allows health practitioners to identify gaps in the care cascade and where some patients may still be infectious.

The current study has policy implications, including bridging the gaps for poor insurance coverage negatively impacting care. Persons living with HCV need appropriate health insurance for those uninsured to help initiate treatment. Connections to HCV care with more expansive insurance plans could be implemented using peer navigators and specialty pharmacies to target those ages 65 and younger and those with lower incomes.[122] Scientists must conduct further research to identify patients who fall out of the care cascade and better target interventions to link patients to care.

Limitations

Some of the limitations are directly related to using surveillance data for secondary analysis. The missing covariates in surveillance data do not capture or indicate information relevant to HCV infection such as risk factors (e.g., race, employment), occupation, individual insurance providers, persons in incarceration settings, or risk behaviors such as injection drug use or those without homes. We cannot examine in this dataset if these groups with increased vulnerability have an increased risk of contracting HCV.[3,14] Those with less access to health care and lower incomes are less likely to have an undetectable viral load, widening the gap of those who are unable to pay for expensive DAA medications. The inability to categorize and analyze these populations may lead to an underestimation of socioeconomic characteristics on the likelihood of undetectable viral load.

Another limitation is the incomplete nature of public health surveillance data with missing values on individual covariates. We do not have accurate race/ethnicity data for these HCV cases, as 80 percent are missing. Regarding lab tests, we only know if individuals are viremic if they have tested for viral load, and we cannot verify if an undetectable viral load was due to spontaneous clearance or treatment. We could not use these cases in the analysis because they had a missing address or failed to geocode. In addition, census tract-level information does not necessarily reflect the status of individuals living in that tract. Also, viremic, out-of-state patients may have returned to their home state for treatment, which we cannot capture in this dataset.

Finally, O.C. is a popular tourism destination for substance use rehabilitation in the U.S. This dataset may not reflect the burden of HCV in other settings such as homeless encampments and incarceration facilities.[1] Our results only reflect an undetectable HCV viral load from one county in California. They may not be generalizable to other locations in the state or the United States as a whole. Despite this limitation, the size of O.C.'s population (> 3 million) indicates that these results have public health implications for this community and counties of similar size and demographics.

Conclusion

In an era of effective treatment, the overwhelming HCV antibody-positive patients in OC do not have an undetectable HCV viral load and are potentially infectious. Only 1 percent of all persons with HCV-Positive antibody tests had an undetectable viral load from 2014 to the beginning of 2020, which indicates a lack of HCV diagnosis and treatment initiation. Disparities in insurance coverage illustrate the potential for severe inequity in treatment. The USPSTF updated its guidelines in 2020, recommending universal HCV screening for all people ages 18 to 79.[73,123]Universal HCV screening and viral load testing will help increase care and treatment initiation. Ensuring that health insurance will cover treatment costs and connecting persons living with HCV to appropriate treatment and treatment completion are top priorities. Subsequent work in this area would benefit from understanding the structural, socioeconomic, and cost barriers to achieving this successful care cascade.

Table 2.1: Descriptive characteristics of individuals with HCV antibody-positive encounters in Orange County, California, from 2014 to 2020 n=23,950

Table 2.1: Descriptive characteristics of individuals with HCV antibody-positive patients in Orange County, California, from 2014- to 2020 (n=23,950)		
Gender (coded as binary)	**N**	**Percent**
Female	9,788	40.87
Male	14,048	58.66
Missing	114	0.48
Total	23,950	100
Ever tested with an out-of-state address?	**N**	**Percent**
Never tested with an out-of-state address (California)	23,532	98.25
Ever tested with an out-of-state address	418	1.75
Total	23,950	100
Undetectable Viral Load (VL tested with <20 copies per ml)	**N**	**Percent**
Detected Viral Load	23,691	98.92
Undetectable Viral Load	259	1.08
Total	23,950	100
Age group 10 years	**N**	**Percent**
<18	194	0.81
18-19	166	0.69
20-29	2,907	12.14
30-39	2,806	11.72
40-49	3,293	13.75
50-59	6,364	26.57
60-69	5,708	23.83
70-79	1,835	7.66
80+	677	2.83
Total	23,950	100
Under 65	19,048	79.53
65 and over	4,902	20.47
Total	23,950	100
Year a person was first tested	**N**	**Percent**
2014	3,150	13.15
2015	5,095	21.27
2016	3,544	14.8
2017	3,940	16.45
2018	3,915	16.35
2019	3,556	14.85
2020	750	3.13

Total	23,950	100

[1] Data up to March 1, 2020

Table 2.2 Multivariable Cox Proportional Hazard Regressions with selected covariates of an undetectable viral load among antibody-positive encounters in Orange County, California

Table 2.2 Multivariable Cox Proportional Hazard Regressions with selected covariates of an undetectable viral load among antibody-positive encounters in Orange County, California (n=91,165)

	Adjusted Cumulative Hazard Ratio (95% CI)
Gender (coded as binary)	
Female	Reference
Male	0.93 (0.86-1.01)
State of residence	
In California	Reference
Out-of-state	0.65 (0.45-0.95)
10-year age group	
<18	Reference
18-19	0.86 (0.32-2.32)
20-29	0.99 (0.47-2.11)
30-39	1.35 (0.63-2.86)
40-49	1.67 (0.79-3.53)
50-59	2.03 (0.97-4.28)
60-69	2.28 (1.08-4.80)
70-79	2.89 (1.37-6.12)
80+	2.39 (1.10-5.19)
Estimated median household income by quartile at the census tract level	
Q1=$31,029-$53,014	Reference
Q2 $53,015-$63,339	0.78 (0.67-0.90)
Q3 $63,340-$83,289	0.87 (0.74-1.02)
Q4 $83,290-$250,000	0.94 (0.78-1.12)
Percent health insurance at the census tract level by quartile	
Q1=71.3%-82.0%	Reference
Q2=82.1%-87.7%	1.02 (0.90-1.16)
Q3=87.8%-92.1%	1.05 (0.92-1.20)
Q4=92.2%-100%	1.36 (1.19-1.57)
Percent with government health insurance at the census tract level (n=91,365)	
Q1=11.1%-28.6%	Reference

Q2=28.6%-36.8%	0.85 (0.77-0.95)
Q3=36.9%-45.1%	0.76 (0.66-0.88)
Q4=45.2%-89.4%	0.56 (0.47-0.66)

Table 2.3: Multivariable Cox proportional hazard model with ACS variables with and without interaction term antibody-positive encounters in Orange County, California n=91,165

Table 2.3: Multivariable Cox proportional hazard model with ACS variables with and without interaction term antibody-positive encounters in Orange County, California(n=91,165)

	Model 1 (base model, no interaction) Adjusted Cumulative Hazard Ratio (95% CI)	Model 2 (interaction by quartiles of health insurance and median income) Adjusted Cumulative Hazard Ratio (95% CI)
Gender (coded as binary)		
Female	Reference	Reference
Male	0.93 (0.86-1.01)	0.91 (0.80-1.03)
State of residence		
In California	Reference	Reference
Out-of-state	0.65 (0.45-0.95)	0.75 (0.67-1.73)
Age groups		
<18	Reference	
18-19	0.86 (0.32-2.32)	0.38 (0.09-1.59)
20-29	0.99 (0.47-2.11)	0.55 (0.22-1.37)
30-39	1.35 (0.63-2.86)	0.80 (0.32-1.96)
40-49	1.67 (0.79-3.53)	0.80 (0.33-1.97)
50-59	2.03 (0.97-4.28)	1.06 (0.44-2.56)
60-69	2.28 (1.08-4.80)	1.18 (0.49-2.86)
70-79	2.89 (1.37-6.12)	1.99 (0.81-4.85)
80+	2.39 (1.10-5.19)	1.74 (0.69-4.39)
Estimated median household income by quartile at the census tract level		
Q1 $31,029-53,015	Reference	Reference
Q2 $53,016-$63,339	0.78 (0.67-0.90)	1.02 (0.71-1.46)
Q3 $63,340-$83,289	0.87 (0.74-1.02)	0.83 (0.50-1.36)
Q4 $83,290-$250,000	0.94 (0.78-1.12)	0.44 (0.14-1.42)
Percent health insurance at the census tract level by quartile		
Q1 =70.8%-82.1%	Reference	Reference
Q2=82.2%-87.7%	1.02 (0.90-1.16)	0.53 (0.34-0.83)
Q3=87.8%-92.1%	1.05 (0.92-1.20)	1.23 (0.79-1.90)
Q4=92.2%-100%	1.36 (1.19-1.57)	1.46 (0.98-2.18)

Percent with government health insurance at the census tract level		
Q1=13.9%-28.5%	Reference	Reference
Q2=28.6%-36.8%	0.85 (0.77-0.95)	0.88 (0.79-0.98)
Q3=36.9%-45.1%	0.76 (0.66-0.88)	0.84 (0.73-0.96)
Q4=45.2%-89.4%	0.56 (0.47-0.66)	0.59 (0.50-0.70)
Interaction between median income and % government health insurance by quartile		
Q2 $53,016-$63,339*Q2=82.2%-87.7%	-	1.22 (0.89-1.68)
Q2 $53,016-$63,339*Q3=87.8%-92.1%	-	1.26 (0.89-1.79)
Q2 $53,016-$63,339*Q4=92.2%-100%	-	2.48 (1.30-2.75)
Q3 $63,340-$83,289*Q2=82.2%-87.7%	-	1.06 (0.72-1.55)
Q3 $63,340-$83,289*Q3=87.8%-92.1%	-	1.30 (0.87-1.95)
Q3 $63,340-$83,289*Q4=92.2%-100%	-	1.88 (0.97-3.65)
Q4 $83,290-$250,000*Q2=82.2%-87.7%	-	0.43 (0.26-0.72)
Q4 $83,290-$250,000*Q3=87.8%-92.1%	-	0.52 (0.36-0.75)
Q4 $83,290-$250,000*Q4=92.2%-100%	-	1.02 (0.56-1.89)
Observations	91,165	91,165

Table 2.4 Stratified cumulative hazard ratios of an undetectable viral load among HCV antibody-positive encounters in Orange County, California

Table 2.4 Stratified cumulative hazard ratios of an undetectable viral load among HCV antibody-positive encounters in Orange County, California	Younger than 65 Adjusted Cumulative Hazard Ratio (95% CI) (n=74,136)	Over 65 Adjusted Cumulative Hazard Ratio (95% CI) (n=17,029)
Gender (coded as binary)		
Female	Reference	Reference
Male	0.88 (0.80-0.97)	1.07 (0.92-1.23)
State of residence		
California	Reference	Reference
Out-of-state	0.31 (0.20-0.50)	2.85 (1.56-5.18)
Estimated median household income (from 2017 ACS data)		
Q1=$31,029-$53,014	Reference	Reference
Q2 $53,015-$63,339	0.95 (0.81-1.13)	0.97 (0.74-1.28)
Q3 $63,340-$83,289	0.93 (0.77-1.12)	1.20 (0.91-1.58)
Q4 $83,290-$250,000	1.02 (0.83-1.27)	1.50 (1.14-1.97)
Quartiles of percent insurance		
Q1=71.3%-82.0%	Reference	Reference
Q2=82.1%-87.7%	1.12 (0.97-1.29)	0.73 (0.35-0.63)
Q3=87.8%-92.1%	1.08 (0.93-1.26)	0.63 (0.39-0.75)
Q4=92.2%-100%	1.40 (1.19-1.66)	0.39 (0.22-0.62)
Quartiles of percent government health insurance		
Q1=11.1%-28.6%	Reference	Reference
Q2=28.6%-36.8%	0.93 (0.82-1.06)	0.48 (0.36-0.66)
Q3=36.9%-45.1%	0.88 (0.75-1.04)	0.79 (0.57-1.08)
Q4=45.2%-89.4%	0.67 (0.55-0.81)	0.74 (0.52-1.05)
Observations	74,136	17,029

RESEARCH CHAPTER 3: ENHANCED SURVEILLANCE USING A RETROSPECTIVE COHORT STUDY OF HEPATITIS C DIAGNOSIS AMONG ANTIBODY-POSITIVE CASES USING ELECTRONIC MEDICAL RECORDS.

Abstract

Before the COVID-19 pandemic, Hepatitis C disease (HCV) was the most infectious disease in Orange County, California. All HCV antibody positives were reported to the state; however, public health surveillance data does not capture comorbidities or health behaviors, including smoking history or intravenous drug use. This research seeks to understand how insurance status and other sociodemographic factors related to hepatitis C diagnosis in electronic medical records (EMRs) in a large teaching hospital in Orange County, California.

Methods

Using an electronic medical record (EMR) chart review, 521 medical records from the University of California medical center reported as HCV antibody-positive were analyzed. Bivariable, multivariable, and stratified multivariable regressions were performed to examine associations between predictors and HCV diagnosis.

Results

In a multivariable logistic regression with HCV diagnosis as the dependent variable, those that were ages 65 and older, compared to those who were younger (adjusted odds ratio (AOR)= 1.64 (95% CI=0.96-2.78; those who had private insurance (AOR=3.64 (1.14-11.64)) or government insurance AOR=5.61 (2.00-15.71) compared to no insurance, and current and former smokers compared to never smokers (AOR=1.86 (1.02-3.40), and 2.83 (1.58-5.07) were more likely to have higher odds of HCV diagnosis.

