A Bayesian Meta-Analysis of the Effect of Alcohol Use on HCV-Treatment Outcomes with a Comparison of Resampling Methods to Assess Uncertainty in Parameter Estimates

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Abstract
There is mounting evidence that alcohol use is significantly linked to lower HCV treatment response rates in interferon-based therapies, though some of the evidence is conflicting. Furthermore, although health care providers recommend reducing or abstaining from alcohol use prior to treatment, many patients do not succeed in doing so. The goal of this meta-analysis was to systematically review and summarize the English-language literature up through January 30, 2015 regarding the relationship between alcohol use and HCV treatment outcomes, among patients who were not required to abstain from alcohol use in order to receive treatment. Seven pertinent articles studying 1,751 HCV-infected patients were identified. Log-ORs of HCV treatment response for heavy alcohol use and light alcohol use were calculated and compared. We employed a hierarchical Bayesian meta-analytic model to accommodate the small sample size. The summary estimate for the log-OR of HCV treatment response was -0.775 with a 95% credible interval of (-1.397, -0.236). The results of the Bayesian meta-analysis are slightly more conservative compared to those obtained from a boot-strapped, random effects model. We found evidence of heterogeneity ($Q = 14.489$, $p = 0.025$), accounting for 60.28% of the variation among log-ORs. Meta-regression to capture the sources of this heterogeneity did not identify any of the covariates investigated as significant. This meta-analysis confirms that heavy alcohol use is associated with decreased HCV treatment response compared to lighter levels of alcohol use. Further research is required to characterize the mechanism by which alcohol use affects HCV treatment response.
Key Words: Bayesian meta-analysis, resampling, hepatitis C, alcohol, uncertainty quantification

1. Introduction

Hepatitis C virus (HCV) infects an estimated 130 to 150 million people globally and 3.2 million people in the United States (US).[1,2] Among people with chronic HCV in the US, 60 – 70% will develop chronic liver disease, 5 – 20% will develop cirrhosis of the liver over a period of 20 – 30 years, and 1 – 5% will die as a result of chronic liver infection.[2] Excessive alcohol use increases the risk of advanced liver disease, cirrhosis, and hepatocellular carcinoma.[3-6] The effectiveness of HCV treatment is decreased for heavy drinkers compared to results for infrequent or non-drinkers in studies in which participants have abstained from alcohol for less than six months before starting

treatment.[7,8,9,10] Alcohol use and HCV infection are common comorbidities: a 2003 English-language literature review found studies indicating that 14-36% of alcohol-dependent populations were infected with HCV, and that 51% of study participants with liver disease were infected with HCV.[11] In a study of 6,664 French patients with HCV, 18% reported excessive alcohol use.[12] Another study showed that up to 60% of HCV patients have a history of alcohol use.[13]

Although current guidelines for HCV treatment encourage alcohol use reduction,[1,10,14] and health care providers both recommend reduction and implement interventions, not all individuals reduce or eliminate drinking. In a study of the efficacy of a brief alcohol treatment program for heavy-drinking HCV patients, researchers found that the intervention did decrease drinking and increase abstinence overall, but at the follow-up four to eight weeks after intervention 32% were still drinking at least five drinks per day (70 g/day) and 32% were still drinking between one and four drinks per day (14 – 56 g/day).[15] Even in an extended 24-week integrated alcohol-use reduction and HCV treatment program for individuals with hazardous levels of alcohol use, only 40% and 44.4% reported abstinence 12 and 24 weeks into treatment, respectively.[16] In a randomized-controlled trial of the efficacy of Motivational Enhancement Therapy for reducing alcohol use in individuals with HCV and an alcohol-use disorder, no differences in the number of drinks per week were found between the treatment and control groups.[17] Although current HCV treatment guidelines do not recommend excluding alcohol users from treatment[1,10,14] many of the often-cited studies investigating the relationship between alcohol use and HCV treatment outcomes require patients to abstain before and during treatment.[7,8,18-20]

Given the rapidly changing landscape of HCV treatment, traditional interferon-based treatments are likely to be only rarely used in clinical practice in the US. Interferon-based therapies were long (24-48 weeks), had multiple side effects including problematic neuropsychiatric side effects, and were not as effective in genotype one HCV (the most common in the US)[21,22]. Current treatments are much shorter in duration, have a much lower pill burden, a more manageable side effect profile, and higher efficacy[23]. Even though treatments are changing, the relatively high use of alcohol in the HCV-infected population remains a critical clinical issue, both for overall liver health and longevity as well as its potential impact on treatment outcomes.

