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Impact of Hepatitis C Treatment on Long-term Outcomes for Patients with Hepatocellular Carcinoma

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Impact of Hepatitis C Treatment on Long-term Outcomes for Patients with Hepatocellular Carcinoma

By

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MD, University of Cincinnati College of Medicine, 2017

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An abstract of
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ABSTRACT

Impact of Hepatitis C Treatment on Long-term Outcomes for Patients with Hepatocellular Carcinoma

By

Michael K. Turgeon, MD

The purpose of this study was to 1) assess the impact of hepatitis C virus(HCV) treatment on survival in patients with hepatocellular carcinoma(HCC) at safety net hospitals(SNH) and tertiary referral centers(TRC) 2) determine the barriers to receiving HCV treatment and 3) assess the impact of timing of DAA therapy on rates of SVR and RFS in patients undergoing liver transplantation(LT).

For aims 1 and 2, patients from the US Safety Net Collaborative Database(2012-2014) with HCV and HCC were included. For all patients, HCV treatment was associated with improved median OS compared to no HCV treatment(70vs21 months, $p<0.01$). On MVA, HCV treatment was associated with improved OS. Considering patients who underwent complete tumor extirpation, those who received HCV treatment had improved median RFS compared to those who did not(91vs80 months, $p=0.03$). On MVA, factors associated with not receiving HCV treatment included Black race, uninsured status, and treatment at a SNH(all $p<0.03$). When this patient demographic received HCV treatment, however, the degree of improvement in survival was similar regardless if treated at a TRC or SNH.

For aim 3, patients from the US Hepatocellular Carcinoma Liver Transplantation Consortium(2015-2019) with primary HCV-associated HCC who underwent LT and completed DAA therapy were included. 427 HCV interferon treatment-naive patients who achieved SVR with DAAs had improved 5-year RFS(93%vs76%, $p<0.01$). Patients who received DAAs pre-LT, 0-3 months post-LT, and ≥3 months post-LT had SVR rates of 91%, 93%, and 78%($p<0.01$) and 5-year RFS of 93%, 100%, and 83%($p=0.01$).

HCV treatment for patients with HCC portends improved survival and oncologic outcomes, irrespective of clinical stage, HCC treatment modality, or type of treatment facility. Despite this, given associated barriers, a minority of patients treated at SNH receive HCV treatment. Efforts must be directed towards removing obstacles that prevent this vulnerable patient population from receiving the standard-of-care treatment for HCV with HCC.

The optimal timing of DAA therapy appears to be 0-3 months after liver transplantation for HCV-associated HCC, given increased rates of SVR and improved RFS. Delayed administration after transplant should be avoided. A randomized prospective trial is warranted to validate these results.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary neoplasm of the liver, affecting 6 per 100,000 persons in the United States each year.(1) Between 2008 and 2016, the incidence of HCC has steadily increased by 3% annually, with recent projections indicating its continued growth.(2) This is likely attributable to a high prevalence of hepatitis C virus (HCV), the most common etiology of HCC in the U.S.(1)

Historically, the mainstay of treatment for HCV included interferon-based regimens with or without ribavirin. Given a significant adverse drug reaction profile, this regimen had poor adherence and low overall rates of sustained virologic response (SVR).(3) Fortunately, the introduction of direct acting antivirals (DAAs) in 2011 and their widespread dissemination in 2015 offered a more favorable side-effect profile and SVR rates exceeding 95%.(4) With the successful treatment of HCV, studies have established a marked improvement in HCC patient outcomes.(5) Furthermore, a recent retrospective review of HCV-infected patients at 129 Veterans Health Administration hospitals who achieved SVR with DAAs had a 76% reduction in risk of developing HCC compared to those who did not achieve SVR.(6)

Chronic HCV infection leads to hepatic inflammation and fibrosis, conferring an over 20-fold increased risk for developing HCC.(7) DAAs halt the continuous insult on the liver and improve liver function and fibrosis, reducing the risk for developing de novo HCC.(8, 9) While DAAs offer an avenue for improved clinical outcomes for HCC patients, with a median survival of 72 vs 12 months ($p<0.01$) when comparing patients who received DAA therapy to those who did not, access remains a major concern.(10) Known barriers to treatment include prohibitive costs, as well as patient, provider, and system-level factors which span health insurance status, socioeconomic status, and referral-associated delays, all of which can be compounded in a

safety net hospital setting.(11, 12) Currently, there is limited data directly comparing barriers and clinical outcomes based on treatment facility in high-risk patient populations.