Conclusion

Only 22 percent of those who tested HCV antibody-positive were diagnosed as having HCV in their EMR. This indicates an alarming loss of follow-up and an inability to link patients to care with an opportunity to improve outcomes. Future research should examine barriers to HCV diagnosis and treatment. This research should inform policies ensuring that those without insurance can access HCV treatment and prevent further liver disease or liver-related mortality.

Introduction

In 2017, The Centers for Disease Control and Prevention reported that the hepatitis C virus (HCV) infected over 143,000 individuals in the United States. HCV Incidence rates have steadily increased since 2013.[3] Hepatitis C diagnosis is now more critical than ever as the United States Preventive Services Task Force (USPSTF) updated its screening guidelines in March 2020 to test everyone ages 18 to 79 regardless of risk factors.[80]

HCV (HCV) is an infectious disease caused by the HCV virus, leading to chronic liver disease and mortality in patients without treatment.[3,5-7] HCV is generally transmitted by infected blood exposures, sexual fluids, or from mother to child.[5] Some people are infected with HCV without showing symptoms and could infect others without knowing, causing a silent public health crisis. HCV has a variable Reproductive Rate (R0) ranging from 1.92 to 3.96 among high-risk populations such as injection drug users. This reproductive rate indicates that every infected individual could infect up to 4 susceptible individuals at risk.[5-7,11] If left untreated, HCV can lead to severe sequelae, including liver fibrosis, liver cancer, and liver-related mortality.[5-7] Those at increased risk for HCV include those over the age of 65, veterans, people who inject drugs (PWID), veterans, and those living with HIV.[3,5,14,63,108]

HCV Diagnosis and care cascade

One of the challenges with HCV diagnosis is linkage to care and treatment following the care cascade.[59] The key to getting patients into treatment is diagnosing them with two different laboratory test tests confirming active HCV infection. The recommended diagnosis procedure begins with an HCV antibody enzyme-linked immune absorbed assay (ELISA) test and a viral load test.[61,62] Antibody testing alone cannot determine current infection, which must be confirmed using the RNA viral load test. [56] A study in 2013 in New York City noted that one-third of patients using surveillance records did not get complete testing for HCV, with both an antibody and viral load test.[124]

Despite its potential sequelae and asymptomatic nature, HCV is treatable and curable using highly effective (estimated at 95%) direct-acting antiviral medications (DAAs), which were FDA approved in 2014.[51,54,64-72,119] These medications are vastly improved compared to previous interferon-based medications, which had many side effects and did not actually clear the virus from the patient. [51,54,64-72,119] One of the greatest barriers to using DAAs is their overall cost which can range up to $100,000. [79,92,93] Expensive treatment costs may exacerbate existing social inequalities between patients regarding who can afford these medications and get treatment. [94]

Significance

As discussed earlier, public health surveillance data does not show the intricacies of the care cascade. Electronic medical records, required by law in 2014,[125] often provide more information such as comorbidities, type of insurance, smoking, and injection drug use.[101]

[101]The care cascade for HCV is complicated, and patients falling out of that care cascade may not receive or interrupt treatment. Electronic Medical Record (EMR) data can help show some of the nuances that surveillance data does not capture, including insurance status, comorbidities, prescriptions, and smoking and drug use.

Aims

This research seeks to understand how insurance status and other sociodemographic factors related to HCV diagnosis among HCV antibody-positive patients using electronic medical records (EMRs) in a large teaching hospital in Orange County, California,

Sample description

From January 2010 to March 2020, 743 individual medical records from the California Reportable Disease Information Exchange (CalREDIE) originated from the University of California, Irvine Medical Center (UCIMC). Out of the 743 records, only 521 were downloaded and analyzed.[2]

A visual description is found in figure 5.1

Methods and Data Sources

Participants

Descriptive characteristics of the sample appear in Table 1.1. This research received approval from the Institutional Review Boards of the University of California, Irvine protocol HS # 2019-548 and the Orange County Health Care Agency.

Measures

We measured the previous history of HCV infection by extracting data from the UCIMC database for patients assigned to the Orange County Health Care Agency who tested positive using an HCV antibody test. If the home address for the case was not in California, the case was out-of-state. Statistical analysis of these data included frequencies, measures of central tendency, bivariable multiple logistic regression, multivariable multiple logistic regression, chi-square tests, and additional *post hoc* analyses.

The dependent variable was HCV diagnosis with a viral load test. We defined this in one of two ways first, if it was a problem in the “problem list” drop-down text field of the EMR. Second, in

[2] Records unable to be obtained included 33 records were restricted for chart review or had a “break the glass warning” by UCIMC which were unobtainable, 4 were duplicates, and 183 surveillance records did not have an EMR associated with the patient.

the registries portion of the medical record, where a patient was defined as part of the "HCV registry" in the registry field, which indicated a positive diagnosis.[3]

Independent variables included insurance status (recoded into three categories: no insurance listed, government insurance (either Medicare, Medicaid, TRICARE), or private insurance. The patient's age was defined as it was in the chart when it was pulled. HCV treatment (when the medications list included HCV). Intravenous drug use (indicated in the chart) Emergency room visits were coded (when there is no insurance listed and nothing on the problems list. Smoking status (as indicated in the chart) and opioid treatment (indicated in the chart or their medications.) Comorbidities were indicated in the chart and coded using string matching. Comorbidities included heart disease, stroke, cancer, cirrhosis, and diabetes. The data were analyzed using Stata version 13 (StataCorp, College Station, TX).

Results

A detailed table of demographic statistics of the individuals is in table 3.1. As of November 2020 (when EMRs were extracted), 7.29 percent of all patients were deceased, and 92.71 were still alive when the chart was pulled. The sample was 63 percent male and 35 percent female, with approximately 2 percent identifying as transgender or genderqueer.

In terms of insurance, most patients were on Medicaid only (36.08 percent). Nearly 30 percent did not have any insurance noted on their chart. Another 16.89 percent were on Medicare and Medicaid, and eight percent were on private insurance only.

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[3] All of these patients were reported to CalREDIE as a positive hepatitis C antibody test and considered a probable, suspected, or confirmed case assigned to Orange County, California. However, an antibody positive test in CalREDIE does not measure active hepatitis C infection and does not mean they are diagnosed with hepatitis C as a viral load test of >20 copies/ml in addition to the antibody test is needed for a diagnosis. Association of Public Health Laboratories. Interpretation of Hepatitis C Virus Test Results: Guidance for Laboratories. Silver Spring, MD 2019.

Insurance was coded into broader categories for analysis and to avoid small cell sizes to maintain the power of the regression. In this sample, 29.75 percent had no insurance, 56.81 had some sort of government insurance (Medicare, Medicaid, or TRICARE) only 13.44 had private insurance or other coverage (that was not one of the previously stated services). Out of 521 patients, only 116 (22.26%) were diagnosed with HCV, as noted in their chart.

Multivariable logistic regression results

In a multivariable regression with HCV diagnosis as the dependent variable, (table 3.2) binary predictors included: over 65, insurance status, and smoking status: When over 65 was used as a binary covariate, it was still statistically significant Odds ratio (OR)=1.64, government insurance (OR=5.61, 95% CI 2.00-15.70) and private insurance (3.64, 1.14-11.64) when compared to no insurance. Among ever smokers, former smokers OR=2.78 (95% CI 1.56-4.98) and current smokers (OR compared to nonsmokers were statistically significant.

In a multivariable logistic regression with government insurance as a binary variable: (no government insurance vs. government insurance those with government insurance had higher odds of HCV diagnosis compared to no insurance (table 3.3.) Compared to those without government insurance, those with government insurance had an odds ratio of 2.36, 95% CI is 1.35-4.13, with current smokers and former smokers both having higher odds of 1.86 (1.02=3.40) and 2.83 (1.58-5.97) respectively. Among those who are under 65, it is not statistically significant; however, current and former smokers compared to never smokers were still statistically significant.

While significant at the bivariable level, intravenous drug use, emergency room visits, and opioid treatment were not significant in multivariable regression.

Stratified regressions

We stratified the regressions by age group (table 3.4) because the two samples, ages 65 and older and under 65, were statistically significantly different from each other. [126] in a chi-squared test with 1 degree of freedom with those who were 65 and over and those who were younger and HCV diagnosis, there was a chi-squared value of 6.61, which was statistically significant at p=0.01.

In a stratified regression among those who are under the age of 65, patients with government insurance had 3.41 times higher odds of being more likely to get diagnosed with HCV (95% CI 1.16-10.00) compared to patients with no insurance. Current smokers OR=2.68 (95% CI 1.27-5.67) and former smokers OR=4.74 (95% CI 2.16-10.42) had higher odds of being diagnosed compared to never-smokers

In a stratified regression with those over 65, none of the coefficients were statistically significant. Only 12 percent of those over 65 did not have any insurance, so the statistical package omitted them in this regression. In this regression, government insurance compared to no insurance is not statistically significant as government insurance positively correlated with being over 65. Among those 65 and over, those with government insurance had odds that were 4.20 times higher (95% CI is 1.31-13.43); however, smoking status is no longer statistically significant.

Discussion

In this subsample of HCV antibody-positive patients at UCIMC in Orange County, California, we found that those who were 65 and older had government insurance or private insurance compared to no insurance and had higher odds of HCV diagnosis than those without insurance. In addition, ever smokers, comprised of current and former smokers compared to never-smokers, had higher odds of being diagnosed with HCV.

At the time of writing, there appears to be a dearth of literature looking at EMRs and HCV diagnosis; however, many studies examined EMRs and initial screening. In a study by Kasting et al.,[127] they found that those with Medicaid, Medicare, military, and others were less likely to be screened compared to private insurance for average risk baby boomers between 2015 and 2017. The researchers found that patients with a Medicare supplement had the highest odds of screening.

A similar endpoint to HCV diagnosis in a large population can be seen in studies looking at DAA treatment uptake among those who are HCV-Positive. [55,128-132] Other studies indicated that there were significant disparities in access to DAA treatment for HCV. Researchers found lower treatment uptake among those with Medicaid/state insurance, under the age of 45, and Hispanic/Latino individuals. [133]

Only five patients in this sample of 521 had a record of receiving the DAA Mavryet in this sample. A similar study looking at the uptake of DAAs in 4 metropolitan areas found similar results with those who were enrolled with Medicaid compared to privately insured patients and that behavioral factors such as drug abuse, alcohol use, and smoking were associated with a lower likelihood of DAA uptake.[128,130]

early 30 percent of this sample (n=155) did not have health insurance noted in their chart, which is a notable barrier to HCV diagnosis and treatment.[134-136] Javanbakht et al.[134] found that prior insurance authorization for HCV treatment is one of the most significant barriers to initiating HCV treatment, particularly shorter eight-week course treatments. [134] A review by Shehata et al. l found similar results that among providers, the cost of testing, lack of health insurance, stigma and discrimination, and lack of knowledge and low perceived risk of infection were the greatest barriers to treatment across many studies in the United States, United Kingdom, Canada, and other countries. [137]

The strengths of this analysis are the attributes of this dataset and how it augments the data routinely collected by CalREDIE as part of public health surveillance. We can see the comorbidities for each patient, information on drug use, and also have information on what insurance paid for the hospital visit or if there was no insurance at all. Previous analysis used the surveillance data from CalREDIE, which had limited information at the patient level. Generally, surveillance data is quite limited and does not include comorbidities or other problems. It also shows what types of medications the patient is taking. In general, the sicker patients who seem to get care more regularly are more likely to be diagnosed.

Limitations

There are a number of limitations to this study. Limitations of this data include the following: first, these UCIMC medical records are only a small subsample of the over 33,000 cases of antibody-positive HCV in Orange County from 2010 to 2020. This data may also not be generalizable to other settings and counties in the United States or the state of California. UCIMC is a large public teaching and research hospital, which makes it unique compared to other health care settings in the county, such as private hospitals.

There also may be some selection bias in patients going to UCIMC who may be fundamentally sicker than other HCV antibody-positive patients because of UCIMC's research and academic nature. In addition, this subsample could be fundamentally sicker than the general population introducing some bias.[138] In addition, medical records from a hospital setting with many indicated ER visits resulted in incomplete chart data such as smoking status, comorbidities, and current medications. Over 30 percent of the sample did not have their smoking status assessed in their chart, which may grossly underestimate the smoking status of these patients. Only the chart snapshots were able to be downloaded, so it is unclear to see if those individuals were indeed viral load tested in their chart or when exactly they were diagnosed with HCV.

Implications

This paper examines the risk of Hepatitis C, a treatable and curable infection, in a large teaching hospital, augmenting existing routinely collected public health surveillance data, with less than 1 percent of all patients receiving treatment highlighting opportunities for improvement. In this sample, HCV diagnosis is far higher among patients with government insurance than no government insurance, indicating the need to reach out to patients with no insurance.