To gain an understanding of the impact of alcohol use on HCV treatment outcomes, we summarize the findings of studies that address representative samples of patients undergoing interferon-based HCV treatment. Given that many individuals fail to reduce or eliminate drinking before or during treatment, such representative samples do not exclude alcohol users.

This meta-analysis quantifies the relationship between alcohol use and HCV treatment outcomes among individuals who were not required to abstain from alcohol use in order to receive treatment. We compared a hierarchical Bayesian approach to a non-parametric bootstrap of a random-effects model to accommodate the small sample size (n = 7) and estimated the overall log-Odds Ratio(OR) of HCV treatment response for heavy compared to light alcohol use.

2. Methods

2.1 Data Collection

Analysts conducted a systematic search of English-language publications on HCV treatment and alcohol use published up through June 30, 2014. Using Google Scholar, PubMed and Thomson Reuters, articles assessing the relationship between alcohol use and HCV treatment outcomes were identified using combinations of the following words: Hepatitis C, HCV, Hep-C, interferon, sustained viral response (SVR), outcome, alcohol and treatment. Of the relevant articles identified, all references were also examined for potentially pertinent articles. The inclusion criteria for articles in the study were:

(1) Observational studies of HCV-infected patients as confirmed by a positive test for HCV-ribonucleic acid (RNA) or HCV-antibodies, or liver biopsy.
(2) Patients were not restricted from using alcohol while receiving HCV treatment.
(3) Article included enough information to calculate the odds ratio (OR) (and its variance) of HCV-treatment response for categories of heavy and light alcohol use.

The team found 16 papers investigating the effects of alcohol use on HCV treatment response.[7,8,18-20,25-35] Nine of these were excluded from the meta-analysis because the study (1) required a restriction on alcohol use to receive treatment,[7,8,18-20] (2) only included individuals with comorbid human immunodeficiency virus (HIV),[24] (3) only included individuals with HCV genotype 3,[25] (4) lacked sufficient information to calculate ORs,[26] or (5) was written in a language other than English.[27] The remaining seven studies were included in the meta-analysis.[28-34]

Studies varied in their categorization of alcohol use. For example, some allowed a separate category for abstainers while others did not, some used a metric of grams of ethanol per day while others used the number of standard drinks per day. All studies used different thresholds to form categories for alcohol use. To improve consistency across studies, we standardized the units of measurement to grams of ethanol per day (1 standard drink = 14 g ethanol[35]), and consolidated alcohol use into two categories: light and heavy. The light alcohol use category also included no alcohol use. Study-defined categories were merged such that the threshold delineating light and heavy alcohol use was as close as possible to the NIAAA's threshold separating no- and low-risk from high-risk for developing alcohol-use disorder (3 standard drinks/day for women and 4 standard drinks/day for men).[36] Characteristics of the studies used in this meta-analysis are summarized in Table 1. Meta-analysis alcohol-consumption thresholds (light or heavy) are based on the individual studies' alcohol-use category thresholds.