The management of HCC is largely dictated by the Barcelona Clinical Liver Cancer (BCLC) criteria, which takes into account patient factors such as performance status and Child-Pugh status, as well as oncologic considerations such as the size and number tumors.(13) For early-stage disease meeting radiographic Milan criteria, liver transplantation remains the gold-standard curative treatment option.(14) In the U.S., an estimated 900 liver transplants performed each year for HCV-associated HCC.(15) In light of controversial data suggesting DAAs may accelerate HCC recurrence, there is significant practice pattern variability across the country for when DAAs are administered.(16, 17) Moreover, there is a paucity of data investigating the impact of the timing of DAAs in the setting of liver transplantation.

The overarching aim of our study was to determine the impact of hepatitis C treatment on long-term outcomes in patients with hepatocellular carcinoma. More specifically, we sought to 1) assess the impact of HCV treatment on survival in patients with concurrent HCC treated at safety net hospitals compared to tertiary referral centers, 2) determine the associated barriers to receiving HCV treatment in these two populations, and 3) assess the optimal timing of DAAs in patients with HCV-associated HCC who underwent liver transplantation.

AIMS 1 & 2

We hypothesize that HCV treatment is associated with improved overall survival and recurrence-free survival in patients with HCC

We hypothesize barriers to HCV treatment include lack of health insurance and higher clinical stage for HCC

METHODS

Study Design and Study Population

In this retrospective cohort study, patients were selected from the United States Safety Net Collaborative (USSNC), a consortium of five large safety net hospitals and their tertiary referral center counterparts, including Grady Memorial Hospital, Parkland Memorial Hospital, Jackson Memorial Hospital, Bellevue Hospital, Ben Taub Hospital, Emory University, University of Texas Southwestern Medical School, University of Miami Miller School of Medicine, and New York University Medical School. All patients greater than 18 years of age with a diagnosis of HCC due to HCV etiology with known HCV treatment status were included from 2012-2014. Patients with extrahepatic disease (stage IVb), a positive macroscopic margin on liver resection (R2), recurrent disease, and non-hepatocellular carcinoma histology were excluded. Institutional Review Board approval was obtained at each site prior to data collection.

Study Variables and Outcomes

Demographic, pathologic, operative, post-operative, and survival outcomes data were collected via retrospective review of patient electronic medical records. Clinical staging was based on American Joint Committee on Cancer (AJCC) Guidelines 8th edition. HCC treatment was categorized as no treatment, surgery (right hepatectomy, extended right hepatectomy, left hepatectomy, extended left hepatectomy, sectionectomy, and non-anatomic resection), liver transplant, liver-directed therapy (radiofrequency ablation [RFA], microwave ablation [MVA], transarterial chemoembolization [TACE], radioembolization [Y90], and radiation, regardless of repetitive procedures) and chemotherapy. HCV treatment included DAAs, interferon-based regimens, and multiple treatment types. Health insurance included private, government provided, including Medicaid and Medicare, or a hospital card. Analysis was stratified by receipt of HCV treatment and treatment facility. The primary outcome was overall survival (OS). Secondary outcomes were recurrence-free survival (RFS) and receipt of HCV treatment.