This research helps conduct enhanced public health surveillance to better target individuals (those born outside of 1945-65, those with private insurance) who may miss being diagnosed

In this sample of 521 patients, only 22 percent of those with a positive HCV antibody test were diagnosed with HCV, meaning that there may be undetected individuals who are asymptomatic and infectious and potentially spread the virus to others. Unfortunately, the care cascade was not continued as not all patients had a follow-up viral load test and treatment evaluation and were lost to follow-up. This may be because patients would need to see a specialist or come back for a second laboratory test. These findings have important policy implications for HCV in a large academic research hospital that has many emergencies room visits with missing sociodemographic data and nearly a third of the sample without health insurance. The gap must be bridged for those without health insurance to get diagnosed with HCV and get treated and cured to avoid further health complications such as liver cancer and liver-related mortality and potentially spreading the infection to others without knowing it. We are unable to track patients through this care cascade and found that less than 1 percent of this entire sample (n=5) received

HCV treatment in their chart. Eleven percent of people were lost to follow-up. Unfortunately, the high numbers of reported HCV cases in the county even before the COVID-19 pandemic made it inefficient to conduct contact tracing and get individuals into care, leaving it to primary care providers to diagnose them and initiate the care cascade.

This dataset has additional covariates that may aid county health departments in performing enhanced surveillance at hospitals that receive many high-risk patients and ensure that everyone diagnosed with HCV can have access to treatment. Future research should look at more individual data and perhaps key informant interviews with HCV-positive patients and providers to better understand barriers to diagnosis and treatment, and finally, to make sure that those without insurance can get the treatment to cure this infection and prevent further progression of liver disease or liver-related mortality.

Declarations

Ethics approval and consent to participate:

This research was approved by the Institutional Review Boards of the University of California, Irvine protocol H.S. # 2019-548 and the Orange County Health Care Agency (Research Project 2020-03). No consent was obtained as this is routinely collected public health data.

Consent for publication:

not applicable

Statement of Permission

As part of routine infectious disease surveillance under California State Health Code Title 17 a §2500, §2593, §2641.5-2643.20, and §2800-2812 Reportable Diseases and Conditions. This data is collected regularly and may be used for enhanced surveillance. Ms. Goodman's role as an intern epidemiologist at the Orange County Health Care Agency, the director of the communicable disease control branch, Dr. Matthew Zahn (a co-author on this paper), through the California Department of Public Health granted permission for Ms. Goodman to use this anonymized data for analysis as part of her doctoral dissertation. See attached documentation from the Orange County Health Care Agency IRB application and approval letter. In addition, the Orange County Health Care Agency has a data-sharing agreement with the University of California, Irvine Medical, for chart review as it pertains to enhanced public health surveillance.

Availability of data and materials

The data that support the findings of this study are available from the California Department of Public Health CalREDIE data warehouse at the University of California, Irvine Medical Center, but restrictions apply to the availability of these data, which were used under data sharing agreements for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the University of California, Irvine Medical Center, and the California Department of Public Health (CDPH). UCIMC can be reached by phone at 714-456-3333 (Orange) / 949-824-3434 (Irvine)CDPH can be reached by phone or email: Point of contact: +1 866-866-1428 or CalREDIEHelp@cdph.ca.gov.

Competing interests

There are no competing interests to report in this paper

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Authors' Contributions: SG was responsible for extracting and coding the data, performing the analysis, drafting, and writing the manuscript. MZ provided technical expertise, BBA and CL also provided technical and writing advice for this manuscript.

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Table 3.1: Demographic Characteristics of HCV antibody-positive patients at UCIMC from 2010 to 2020

Table 3.1: Demographic Characteristics of HCV antibody-positive patients at UCIMC from 2010 to 2020 (n=521)		
10-year age categories	**N**	**Percent**
20-29	52	9.98
30-39	92	17.66
40-49	64	12.28
50-59	120	23.03
60-69	124	23.8
70-79	49	9.4
80+	20	3.84
Total	521	100
Health insurance	**N**	**Percent**
No insurance	155	29.75
Government insurance	296	56.81
Private insurance/other	70	13.44
Total	521	100
Gender	**N**	**Percent**
Female	183	35.12
Male	328	62.96
Transgender/genderqueer	10	1.92
Total	521	100
Mortality	**N**	**Percent**
Alive	483	92.71
Deceased	38	7.29
Total	521	100
Hepatitis C diagnosis in the chart?	**N**	**Percent**
No	405	77.74
Yes	116	22.26
Total	521	100
ER Visit due to missing chart data and no insurance	**N**	**Percent**
No	462	88.68
Yes	59	11.32
Total	521	100
Smoking status	**N**	**Percent**
Non-smoker	146	28.02

Current smoker	123	23.61
Former smoker	99	19
Never assessed	153	29.37
Total	521	100

Prescribed hepatitis C treatment	**N**	**Percent**
No	516	99.04
Yes	5	0.96
Total	521	100

Intravenous Drug use noted in the chart	**N**	**Percent**
No	448	85.99
Yes	73	14.01
Total	521	100

Opioid treatment	**N**	**Percent**
No	490	94.05
Yes	31	5.95
Total	521	100

Heart disease	**N**	**Percent**
No	468	89.83
Yes	53	10.17
Total	521	100

Hypertension	**N**	**Percent**
No	381	73.13
Yes	140	26.87
Total	521	100

Cirrhosis	**N**	**Percent**
No	457	87.72
Yes	64	12.28
Total	521	100

Diabetes	**N**	**Percent**
No	434	83.3
Yes	87	16.7
Total	521	100

Any cancer	**N**	**Percent**
No	445	85.41
Yes	76	14.59
Total	521	100

Stroke	N	Percent
No	495	95.01
Yes	26	4.99
Total	521	100

Table 3.2: Multivariable logistic regression of Hepatitis C diagnosis in EMR among HCV antibody-positive patients at UCIMC on explanatory variables

Table 3.2: Multivariable logistic regression of Hepatitis C diagnosis in EMR among HCV antibody-positive patients at UCIMC on explanatory variables (n=521)

Age group (binary)	
Younger than 65	Reference
Over 65	1.64 (0.96-2.78)
Health insurance	
No Insurance	Reference
Government Insurance	5.61 (2.00-15.71)
Private insurance/other	3.64 (1.14-11.64)
Smoking Status	
never smoker	Reference
current smoker	1.91 (1.04-3.51)
former smoker	2.78 (1.56-4.98)
never assessed	0.40 (0.15-1.10)
Constant	0.05 (0.02-0.14)
Observations	521

Table 3.3: Multivariable logistic regression Hepatitis C diagnosis in chart among HCV antibody-positive patients at UCIMC with government insurance coded as binary

Table 3.3: Multivariable logistic regression Hepatitis C diagnosis in chart among HCV antibody-positive patients at UCIMC with government insurance coded as binary (n=521)	
Age group	Adjusted OR AOR, (95% CI)
Younger than 65	Reference
Over 65	1.70 (1.00-2.88)
Health Insurance	
No government insurance	Reference
Government health insurance	2.36 (1.35-4.13)
Smoking Status	
Never smoker	Reference
current smoker	1.86 (1.02-3.40)
Former smoker	2.83 (1.58-5.07)
never assessed	0.25 (0.10-0.65)
Constant	0.11 (0.06-0.21)
Observations	521

Table 3.4: Side by side comparison of stratified and unstratified Multivariable logistic regression of Hepatitis C diagnosis in chart among HCV antibody-positive patients at UCIMC on explanatory variables

Table 3.4: Side by side comparison of stratified and unstratified Multivariable logistic regression of Hepatitis C diagnosis in chart among HCV antibody-positive patients at UCIMC on explanatory variables

Unstratified Multivariable logistic regression of Hepatitis C diagnosis in EMR on explanatory variables (same as table 3.2)		Stratified Multivariable regression of Hepatitis C diagnosis in the chart on explanatory variables	
	Unstratified N=521	Under 65 n=401	65 and Older n=101
Age group	Adjusted OR (AOR), (95% CI)	Adjusted OR (AOR), (95% CI)	Adjusted OR (AOR), (95% CI)
Younger than 65	Reference	-	-
Over 65	1.64 (0.96-2.78)	-	-
Health insurance			
No Insurance	Reference	Reference	Reference
Government Insurance	5.61 (2.00-15.71)	3.41 (1.16-10.00)	2.26 (0.67-7.64)
Private insurance/other	3.64 (1.14-11.64)	2.91 (0.85-10.00)	1.00 (0.00-0.00)
Smoking Status			
never smoker	Reference	Reference	Reference
current smoker	1.91 (1.04-3.51)	2.68 (1.27-5.67)	1.39 (0.28-7.01)
former smoker	2.78 (1.56-4.98)	4.74 (2.16-10.42)	1.35 (0.54-3.37)
never assessed	0.40 (0.15-1.10)	0.32 (0.08-1.30)	0.72 (0.16-3.14)
Constant	0.05 (0.02-0.14)		
Observations	521	401	101[4]

[4] Sample size dropped from 521 to 502 as some observations were dropped due to missing data.

CHAPTER 4: DATA CONSTRAINTS AND LIMITATIONS

Data Constraints

As mentioned in the introduction, education, race/ethnicity, and socioeconomic status are generally associated with HCV infection. However, there are many missing covariates that we cannot account for in the data. Gender is coded as binary because the number of those who are transgender or of unknown gender was too small of a sample leading to small cell sizes and breaking those assumptions for categorical analysis such as chi-squared tests. From 2014 to 2016, up to 84 percent of the race/ethnicity data is missing. If race/ethnicity is not volunteered by the patient, could this be a bias if someone else (not the person themselves) defines it. I do not know how it works in these databases. This level of missingness is too high for multiple imputations to estimate these groups in the dataset. Though laboratories are required to submit electronic lab reports, they often do not get information on these sociodemographic characteristics that impact health and leave only the most essential information. The state of California is required by law to collect these data; however, race/ethnicity, address, and other covariates are not required.

If there is going to be no contact tracing of HCV antibody-positive cases, we could take the state-mandated data collection and analyze it and match it with other data sources. These data sources could include United States Census Bureau data and American Community Survey data. This joined dataset helps researchers gain a better understanding of the representativeness of our study population. Surveillance data, by its very nature, is messy; however, analyzing these large datasets may be the only way to determine risk factors at a county level and test hypotheses before launching a more in-depth survey targeting certain groups (race/ethnicity, geographic area, etc.) to collect individual data on social determinants of health. Surveillance data itself is imperfect, and it depends on who is collecting the data (primary care providers, public health nurses, electronic lab reports). Errors and omissions of data points can occur along the way, and there is no good way to keep track of it. It was very difficult to match the data from the public health surveillance database and EMRs. I only had access to the UCIMC EMR system, which may induce bias compared to the many other hospital systems in Orange County.

One of the other issues is matching the public health surveillance data to the American Community Survey data from the United States Census Bureau. This can result in the ecological fallacy, which implies that the census tract level of median household income and percentage of health insurance coverage can be falsely projected onto the individual. Census tracts can be small enough to infer from; however, there may be some bias there. Also, it is not clear that all of the addresses are accurate. There may be those who did not put an address, and the address listed is the one where they tested. In addition, those in substance use rehabilitation facilities or those without housing may not be accurately captured by this dataset.

Limitations related to using surveillance data for secondary analysis

Some of the limitations related to using surveillance data for secondary analysis are described below. The missing covariates in surveillance data do not capture or indicate information relevant to HCV infection risk. These risk factors include (e.g., race, employment), occupation, individual insurance providers, persons in incarceration settings, previous history of incarceration, or risk behaviors such as injection drug use or those without homes. We cannot examine if these groups with increased vulnerability indeed have an increased risk of contracting HCV.[3,14] Those with less access to health care and lower incomes are less likely to be tested, diagnosed, or have an undetectable viral load, widening the gap of those who are unable to pay for expensive DAA medications. One issue is that these missing data may not allow us to determine at-risk groups who are not captured in the database because they are not being tested. The only people in this report are those who tested antibody-positive for HCV. In addition, we do not have a true denominator, as we do not have the information on those who tested HCV antibody-negative. The inability to categorize and analyze these higher-risk populations from public health surveillance data alone may lead to an underestimation of socioeconomic characteristics on the likelihood of undetectable viral load, viral load testing, and HCV diagnosis. Another limitation is that we only have data from one county in one state and that there may be implied bias because of the over 400 substance use rehabilitation facilities, which may be inflating the numbers compared to other geographic locations. In order to complete the picture of the disease burden of HCV in Orange County, multiple data sources must be used to provide enough information for each patient to better understand sociodemographic factors of infection. Despite these limitations, this dataset over many years and a large sample size provide an improved insight into HCV infection in Orange County than ever before. Similar methods to this research could be used to evaluate the HCV burden in counties of similar size (approximately 3 million) and with similar demographics (large Asian/Pacific Islander and Hispanic populations) Although these data have many weaknesses, including missing race/ethnicity, missing occupation information, may not be externally generalizable outside of Orange County, and the inability to capture all at-risk individuals in this County, there is so much to gain from these data. The strength of these datasets is that we have a large sample size (over 27,300). These data were further joined to census tracts providing us with a large enough statistical power to make inferences about the data. We also have a lot of individual patient information from the EMRs that we would not generally have with surveillance data alone. These covariates include comorbidities, insurance payer/type, history of injection drug use, and what medications they were taking. This research is only the beginning and can help inform future survey questions and public health information to make informed policies and procedures to better test and diagnose HCV in Orange County.

CHAPTER 5: CONCLUSIONS

This dissertation research found that, in general, there is an association between HCV testing and diagnosis with sociodemographic factors. Those who are likely to be viral load tested include those who are over the age of 65, and individuals in Orange County census tracts that have increased insurance coverage, suggesting that those who are viral load tested are more likely to afford Hepatitis C (HCV) treatment. This research provides a better understanding of sociodemographic factors leading to viral load testing. This research is unique as it uses county-level surveillance data and integrates it with existing census tract data, and can be applied to future public health interventions in similar county settings.