Table 1: Characteristics of the seven studies included in the meta-analysis

First Author	Year of Publication	Country	N	Male, n (% of N)	Treatment	Treatment Response	Heavy Alcohol Use	
							Definition (g/day)	*n* (% of *N*)
Anand	2006	USA	726	701(97)	IFN-α-2b, Ribavirin	SVR	> 28	114(16)
Bruggmann	2010	Switzerland	554	348(63)	Peg-IFN- α-2a/b, Standard IFN	SVR	> 24	16(3)
Le Lan	2012	France	67	-	Peg-IFN, Ribavirin	SVR	> 42 for men > 28 for women	24(36)
Lin	2014	Taiwan	195	97(50)	Peg-IFN- α-2a/b,	SVR	*Drinker (vs. non-*	114(58)

					Ribavirin		*drinker)*	
Loguercio	2000	Italy	65	42(65)	IFN-α	SVR	> 40	31(48)
Mochida	1996	Japan	92	-	IFN-α, IFN-β, recombinant IFN-α-2a, or recombinant IFN-α-2b	SVR	*Presence of intake (vs. no presence of intake)*	-
Oshita	1994	Japan	53	40(75)	IFN-α	SVR	> 60	16(30)

Table Note: SVR = sustained virologic response (undetectable HCV RNA at 24 weeks after treatment completion).

2.2 Statistical Analysis

The numbers of alcohol-consuming individuals in each study who responded to HCV treatment were used to calculate the odds ratio (OR) for HCV treatment response between heavy and light alcohol use. For the Bayesian meta-analysis, these ORs were converted to the natural log scale to meet the assumption of normality of the individual log-OR estimates. The team then calculated the variances of the log-ORs. The log-ORs and their variances were used to conduct the meta-analysis.

We compared a Bayesian approach to a non-parametric bootstrap for the traditional random-effects model for this meta-analysis. Bootstrapping procedures are often used when sample sizes are small, and they are less computationally demanding than a Bayesian approach. However, traditional meta-analyses estimate between-study variance imprecisely when the sample size is small; a Bayesian variance estimate is more precise for small samples.[37] Further, a Bayesian approach accounts for parameter uncertainty in estimating the combined log-OR for all studies, the overall effect.[38]

Before selecting the model type to be used in this analysis the heterogeneity of study results is investigated. Heterogeneity refers to the differences between the log-ORs that cannot be explained by simple chance, and thus must be systematic. Heterogeneity was tested using Cochran's *Q*-statistic and, when found, was quantified with the I^2 statistic.[38] The I^2 statistic represents the proportion of variation in the observed log-ORs attributable to heterogeneity. Values of the I^2 statistic near 0% indicate that all observed variation in log-ORs is due to random error, and values near 100% indicate that all observed variation in log-ORs is due to heterogeneity. For this analysis, where evidence of heterogeneity was found, a random-effects model was employed. In the absence of heterogeneity a fixed-effect model would be used.[39]

A bias-corrected accelerated percentile interval (BC_a) and 10,000 bootstrap samples were used for the non-parametric bootstrap approach to the random-effects model. The Bayesian hierarchical modeling approach used here assumes that the observed log-ORs for each study are normally distributed around the true log-ORs for each study, and that the true log-ORs for each study are normally distributed around μ, an overall log-OR for all studies (with between-study variance, τ^2). The assumption of normality of the log-ORs was assessed using a standard Q-Q plot.

The following steps were taken to fit the model.

- Specify prior distributions for the parameters τ^2 (between-study variance) and μ (overall effect)
- Estimate posterior distributions of the parameters using the data to update the priors.
  - The posterior estimate of the parameter μ is the estimated log-OR for all studies.

- Conduct sensitivity analysis to determine the effects that changes in the prior distributions had on the parameter estimates for μ and τ^2.
  - Distributions used for the sensitivity analysis include: $\mu \sim N(-1,1)$, $\mu \sim N(0,10)$, $\tau^2 \sim U(0,1)$, and $\tau^2 \sim U(0,10)$.
  - When little change is observed in model parameter estimates during sensitivity analysis, the model results are said to be robust to the exact formulation of the prior distribution used.[40] Such a finding would indicate that the small sample size of publications is sufficient for conducting the meta-analysis.
- Determine which prior distributions to employ in the model using the deviance information criterion (DIC), a model fit statistic for which a smaller value indicates a better fitting model.[41]
  - DIC is a hierarchical modeling generalization of AIC (Akaike information criterion) and BIC (Bayesian information criterion).
- Approximate the overall log-OR of HCV treatment response for heavy versus light drinkers (μ) and the between-study variance (τ^2) using Markov chain Monte Carlo (MCMC) methods.
  - Fit the model using JAGS (Just another Gibbs Sampler) in the R programming language with 40,000 iterations per chain for five Markov chains.[42]