Analytic Plan

Statistical analysis was performed using SPSS 26.0 software (IBM Inc., Armonk, NY). Analyses were conducted specifying a significant level (alpha) of 0.05. Chi-squared or Fisher's exact tests were used for comparing categorical variables. Student's t-test or Mann-Whitney tests were used for comparing the means and medians of continuous variables, respectively. Comparative analyses were performed to differentiate the cohorts that did and did not receive HCV treatment. Kaplan-Meier analyses, log-rank tests, and univariate Cox regression were performed to determine associations between HCV treatment status and OS. Univariate and multivariable binary logistic regression were used to determine the association of clinicopathologic variables and receipt of HCV treatment. Covariates that were deemed clinically relevant and/or statistically significant on univariate analyses were selected for inclusion in multivariable models.

RESULTS

Patient Characteristics

Of the 1910 patients in the U.S. Safety Net Collaborative database, 941 met inclusion criteria. The demographic and clinicopathologic characteristics of the study population are outlined in Table 1.1. Twenty-six percent (n=245) of patients received HCV treatment. The median age of patients was 60 years (IQR 56-64). Seventy-eight percent (n=734) were male and 22% (n=207) were female. The majority of patients were insured (89%, n=769). Ninety-five percent (n=887) had cirrhosis with a median MELD score of 10 (IQR 8-15). Most patients had clinical stage I (48%, n=428) and II (24%, n=215) disease. Patients who received care at a tertiary referral center comprised 57% (n=533) of the study population, compared to 43% (n=408) who received care at a safety net hospital. Among those who received HCV treatment, 76% (n=186) of patients received care at a tertiary referral center, while 24% (n=59) received care at a safety net hospital. Conversely, only 35% and 14% of eligible patients received HCV treatment at tertiary referral centers and safety net hospitals, respectively. For the management of HCC, 6% (n=54) underwent resection, 17% (n=163) received a liver transplant, 50% (n=473) received liver-directed therapy, 6% (n=60) received chemotherapy, and 20% (n=191) received no treatment. Median follow-up was 18 months (IQR 6-46).

Patients who received HCV treatment were older (62 vs 59 years, $p<0.01$), more likely to be White (68 vs 51%, $p<0.01$), to have insurance coverage (96 vs 86%, $p<0.01$), and to have a lower MELD score at diagnosis (10 vs 11, $p=0.03$) compared to those who did not receive HCV treatment. These patients were also more likely to have clinical stage I disease (58 vs 44%, $p<0.01$), to receive treatment at a tertiary referral center (76 vs 50%, $p<0.01$), to receive HCC treatment (93 vs 75%, $p<0.01$), and had longer follow-up (39 vs 14 months, $p<0.01$). These patients were less likely to have a mental health diagnosis (8 vs 14%, $p<0.01$).

Survival Analysis

For all patients, HCV treatment was associated with improved median OS compared to no HCV treatment (70 vs 21 months, p<0.01; Figure 1A). This association persisted across all clinical stages (all p<0.01), and all HCC treatment modalities (all p<0.01). On univariate Cox regression, insurance coverage, HCC treatment (resection, transplant, and liver-directed therapy), and HCV treatment were associated with improved overall survival (Table 1.2). On multivariable Cox regression, accounting for age, insurance type, MELD, clinical stage, treatment facility type, and HCC treatment, HCV treatment remained independently associated with improved OS (HR: 0.65, 95% CI: 0.51-0.83, p<0.01). Notably, treatment at a safety net facility was not a predictor for decreased overall survival in the multivariable model. On subset analysis by treatment facility type, when patients received HCV treatment, the degree of improvement in survival compared to no treatment was similar regardless if treated at a tertiary referral center (5-yr OS: 56 vs 31%, p<0.01; Figure 1C) or a safety net hospital (5-yr OS: 51 vs 23%, p<0.01; Figure 1D).

Recurrence-Free Survival Analysis in Patients with Complete Tumor Extirpation

On subset analysis for patients who underwent complete tumor extirpation (surgical resection or liver transplant), patients who received HCV treatment had improved RFS compared to those who did not (91 vs 80 months, p=0.03; Figure1B). On univariate Cox regression, the presence of cirrhosis and HCV treatment was associated with improved RFS. Asian race was associated with worse RFS. On multivariable Cox regression, accounting for race, presence of cirrhosis, and treatment facility, HCV treatment remained associated with improved RFS. Treatment at a safety net hospital was not a predictor for worse RFS on univariate or multivariable analysis.