The second research chapter examined individuals who had an undetectable viral load (a surrogate measure for Sustained Virologic Response (SVR) as per the data constraints). Those over 65 were more likely to have an increased hazard of an undetectable HCV viral load relative to younger adults (HR =2.00). Residents of Orange County census tracts in the third and fourth quartiles of percent enrollment in health insurance showed a greater likelihood of undetectable viral load (HR=1.36). The interaction term or moderating effect of higher tract median household income and higher tract levels of health insurance were more likely to have undetectable viral load and was statistically significant. The extent to which constraints impede HCV care requires further investigation, including follow-up studies on health insurance type to test the relationship of health insurance type to undetectable viral load.

The third research chapter examined a subset of these cases using 521 electronic medical records (EMRs) at the University of California, Irvine, Medical Center (UCIMC). Only 22 percent of those who were reported to the state as being HCV antibody-positive indicated an HCV-Positive diagnosis in their EMR. Less than one percent of patients (n=5) were prescribed HCV treatment, indicating a lack of linkage to care. Those that were ages 65 and older, compared to those who were younger (adjusted odds ratio (AOR)= 1.64 (95% CI=0.96-2.78; those who had private insurance (AOR=3.64 (1.14-11.64)) or government insurance AOR=5.61 (2.00-15.71) compared to no insurance, and current and former smokers compared to never smokers (AOR=1.86 (1.02-3.40), and 2.83 (1.58-5.07) were more likely to have higher odds of HCV diagnosis. These findings indicate an alarming loss of follow-up and an inability to link patients to care with an opportunity to improve outcomes.

HCV is a public health problem that can indeed be solved. Orange County, California, offers a unique setting to address the issues of testing and treatment of HCV. The county has a large and diverse population. In addition, it has a large substance use rehabilitation tourism industry that treats a large number of intravenous drug users. This research allows public health professionals to see where interventions could be done to help eliminate HCV in the county and reduce liver-related morbidity and mortality. On the national level, a changing political landscape with the election of democrat Joseph R. Biden as president of the United States and an increased interest in public health as a result of the COVID-19 pandemic.[139,140]

HCV prevention can be broken down into three categories: primary, secondary, and tertiary prevention. These interventions would be ideally combined with existing HIV prevention strategies, as coinfection with HIV and HCV is common, and the risk factors are similar; however, unlike HIV, HCV can be cured.[141] Primary prevention is preventing exposure to the pathogen itself.[142] This would involve blood-borne pathogen training to help prevent exposure to hepatitis C in the workplace, how to properly clean up blood spills, and dispose of infected cleaning supplies.

Harm reduction is a significant part of HCV prevention. Syringe services programs (SSPs) or needle exchanges can help prevent sharing needles and provide clean drug preparation equipment.[143] Eckhardt et al.,[143] found that HCV testing, evaluation for treatment, blood draws, treatment adherence support, and medication distribution was integrated into an existing syringe service program, known as an "Accessible Care Program." The researchers found high rates of SVR among people who inject drugs (PWID) across subgroups.[143] Another study in Wisconsin [144] used a randomized clinical trial to integrate HCV prevention into an SSP. Hochstatter et al.[144] used an existing SSP who received a computer-based risk reduction education intervention as well as Narcan training.[144] Another study in New York used a retrospective chart review within an existing SSP to evaluate the uptake of co-located HCV services.[57] They also saw additional benefits of this program, including the initiation of Opioid Use Therapy, transitions from being homeless to having housing, and found approximately 52% of their small sample (n=31) were able to undergo behavior change to increase their psychosocial stability.[57] The researchers found more importantly that SVR rates were not associated with housing status and evidence of opioid use treatment, meaning that psychosocially unstable persons were still able to achieve SVR. [57]

However, SSPs have become quite controversial in Orange County, and their implementation was blocked by a county judge due to concerns about needle refuse and dealing with homeless individuals.[91] In 2021, the presidential administration changed, and policies moved forward. President Joseph R. Biden signed the American Rescue Act, which allocates $30 million dollars to support overdose prevention, SSPs, and other harm reduction interventions. Furthermore, this funding is exempt from the long-standing federal restrictions on the use of federal funds to purchase clean syringes.[145,146]

Secondary prevention involves screening for HCV among all people and intervening earlier in the natural course of the disease to improve outcomes and prevent disease progression to liver fibrosis and hepatocellular carcinoma. Universal opt-out screening means screening all patients for HCV unless the patient elects not to test.[96] This is currently done in large emergency rooms.[147] Universal opt-out HCV screening should be expanded to all primary care hospitals and preventive care visits. This has been done across the United States in previous years with HIV and could be implemented here.[147-149] Opt-out screening would help identify HCV-infected asymptomatic individuals, who make up 45-85% of all cases,[150] and get them into treatment and ultimately cured. The King County Public Health Department in Seattle implemented a successful linkage to care program from 2014 to 2018 to integrate clinical data and laboratory tests into public health surveillance and provide case management to promote linkage to care.[58]

The other important part of HCV screening, besides opt-out testing, is to perform universal reflex testing on all positive antibody samples.[151-153] Reflex testing involves testing the same sample twice: once for HCV antibodies, and if that antibody test is positive, then testing the same sample with a PCR RNA test for HCV viral load.[154] Implementation of reflex testing is challenging because conducting reflex testing requires phlebotomists and a laboratory that is equipped to analyze and store these samples. This is already being done at the University of California, Davis, Medical Center in Sacramento, California, with a total sample size in the intervention period of n=14,981.[155] Internationally, Spain has a robust HCV reflex testing program to measure viral load in HCV antibody-positive patients.[156,157] Another option is offering screening in facilities that see an increased number of patients with higher vulnerability to HCV, such as people who inject drugs (PWID). In 2020 a Substance Abuse and Mental Health Services Administration (SAMHSA) evaluated that only 30.8% of substance use rehabilitation facilities offered screening for HCV.[158] In California, 27.8% of substance use rehabilitation facilities screen for HCV. This is below has less than the national average.[158]

The final form of prevention is tertiary prevention of HCV using medical interventions once a diagnosis is made. Tertiary prevention involves providing medical treatment to those who have been diagnosed with HCV. There are two barriers to tertiary prevention for HCV, which are the cost of DAA medications and the initiation of treatment.

The first tertiary prevention strategy is training non-gastroenterologists/hepatologists to evaluate those who are HCV-Positive and get them on to treatment.[151] The second strategy integrates HCV treatment initiation in Orange County's large substance use rehabilitation facilities. Integrating HCV treatment with substance use rehabilitation facilities has been done before with methadone maintenance facilities,[159-161] and it would be an ideal implementation if patients are already coming several times a week or are there for an extended stay for their opioid substitution therapy. Clinicians can evaluate the patients and help them with medication compliance. [159-161],

The third strategy is to lower the overall costs of HCV drugs. The Veterans Administration Hospitals have made this a priority and made concerted efforts to reduce the cost of HCV direct-acting antivirals for its patients.[162] Other price Initiatives include the 340B drug program among "safety-net" hospitals to help provide Direct-Acting Antivirals (DAAs) at high discounts to entities covered under the 340B program.[163,164] One study estimates that the net cost per patient with the 340B program would be $930 per patient compared to -$370 without.[163] Programs like

340B help increase access; however, they need perpetual government support in order to be maintained.[163]

Other studies call for other methods outside of the 340B program to help lower costs. One study calls for worldwide access to DAA drugs and lowering their overall costs. This involves government negotiation with pharmaceutical companies, licensing practices, patent opposition, joint procurement (where many payers can negotiate prices), and allowing patients to import several months of medication.[136,165]

Another strategy involves ensuring that people living with HCV are insured and have access to medication. In the state of California, HCV medications should be covered by Medicaid,[166] but not everyone is insured by Medicaid,[167] and some people may fall just outside those requirements, making it difficult to pay for the medication they need.[168].

Finally, another strategy borrowed from HIV prevention would be to implement peer navigators to help those who are HCV-Positive get linked to care and get cured.[169-171] These peer navigators would ideally be those who have recovered from HCV and would be able to help answer questions and task-shift some of the responsibilities of clinicians, particularly connections to social services and non-medical resources.[122] These peer navigators would also be able to help people sign up for health insurance and Medicaid. Prisoners are at increased vulnerability for HCV, and many of them do not have health insurance when they are released.[172,173] Peer navigators would be able to help these patients sign up for insurance coverage and be with them throughout their treatment. Peer navigators could benefit from the short treatment time of 8 to12 weeks for HCV and could have multiple patients at once. This strategy could also give individuals such as convicted felons the opportunity to work while helping other HCV patients.

Directions for future research

HCV is a winnable battle in public health and can be solved. This research only provides a small insight into Orange County's HCV problem. Some unanswered questions involve why do patients not enter the care cascade? Why do those who are HCV-Positive not seek treatment? Are there existing barriers such as required substance use abstinence to initiate treatment?[174] Outside of gastroenterology/hepatology or specialty care settings, what are the barriers in primary care to HCV diagnosis and treatment on both the patient side and the facility side? Also, more presciently, how has the COVID-19 pandemic affected HCV and the care cascade in Orange County?

Opportunities for future research include mixed methods studies with HCV care providers to better understand HCV testing, diagnosis, and treatment barriers.[175-177] The same qualitative studies would also be done with HCV-Positive patients to better understand the patient experience and to optimize bottlenecks to HCV diagnosis and treatment. Other ways to better understand clinic and healthcare facility-based bottlenecks could be done using a clinic flow analysis,[178] to identify how patients in that specific facility move through the HCV care cascade and are linked to care in Orange County.[179,180] HCV diagnosis and treatment is something that hospitals and care facilities can measure and report improvements and patient-centered outcomes, making them eligible for service awards, and increased funding for their activities.[103,181,182] Another opportunity for future research would be examining insurance claims data and looking and HCV diagnosis and treatment in larger hospital settings, and hospitals in different states, to find out how each facility is different and what they are doing in terms of best practices to evaluate patients and initiate treatment.