Additionally, Bayesian meta-regressions were conducted to explore the sources of heterogeneity separately for each of the following covariates: year of publication, study size, percent male, alcohol threshold, treatment (interferon and ribavirin versus interferon alone), and world region (Asia versus Western countries). A non-informative N(0, 10^{-6}) prior was assumed for β coefficients.[41] Bayesian analyses do not typically use p-values, so the significance of the μ, τ^2, and β coefficients (for meta-regression) were judged by whether their 95% credible intervals (interval of the posterior probability distribution) involved 0 or not.
Publication bias was assessed using a funnel plot. No statistical tests for publication bias were conducted due to small sample size.[43]

3. Results

3.1 Characteristics of Studies

The characteristics of the seven studies included in the meta-analysis are presented in Table 1. Three studies were conducted in Asia, three were conducted in Europe, and one was conducted in the United States. Study participation ranged in size from 53 to 726 patients, totaling 1,751 HCV-infected patients overall. Of the five studies with data available on gender, males accounted for 50 - 97% of patients for each study, totaling 77% overall. Three (43%) studies utilized both interferon and Ribavirin treatment; the remaining four (57%) used interferon treatment alone. Response to these treatments was measured as SVR in all studies. Different thresholds for heavy alcohol use were specified in five of the studies; two studies delineated alcohol use only as present or not. Among the six studies that provided sufficient information, the percentage of patients who reported heavy alcohol use ranged from 3-58%, with an average rate of 19%. The log-ORs for each study and their respective 95% confidence intervals are shown in the forest plot illustrated in Figure 1. A negative log-OR indicates that heavy drinkers had lower odds of treatment response compared to light drinkers; a positive log-OR indicates higher

odds of treatment response for heavy drinkers compared to light drinkers. These results show that in six of the seven studies analyzed light drinkers had higher treatment response rates than heavy drinkers.

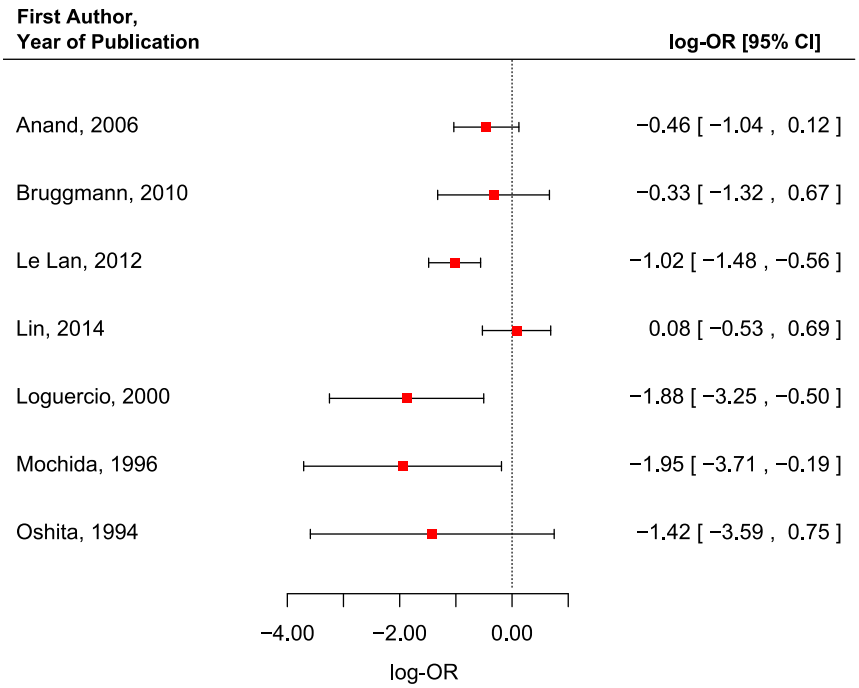

Figure 1: Forest plot of the observed log-odds ratios and 95% confidence intervals for the seven studies included in the meta-analysis. A log-OR to the left of zero indicates that heavy drinkers had a lower odds of response compared to light drinkers, and a log-OR to the right of zero indicates that heavy drinkers had higher odds of response compared to light drinkers.