Barriers to Receiving HCV Treatment

For all patients, factors associated with a decreased odds of receiving HCV treatment on univariate analysis include Black race, higher MELD score, advanced clinical stage, and care at a safety net hospital (all $p<0.05$) (Table 1.4). On multivariable logistic regression, accounting for age, insurance status, and HCC treatment, Black race, higher MELD score, and clinical stage II were associated with a decreased odds of receiving HCV treatment, while receiving a liver transplant or undergoing liver-direct therapy was associated with an increased odds of receiving HCV treatment. When stratifying by treatment facility, no significant barriers to HCV treatment were noted when accounting for the relevant demographic and clinicopathologic factors. At tertiary referral centers, Black race, higher MELD score, and clinical stage II were associated with a decreased odds of receiving HCV treatment in the adjusted model accounting for age, insurance status, and HCC treatment modality. Notably, care at a safety net hospital was not a barrier to receiving HCV treatment in the multivariable model.

DISCUSSION

In this multi-institutional study, HCV treatment was associated with improved OS in all patients and improved RFS in surgical patients, regardless of clinical stage, HCC treatment modality, or treatment facility type. However, only a small subset of patients seen at safety net hospitals and tertiary referral centers received HCV treatment. Identified barriers to receiving HCV treatment include Black race, higher MELD score, and HCC clinical stage. For all patients, while insurance status and treatment facility were significant on univariate analysis, in the multivariable model, these were no longer predictors of not receiving HCV treatment. When the unique challenges patients at safety net hospitals face are addressed and patients go on to receive HCV treatment, long-term outcomes are similar to those of their peers at tertiary referral centers. Deliberate efforts must be directed towards removing the obstacles that prevent this vulnerable patient population from receiving the standard-of-care treatment.

For patients with HCC, HCV treatment portends improved short and long-term outcomes. While a minority of studies in 2016 report a higher risk of HCC recurrence with DAA therapy, more recent prospective studies and meta-analyses demonstrate HCV treatment with DAAs is associated with lower HCC recurrence risk, especially when DAA initiation is delayed 6-12 months from HCC treatment.(16, 18-22) Routinely, participating institutions in the Safety Net Collaborative elected for HCC management to precede HCV therapy. In HCC patients with HCV treated with DAAs, Singal *et al*. demonstrated recurrence rates range from 0 to 59% within 2 years, with a pooled estimate for recurrence of 25% (95% CI: 19.4-31.2).(23) We report 2-year recurrence rates of 5 and 14% for patients who did and did not receive HCV treatment (Figure 1, Panel B). With respect to long-term outcomes, Dang *et al*. reported improved 5-year OS in East Asian HCC patients who received HCV treatment, compared to those who did not receive treatment (88 vs 66%, $p<0.01$).(24) Similarly, in the U.S., a 2019 retrospective cohort study showed a reduced mortality in HCC patients who received DAA therapy compared to those who

did not (HR: 0.54, 95% CI: 0.33-0.90) and a 2-year OS of 88 vs 76%.(21) In our study, 5-year survival was 55 vs 27% for patients who received HCV treatment compared to those who did not ($p<0.01$). This association of HCV treatment with improved survival persisted on multivariable analysis regardless of treatment facility. In addition, the HCV treatment variable was comprised of DAA treatment, interferon, and combination DAA and interferon-based regimens. Regardless, the therapeutic benefit of HCV treatment remains clear.