FIGURES

Figure 1.1: A proposed Syndemic model of HCV

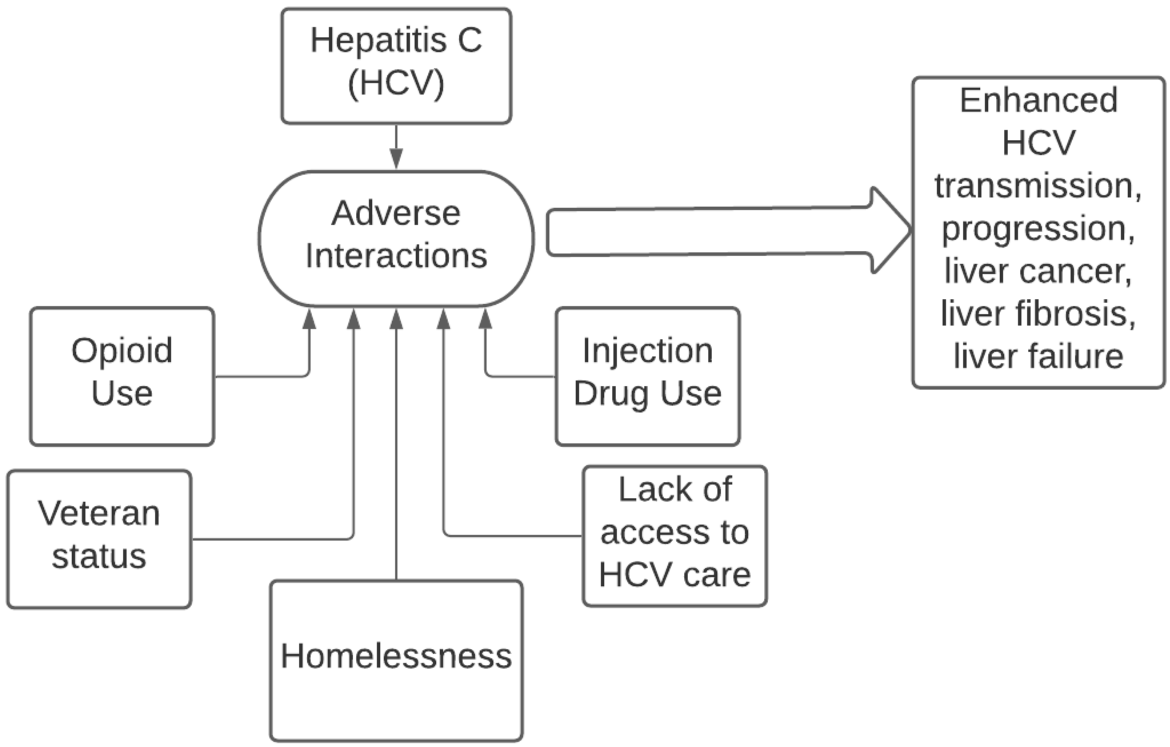
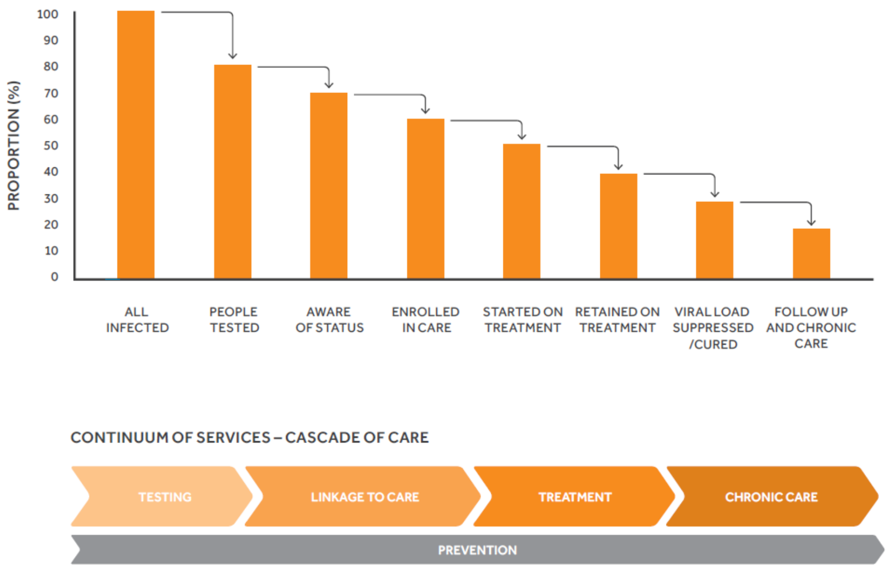
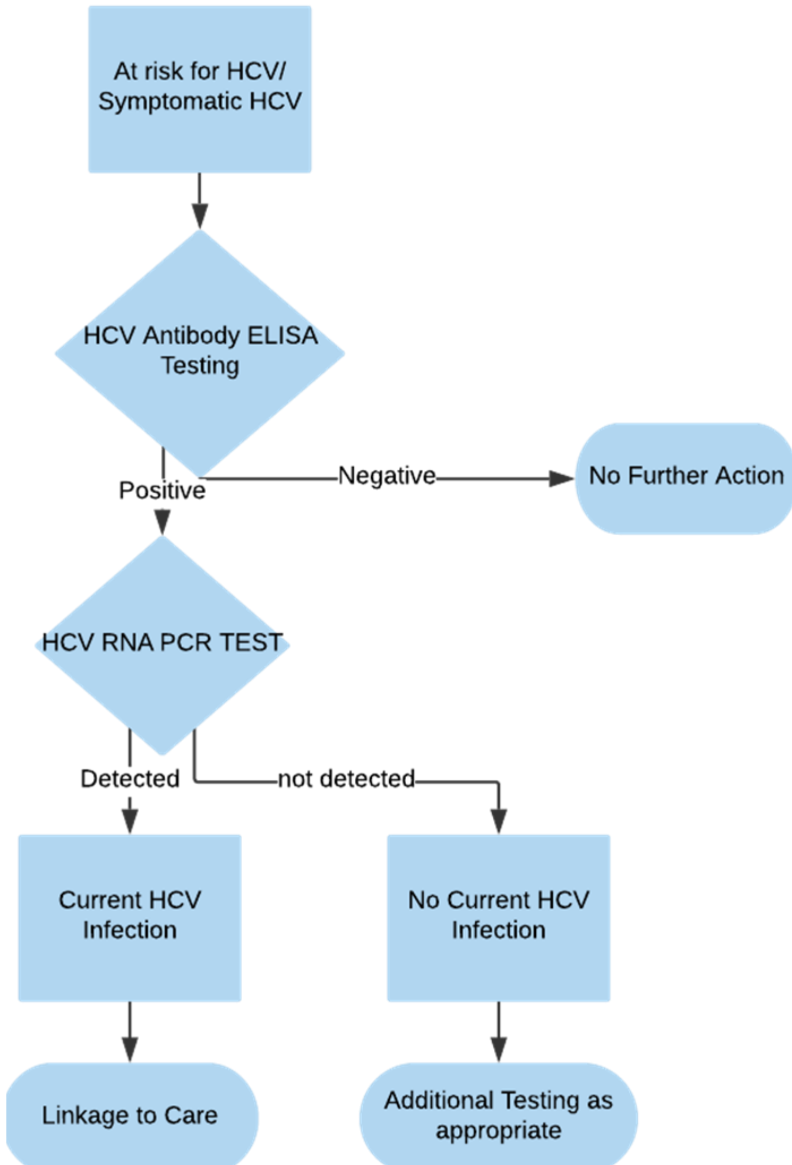


Figure 1.2: WHO Care Cascade



Source: World Health Organization. Global hepatitis report 2017. World Health Organization; 2017.

Figure 1.3: Algorithm for testing for HCV in the United States



Source: United States Department of Veterans Affairs. Viral Hepatitis and Liver Disease: Hepatitis C Screening Flow Chart. 2018; https://www.hepatitis.va.gov/hcv/screening-diagnosis/screening-algorithm.asp. Accessed June 1, 2019.

Figure 2.1 – A conceptual model of sociodemographic correlates of HCV viral load testing in Orange County, CA using public health surveillance data

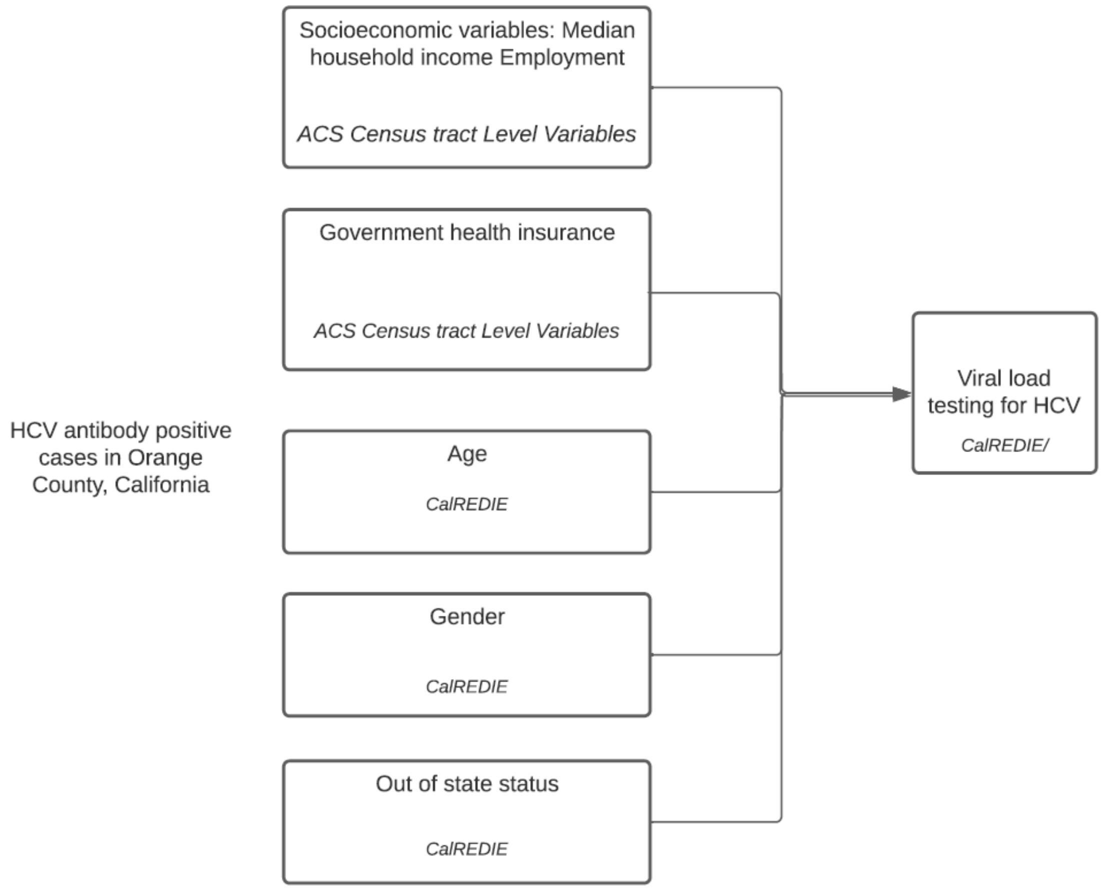


Figure 2.2 – A conceptual model of sociodemographic correlates of evidence of undetectable viral load in Orange County, CA, using public health surveillance data

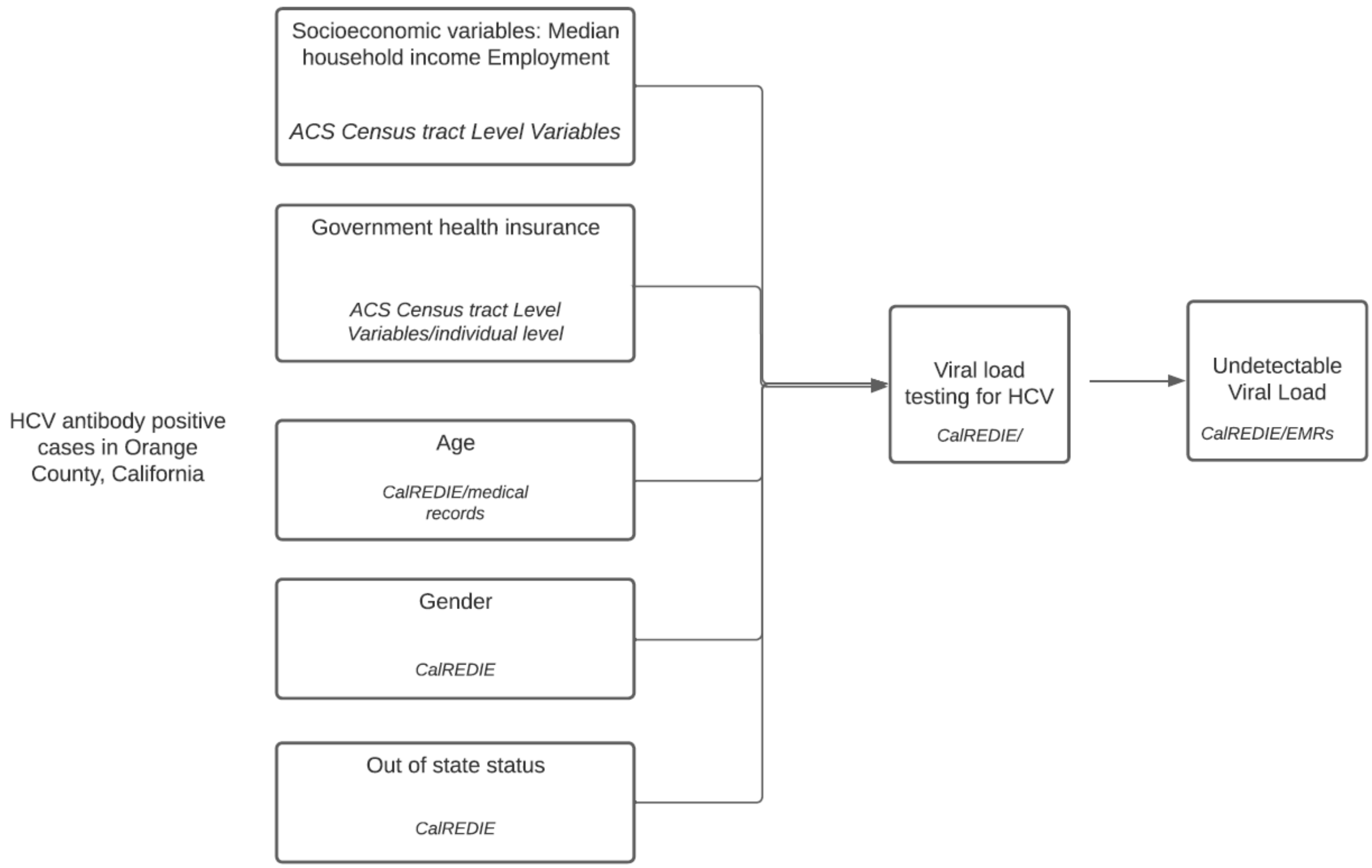


Figure 2.3 – A conceptual model of enhanced surveillance of hepatitis C diagnosis among antibody-positive cases using electronic medical records