3.2 Assessing Heterogeneity

A formal test of heterogeneity using Cochran's Q statistic provided evidence for heterogeneity among log-ORs ($Q = 14.489$, $p = 0.025$). Results indicated a I^2 value of 60.28%, meaning that 60.28% of the observed variation in log-ORs was attributable to real differences in true log-ORs. The remaining observed variation in log-ORs was due to sampling error alone. The Q and I^2 statistics provided strong evidence that the assumption of heterogeneity was met, consequently a random-effects version of a Bayesian meta-analysis model was used to account for the between-study variation.

3.3 Non-parametric Bootstrap Random-Effects Model

The overall log-OR estimate for patient response to HCV treatment given heavy vs. light alcohol use was -0.7395 with a 95% bootstrapped confidence interval of -1.2307 to -0.2331. The corresponding probability associated with the log-OR estimate of -0.7395 was calculated as:

$$p = \frac{e^{-0.7395}}{1+ e^{-0.7395}} = 0.32$$

or 32% with a 95% confidence interval of 23% - 44%.

3.4 Bayesian Hierarchical Model

3.4.1 Diagnostics and Assumptions

The assumption of normality of the log-ORs was tested using a visual inspection of a Q-Q plot in which the percentiles of a standard normal distribution are compared to the corresponding percentiles of the observed data. As seen in Figure 2, the relationship between the percentiles is roughly linear, leading to the conclusion that the log-ORs follow an approximately normal distribution.[44]

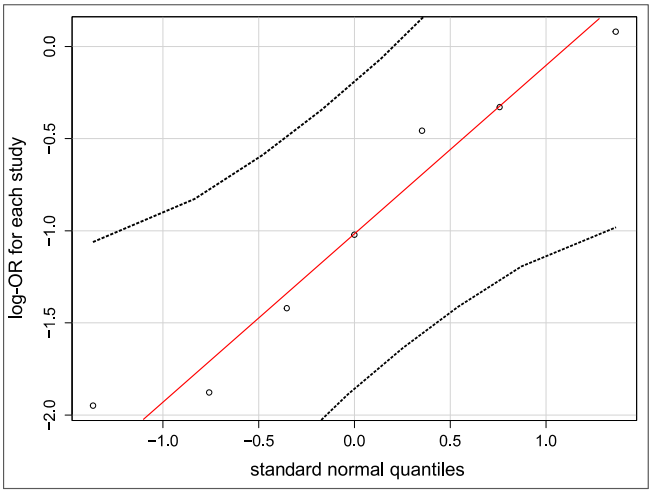

Figure 2: Q-Q Plot of log-OR estimates normality assessment. The percentile of each study's log-OR is matched to the standard normal quantile that gives the same percentile, and then standard normal quantiles are plotted against observed log-ORs. The linear pattern indicates that the log-ORs follow a normal distribution.

Sensitivity analyses of the prior distributions were conducted by comparing the credible intervals for μ and τ^2 under different prior distribution specifications. As illustrated in Figure 3, the credible intervals for μ have a significant amount of overlap when changing the prior distribution, meaning that the estimate of the overall log-OR was not overly sensitive to the choice of a prior distribution.

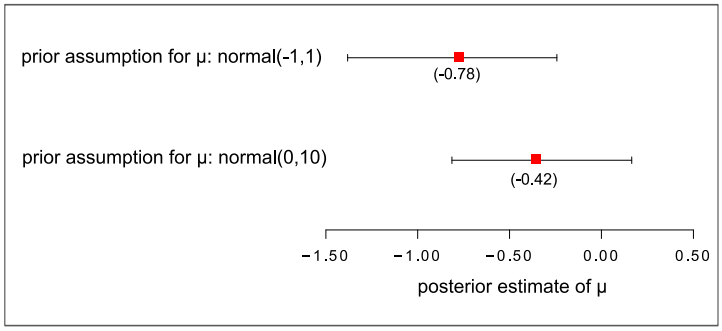

Figure 3: Posterior estimates and 95% credible intervals for μ for different prior distributions of μ. The similarity between posterior estimates of μ for different prior distributions of μ indicates that the analysis is not sensitive to choice of prior distribution.