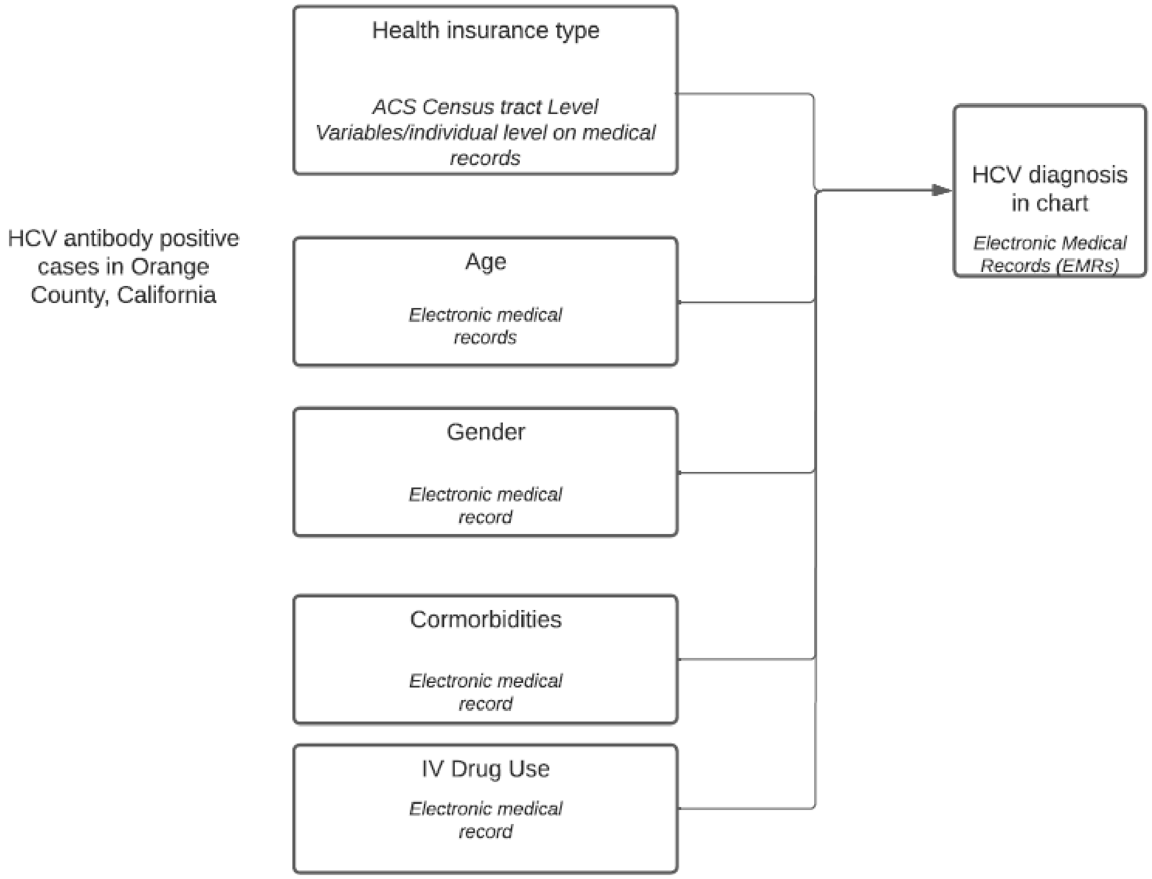


Figure 3.1: Sample description of those who tested for HCV Viral load from CalREDIE and could be joined to census tracts.

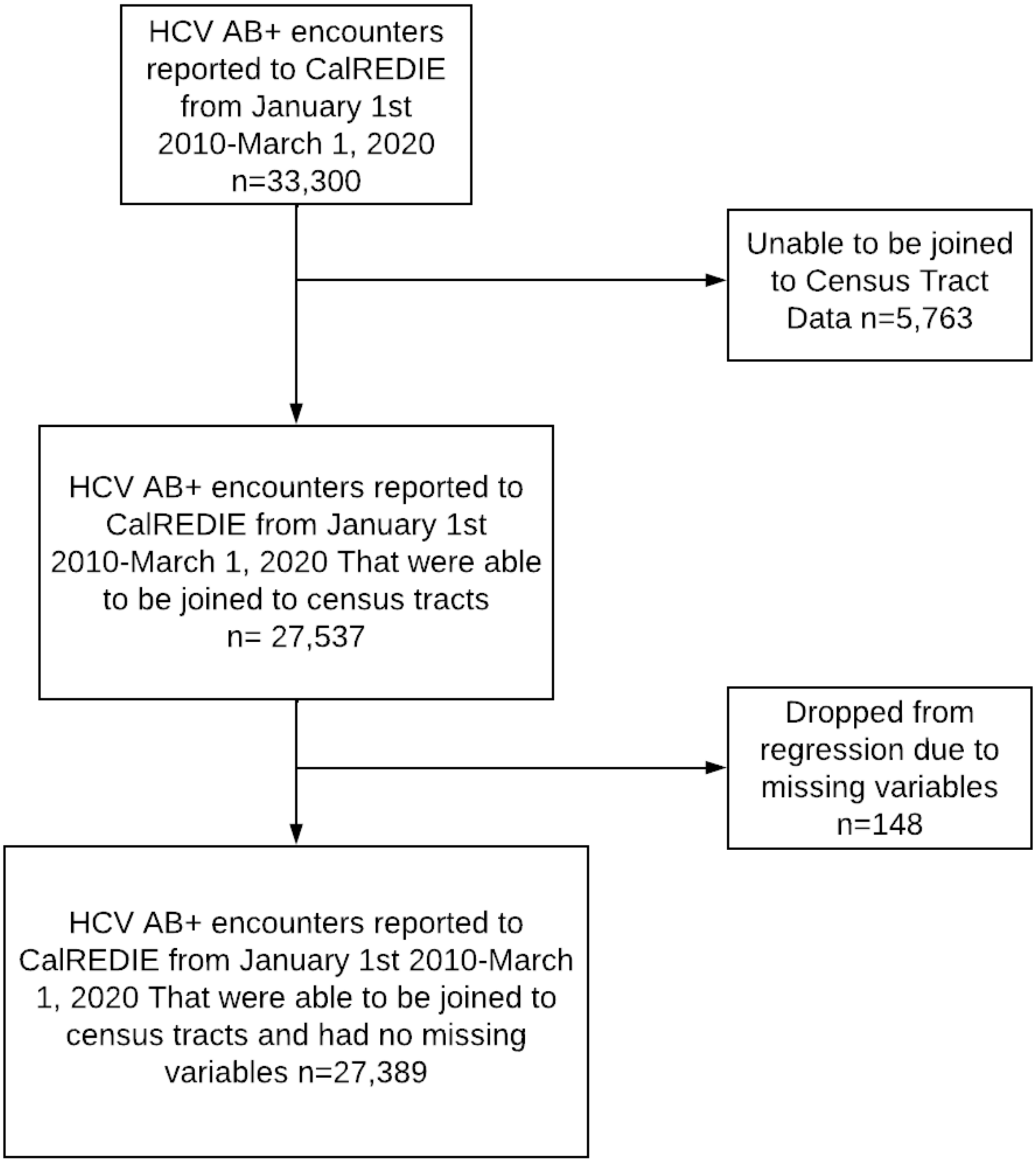


Figure 3.2: Forest plot of Multivariable logistic regression with age coded as binary of HCV antibody-positive patients ever testing for HCV viral load

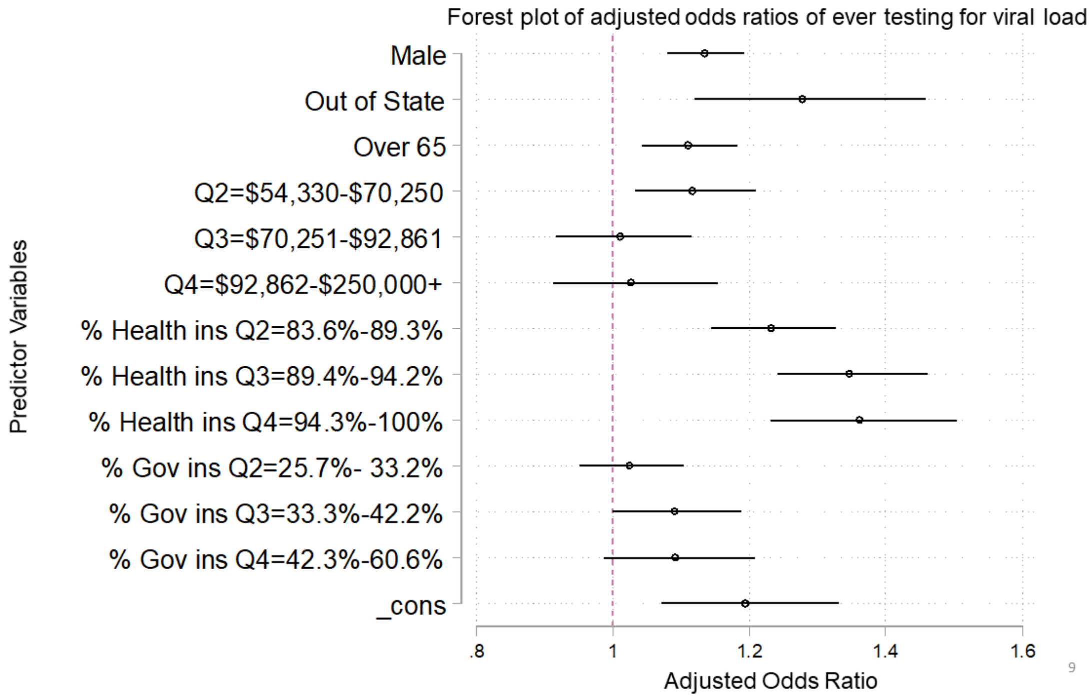


Figure 3.3: Forest Plot of Stratified Multivariable logistic regression with age coded as binary of HCV antibody-positive patients ever testing for HCV viral load

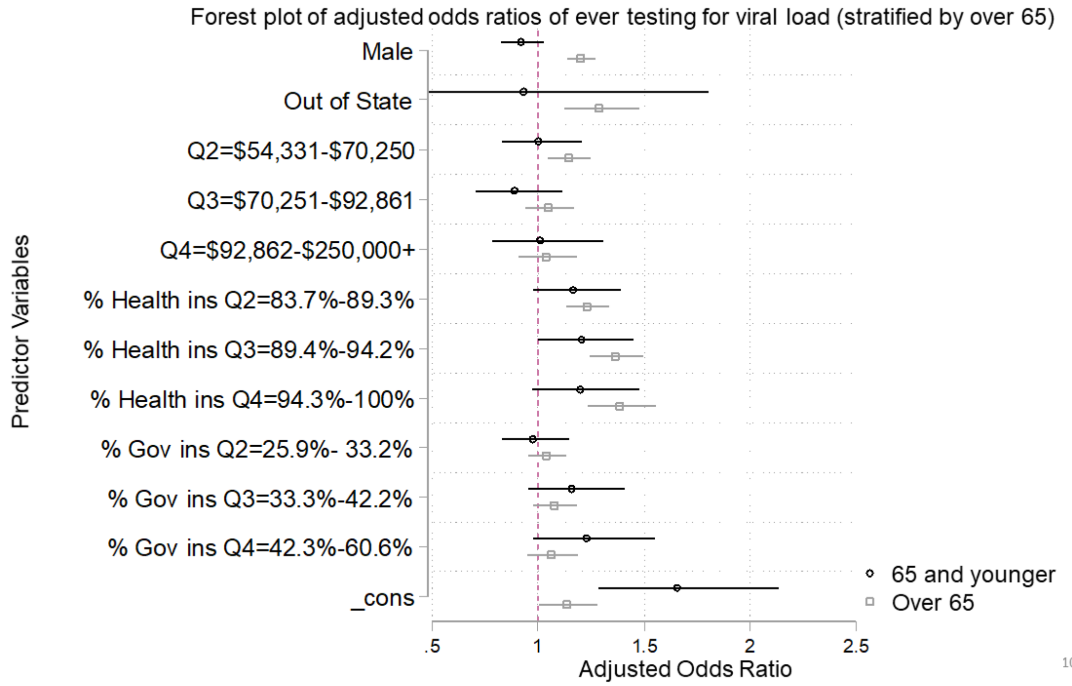


Figure 4.1: Sample description of care encounters those who tested HCV antibody-positive, were reported to CalREDIE, and could be joined to census tracts

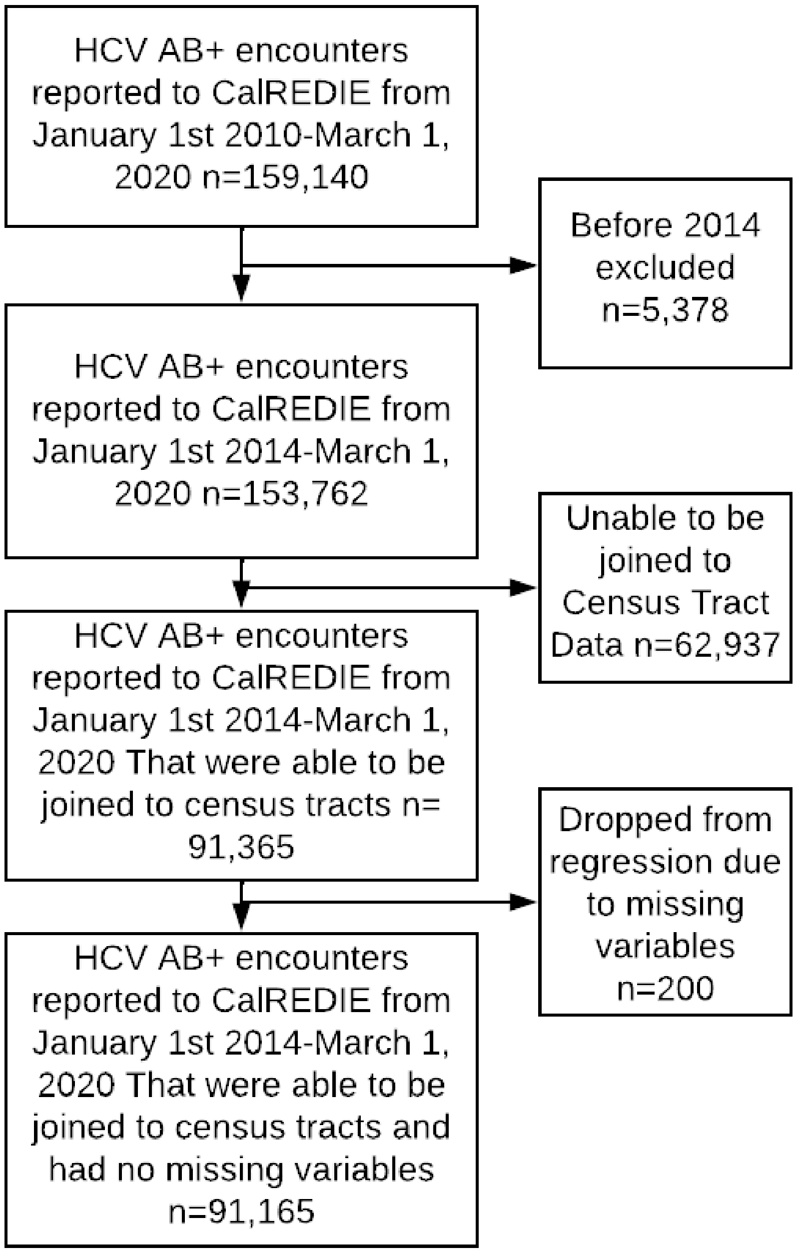


Figure 4.2 Multiple Cox Regression Curve of an undetectable hepatitis C viral load

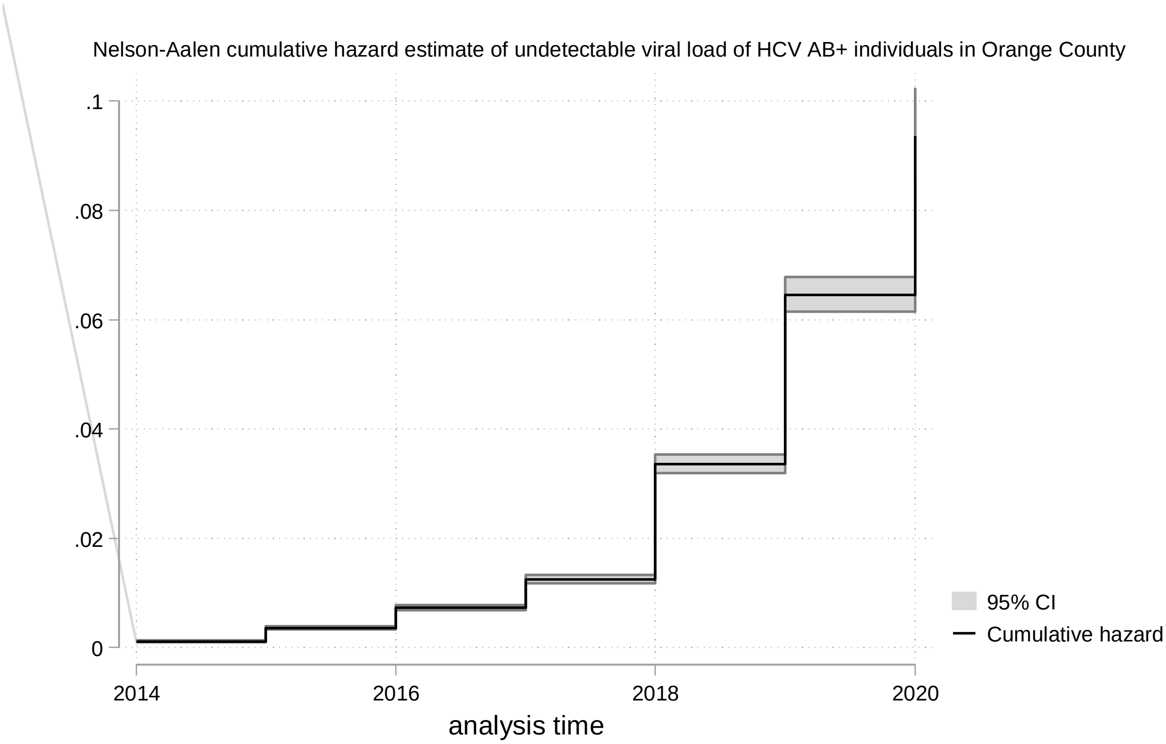


Figure 4.3: Multiple Cox Regression Curve Stratified by age coded as binary (65 and under, and over 65) of an undetectable hepatitis C viral load.

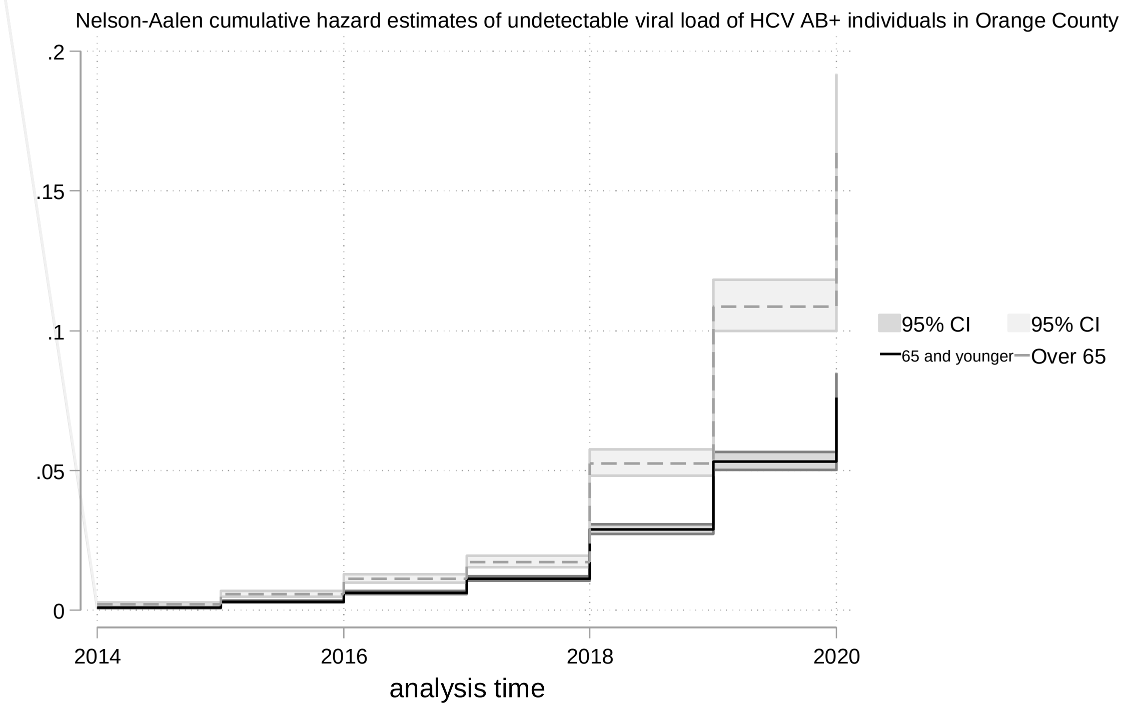


Figure 4.4: Forest plot of predictors of hazard ratios of an undetectable hepatitis C viral load

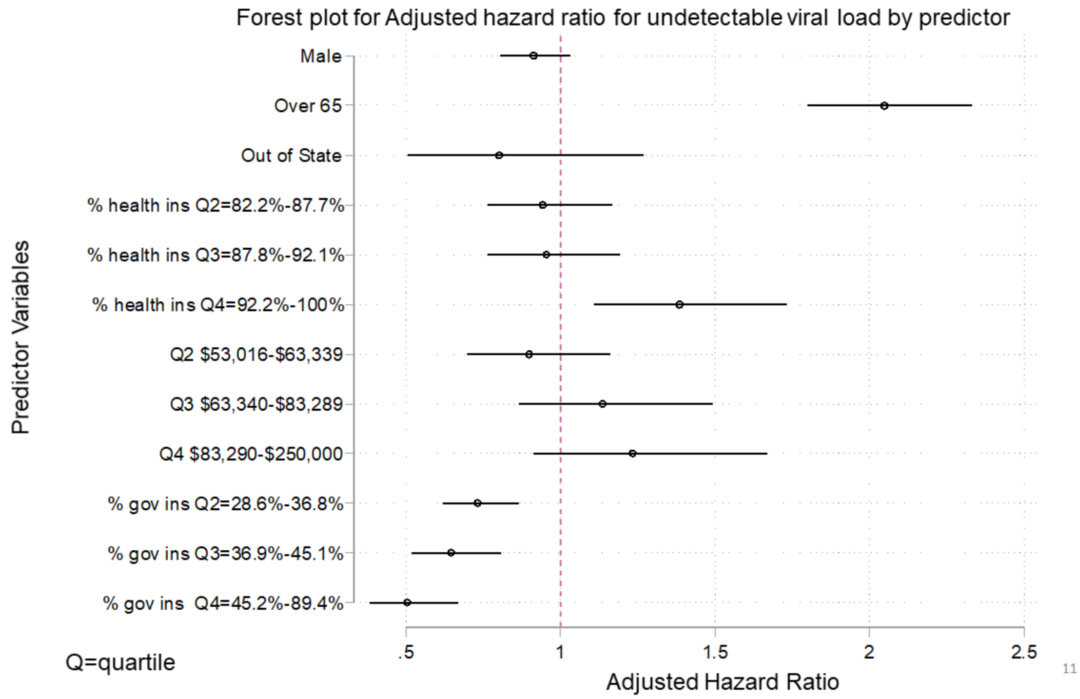


Figure 4.5: Forest plot of hazard ratios of an undetectable hepatitis C viral load showing the base model and the interaction model with health insurance and estimated median income as an interaction term stratified by Over 65 and 65 and Younger

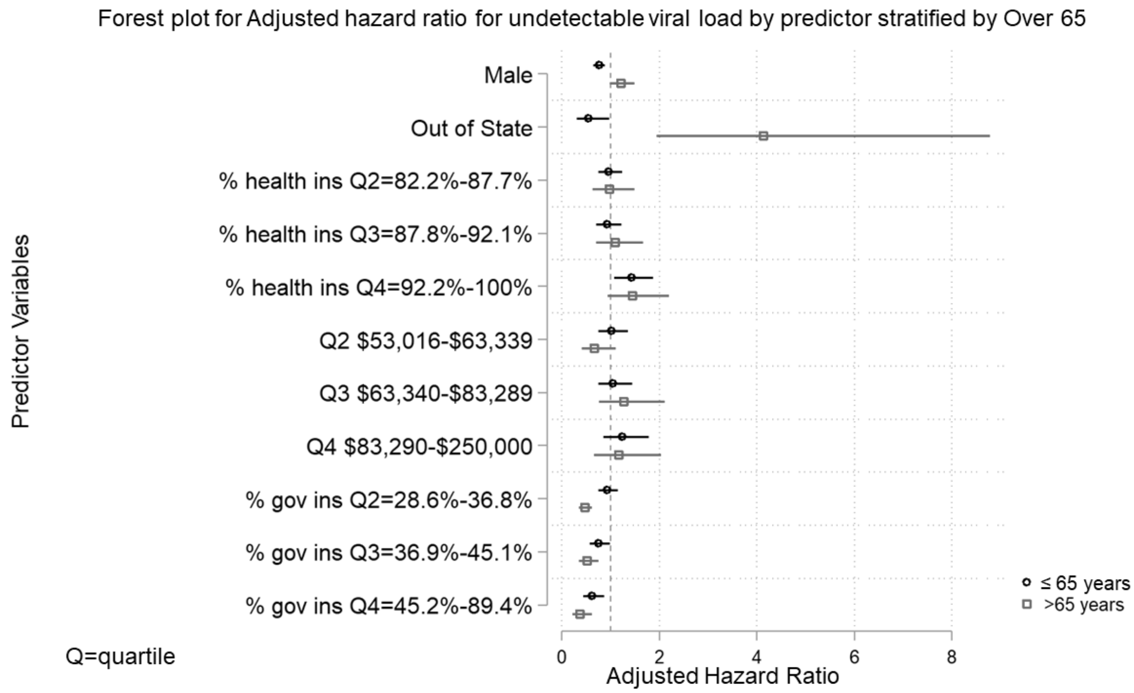


Figure 4.6: Forest plot of hazard ratios of an undetectable hepatitis C viral load showing the base model and the interaction model with health insurance and estimated median income as an interaction term.