Sensitivity analyses of the credible intervals for τ^2 did not show a significant change in the distribution means between the two prior distributions specified (Figure 4), though a

significant difference in the credible intervals was observed. Analyses of additional changes in the prior distribution were conducted for both μ and τ^2 with similar results (small changes in the parameter estimates). These sensitivity analyses provide evidence that modeling results are fairly robust to the prior distribution selected and that the small sample size of publications is sufficient for conducting the meta-analysis.

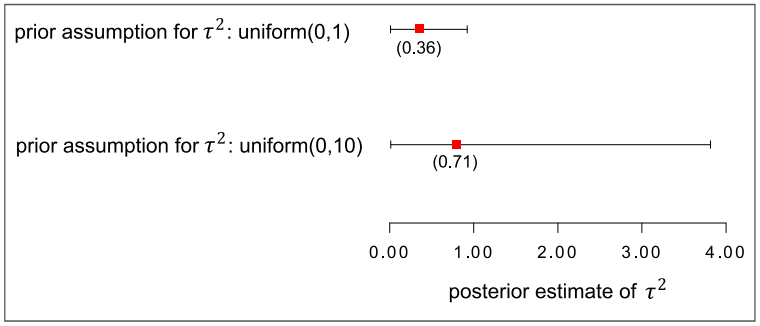

Figure 4: Posterior estimates and 95% credible intervals for τ^2 for different prior distributions of τ^2.

The similarity between posterior estimates of τ^2 for different prior distributions of τ^2 indicates that the analysis is not sensitive to choice of prior distribution.

Hierarchical Bayesian Meta-Analysis

We used the DIC as the criteria for model selection. Of all competing prior distributions tested, $\mu \sim N(-1,1)$ and $\tau^2 \sim U(0,1)$ resulted in the lowest DIC score (17.8). Using these prior distribution assumptions, the overall log-OR estimate for patient response to HCV treatment given heavy vs. light alcohol use was -0.775 with a 95% credible interval of -1.397 to -0.236. The corresponding probability associated with the log-OR estimate of -0.775 was calculated as:

$$p = \frac{e^{-0.775}}{1+ e^{-0.775}} = 0.32$$

or 32% with a 95% credible interval of 20% - 44%. The random-effects and Bayesian models resulted in the same overall log-OR estimate, but we elected to proceed with the Bayesian model since it had a more conservative credible interval.

Meta-regressions were performed on the covariates year of publication, study size, percent male, alcohol threshold, treatment, and world region to assess their potential contribution to heterogeneity. The results of the meta-regressions are shown in Table 2. Because the credible intervals for their beta estimates all contain 0.0, none of the covariates were significant predictors of log-OR.

Table 2: Meta-regression: impact of covariates on log-OR of HCV treatment response. The 95% credible intervals all contain zero, indicating that none of the covariates are related to log-OR.

Variable	Regression Coefficient ($\hat{\hat{\beta}}$)	Standard Error	95% Credible Interval
Year of publication	0.000	0.001	(-0.001, 0.001)
Study size	0.001	0.001	(-0.001, 0.003)
Percent male	0.000	0.012	(-0.022, 0.024)
Alcohol threshold	-0.018	0.015	(-0.045, 0.015)
Treatment	0.682	0.580	(-0.445, 1.871)
World region	0.270	0.634	(-1.109, 1.425)

Although the asymmetric results seen in the funnel plot (Figure 5) suggest evidence of publication bias, analysis based on such a small sample size makes it possible that the observed pattern is due to chance.[45]

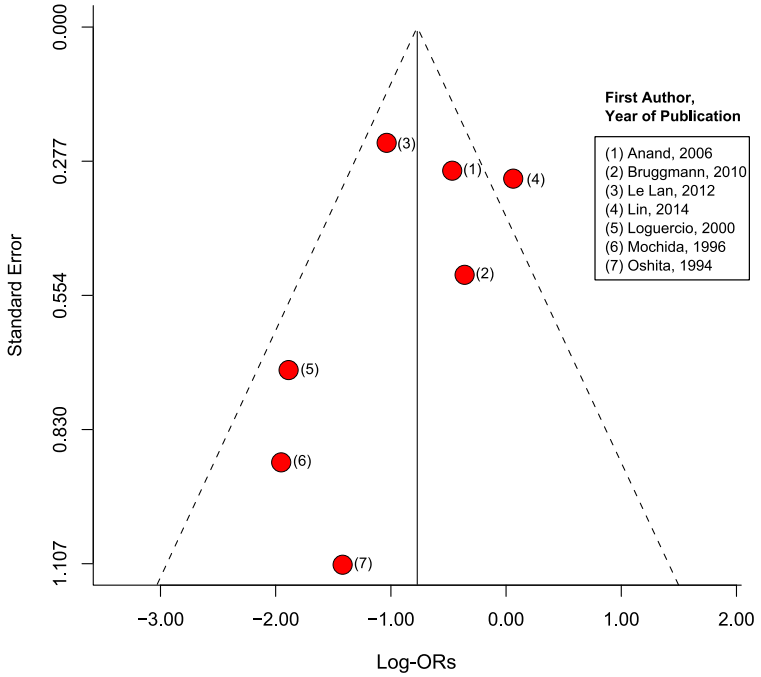

Figure 5: Funnel plot to assess publication bias with 95% contour lines. The lack of studies located in the lower right portion of the triangle suggests the potential presence of publication bias.

The Bayesian model suggests that light alcohol users are 32% more likely to respond to treatment compared to heavy alcohol users, and it was not very sensitive to the choice of prior distribution. Meta-regression revealed that none of the covariates impact the log-OR of HCV treatment response. Publication bias may be present.

3. Discussion

HCV infection and alcohol use are often highly co-morbid. Heavy alcohol use in HCV-infected patients can increase disease progression and the risk of hepatocellular carcinoma and advanced liver disease. HCV-infected individuals who drink heavily experience a decreased rate of response to HCV treatment compared to light and non-

drinkers, given a period of abstinence before treatment[7-10]. Current HCV-treatment guidelines do not require abstinence from alcohol and many patients with HCV are unsuccessful in reducing or abstaining from alcohol use before and during treatment. Taking these facts into consideration, this meta-analysis was conducted to expand our understanding of the relationship between alcohol use and HCV treatment response among individuals who are not restricted from using alcohol to receive treatment. To accommodate the small number of published studies addressing the alcohol-using HCV-infected population, a Bayesian approach was compared to a non-parametric bootstrap for a random-effects model. Although both approaches resulted in the same overall estimate of the effect size, the Bayesian credible interval proved to be more conservative. Our investigation found that HCV-infected individuals who do not drink heavily were between 20% and 44% more likely to respond to HCV treatment than heavy drinkers. These findings proved robust when examined under sensitivity analysis. Meta-regression was unable to capture the sources of heterogeneity, so the factors that contribute to variation in log-ORs among studies remain unknown, although the impact of heavy drinking on adherence warrants further exploration.. We conclude that when health care providers adhere to current treatment guidelines, individuals who drink more heavily are at a substantially greater risk of failing to respond to HCV treatment.