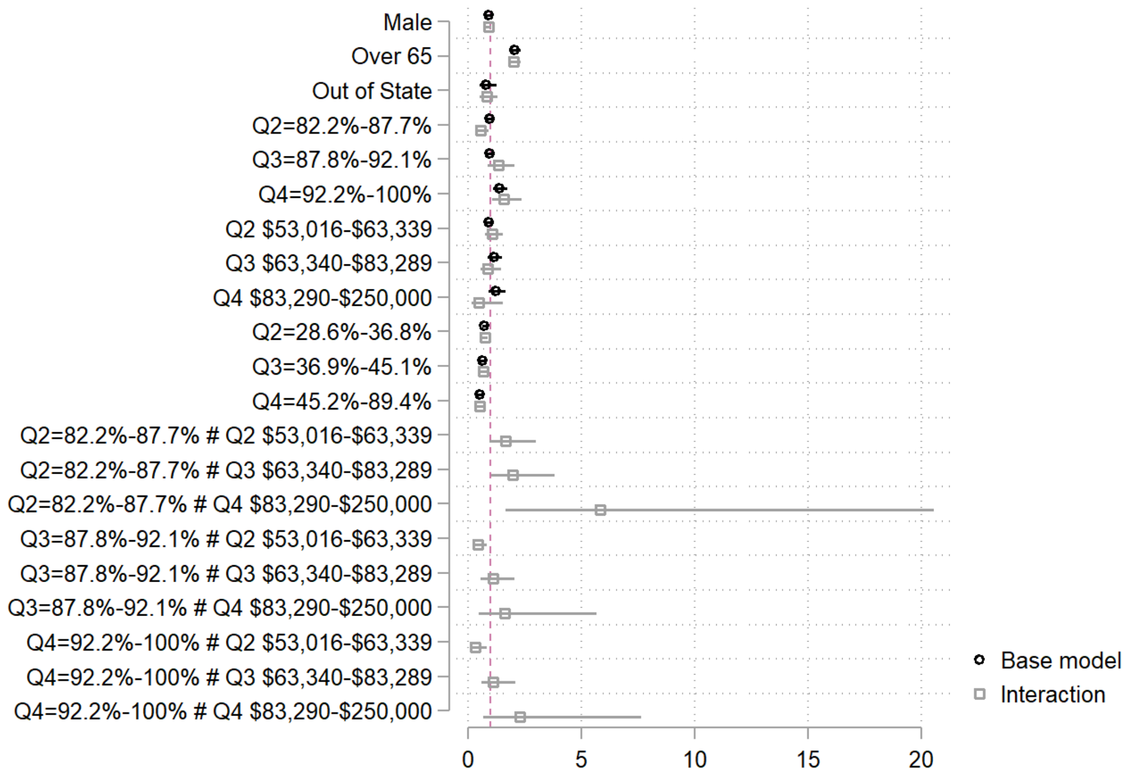


Figure 5.1: Sample description of EMR data extracted from UCIMC and CalREDIE.

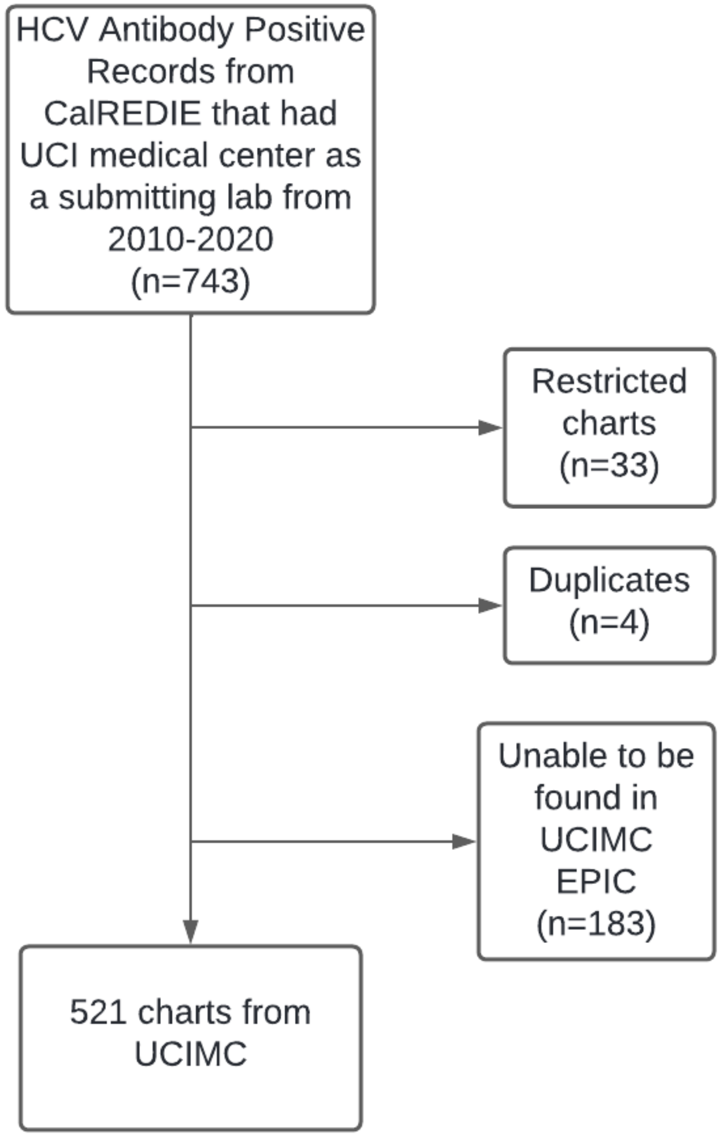


Figure 5.2: Forest plot of multiple logistic regression of sociodemographic correlates of HCV on viral load testing in Orange County

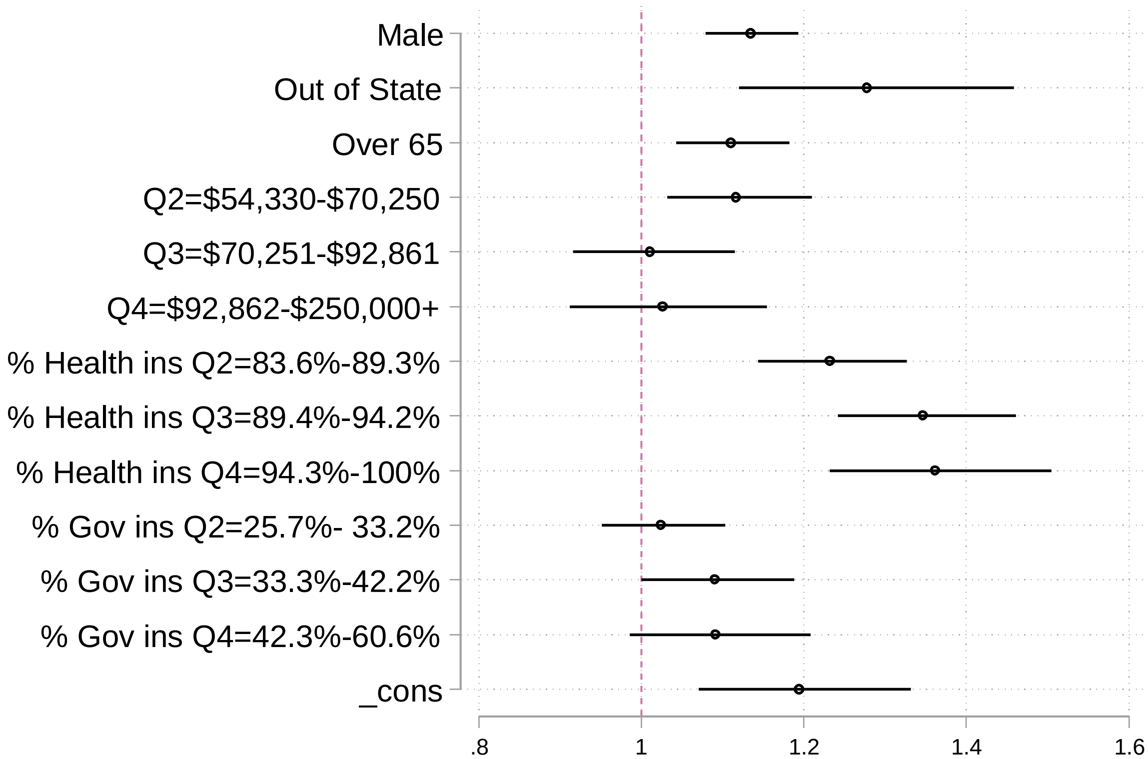


Figure 5.3: Unstratified and Stratified Multiple logistic regression of sociodemographic correlates of using EMR data on HCV diagnosis in Orange County

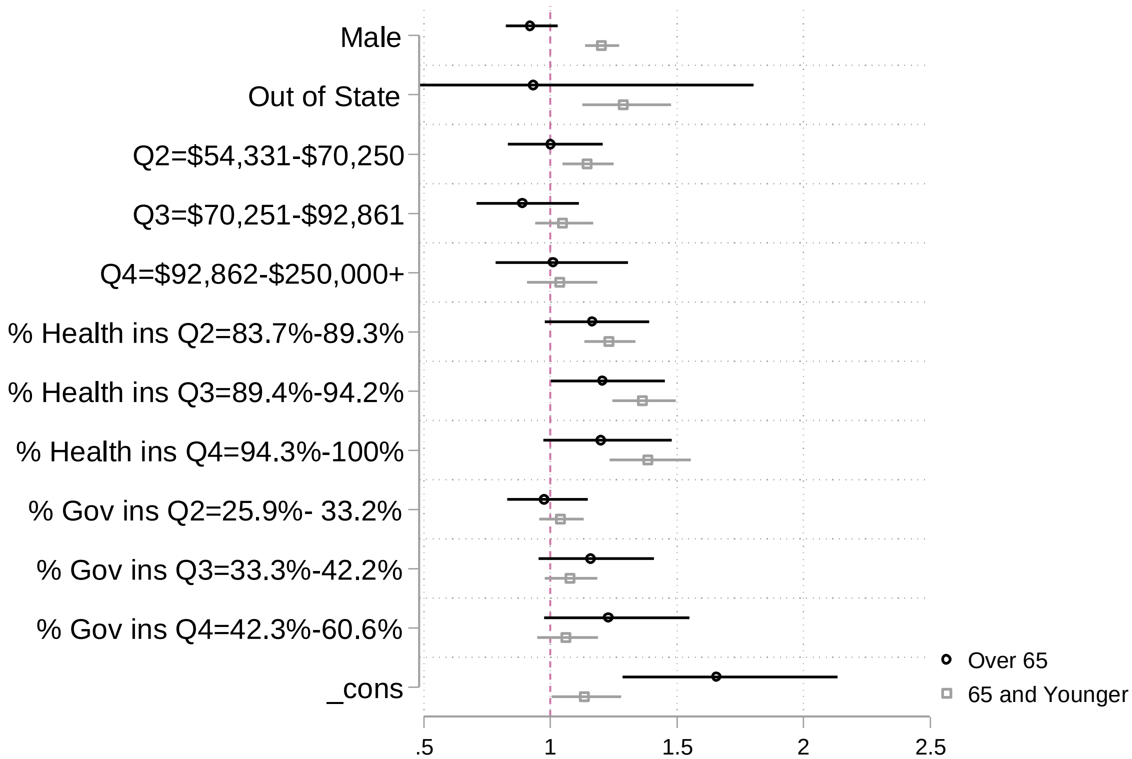
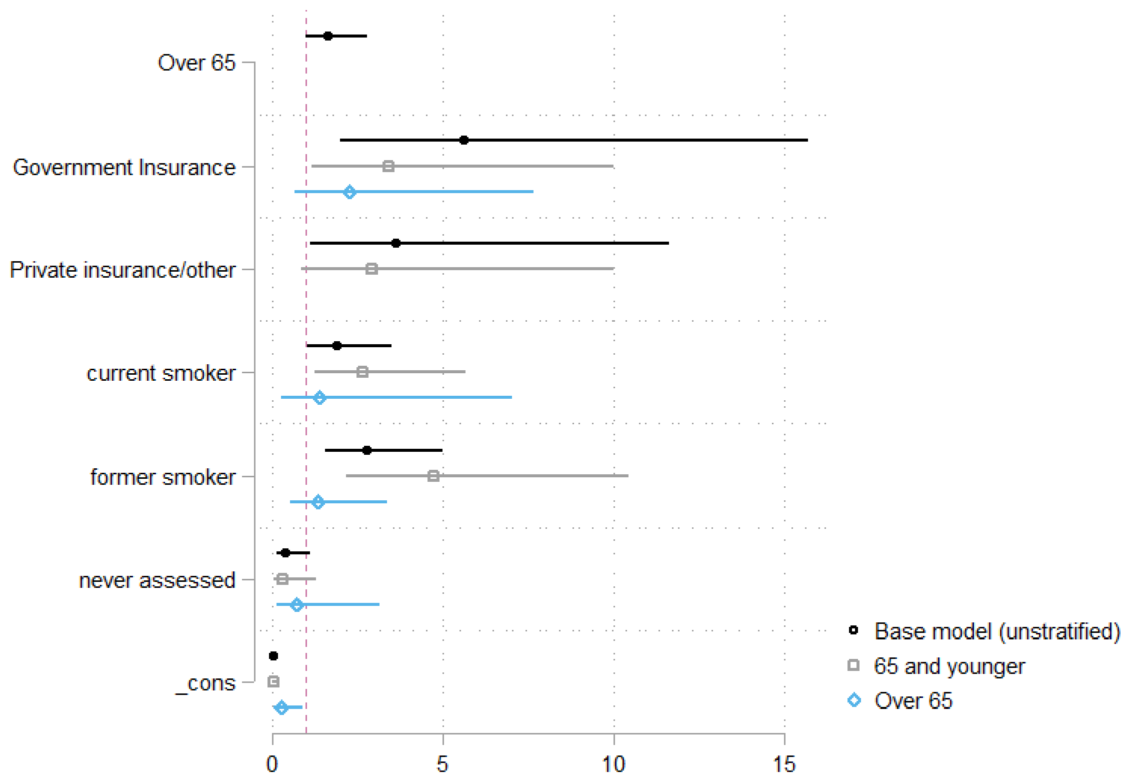


Figure 5.4: Forest plot of stratified Multiple logistic regression of sociodemographic correlates of using EMR data on HCV diagnosis in Orange County



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