4.1 Limitations

While the effect of heavy alcohol use on interferon-based HCV-treatment outcome was substantial in the analyzed studies, several factors may have limited our ability to detect the true effect or to obtain a smaller credible interval. For one, all seven studies used different thresholds to delineate alcohol-use categories, ranging from >24 g/day to >60 g/day, and two studies simply distinguished between abstinence and alcohol use. This variation in alcohol-use categorization may have skewed the estimate of the true overall effect. While the meta-analysis restricted the population to individuals who were not required to abstain, there was still some variation in the populations sampled. Predominantly, three studies[32,34,35] sampled individuals of East Asian ancestry and four studies[29-31,33] sampled individuals of European ancestry. It is known that race is predictive of HCV-treatment outcomes: individuals of Asian descent experience higher HCV treatment response rates than their European counterparts for identical courses of treatment.[46] Furthermore, several genes have been associated with HCV-treatment outcome, and the prevalence of favorable alleles of these genes vary by race.[47-49] Additionally, individuals infected with HCV viral genotypes 2 and 3 are more likely to respond to interferon-based treatments than are individuals infected with HCV viral genotype 1,[50] and the distributions of viral genotypes vary worldwide[51]. The inclusion of studies which varied in racial composition may have widened the credible interval for the overall effect by introducing unaccounted for variation among the log-ORs. Although the funnel plot suggests that publication bias may be present, the observed pattern may have occurred due to chance alone. Heavy drinking may be correlated with other factors known to impact treatment outcomes such as adherence, depression, being male, and insulin resistance. Due to these potentially confounding factors, drinking may not have been solely responsible for low treatment response. Finally the generalizability of these findings may be limited in the current era of interferon-free HCV treatment.

4.2 Strengths

We believe that this is the first quantitative meta-analysis conducted on the relationship between alcohol use and HCV treatment response. By constraining the analysis to only those studies that did not require participants to abstain from alcohol to receive treatment, greater confidence can be placed in inferences made about individuals undergoing

treatment for HCV. A meta-analytic approach allowed for greater power to detect the effect of alcohol use on HCV treatment outcomes in comparison to individual studies. Many of the individual studies grouped individuals by more than two alcohol-use categories, but only found statistically significant differences in HCV treatment response rates between the lowest and highest alcohol-use groups. Despite the compression of the many individual study alcohol-use categories into simply heavy and light groups, this meta-analysis still found significant difference in HCV-treatment response rates. While there was evidence of heterogeneity among log-ORs for different studies, the meta-analysis allowed for the calculation of an overall effect. The precision of the Bayesian approach made the meta-analysis feasible despite the relatively small sample size.

4.3 Clinical Implications

The results of this meta-analysis suggest that different levels of alcohol use differentially impact HCV treatment outcomes and should provide some clinical guidance to providers considering treating active drinkers, particularly in light of shorter, more efficacious and tolerable treatments. Alcohol reduction and elimination interventions should also be considered and deployed to improve not only treatment outcomes for individuals with HCV, but overall liver health. Behavioral health interventions, interventions focused on adherence, the broader use of addition pharmacotherapy for alcohol use disorders, and the delivery of care within an integrated care model may prove useful in addressing this issue.

4.4 Future Directions

This supposition could be more rigorously tested by comparing the results of studies that did require alcohol abstinence to those that did not. Because thresholds used to define heavy alcohol use vary across the source studies, the threshold above which the probability of responding to HCV-treatment begins to decline is still unknown. Since abstinence is not easily achieved for many individuals with HCV, future work to determine the alcohol-use threshold could (1) provide practical alcohol-use goals and (2) optimize HCV-treatment response rates while minimizing the resources spent on alcohol-use reduction programs. It has been suggested that the mechanism by which alcohol use affects HCV-treatment outcomes is indirect, with adherence as a moderating factor.[29,30] Unfortunately not all of the studies in the meta-analysis included information on adherence. Additionally, simulation studies might be used to assess the robustness of classical and Bayesian approaches under small sample size conditions, more generally.

In conclusion, this meta-analysis of observational studies shows a significant relationship between heavy alcohol use and decreased HCV-treatment response. A Bayesian approach resulted in a more conservative credible interval than did a non-parametric bootstrapped approach to a classical random-effects model. Meta-regression failed to identify covariates that could account for heterogeneity, thus further research is required to identify predictors that impact the log-OR of treatment response. Healthcare providers should focus on increasing the success rates of alcohol-use reduction and elimination interventions for heavy drinkers and consider treatment for lighter drinkers. Future research should further investigate the mechanism by which alcohol use affects HCV-treatment response.

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