While the impact of HCV treatment on patients with concomitant HCC is apparent, unfortunately, 86% of patients at safety net hospitals and 65% of patients at tertiary referral centers did not receive HCV treatment. Among those who received HCV treatment, only 19% were administered DAAs, suggesting these patients are confronting substantial barriers to accessing these medications. Significant differences in the proportion of patients receiving DAA therapy at tertiary referral centers (6%) and safety net hospitals (3%) were also noted. Reasons for this are multifactorial and likely stem from patient, provider, and system-level factors. At safety net hospitals, these obstacles are compounded, especially in a patient population where inequities in the social determinants of health, which encompass economic stability, educational attainment, and access to health care, are highly prevalent.(25)

At the individual level, demographic and social factors associated with not receiving DAA therapy are well-documented, which include lack of health insurance, a history of substance abuse, and comorbid disease.(26) Our multivariable analysis determined Black race, higher MELD score, and advanced HCC clinical stage to be associated with decreased odds of receiving HCV treatment. These findings highlight the racial/ethnic disparities present in this vulnerable patient population, with race a likely proxy for low socioeconomic status. Higher MELD score and clinical stage are representative of limited engagement with the health care system. Similarly, Mokdad *et al.* reported a decreased likelihood of patients at safety net

hospitals to receive HCC therapy compared to those not at a safety net hospitals (60 vs 40%, $p<0.01$), despite matched tumor stages.(27) These findings further highlight decreased access of health care resources among safety net hospital patients.

Considering provider and system-level drivers, sub-optimal screening and access to definitive HCV treatment contribute to the high prevalence of untreated disease. In the U.S., 45-85% of HCV patients are unaware of their status.(28) Prior work at a Grady Memorial Hospital, a high-volume safety net hospital in the Southeastern U.S., revealed 74% of HCC patients were HCV-positive, with only 15% of patients receiving treatment at the time of diagnosis.(29) Formalized screening programs are critical for early detection and intervention, especially for at-risk patients.

Once a patient is diagnosed with HCV and is able to seek care, the price of DAA therapy can be prohibitive, with a 12-week course ranging from $40,000-123,000.(30, 31) Further, though DAA therapy is routinely covered by health insurance in the U.S., reimbursement criteria remains inconsistent and often does not align with national treatment guidelines, thus hampering DAA distribution. For example, variable Medicaid prior authorization policies have been shown to further restrict the widespread distribution of DAAs. Clinical indications warranting reimbursement vary based on location and coverage policy, which can include advanced cirrhosis, suppressed HIV levels, and negative drug toxicology screens.(32) These criteria often preclude patients served by safety net hospitals. The fact that a diagnosis of cirrhosis is a requirement of 75% of prior authorizations for DAAs may account for the association of cirrhosis with improved RFS in our univariate analysis (Table 1.3).(30) While costly upfront, treatment of HCV halts the continuous insult on the liver and prevents further liver decompensation, liver-related complications, and accompanying costly interventions. To ultimately decrease HCV and HCC associated morbidity and mortality, we advocate for

unfettered access to these life-saving medications. State Medicaid policies must be updated to ensure equitable access.

While the introduction of DAAs have transformed the management of HCV, there remains significant obstacles for patients to receive treatment. Fortunately, there are approaches that may improve HCV and HCC cure rates. It is important to recognize once a patient received HCV treatment, safety net hospital designation in and of itself was not an independent predictor for decreased survival or early recurrence, underscoring the importance of health care access and delivery.

In our effort to address modifiable barriers, solutions that target HCV and HCC screening, referral, diagnosis, and treatment delivery are essential. Patient outreach, education, screening, and counseling programs that further integrate existing resources at safety net hospitals, spanning patient navigation services, social work, and substance abuse clinics may improve treatment success.(33) In addition, the use of dedicated HCV/HCC treatment clinics and disease management teams help streamline treatment protocols, and have been associated with increased specialist referrals, care delivery, and survival.(34) After treatment, post-SVR HCC surveillance programs at a safety net hospital have also been shown to improve long-term outcomes.(35) Lastly, by working with community resources and primary care providers, pipelines that promote strong referral patterns ensure continued HCV, HCC, and cirrhotic patient engagement.

CONCLUSIONS

In summary, this multi-institutional study provides real-world evidence to support HCV treatment in patients with concomitant HCC. HCV treatment improves overall and recurrence-free survival in all patients with HCC, regardless of clinical stage, HCC treatment modality or type of treatment facility. While DAAs were a major advance for HCV treatment, offering a promising solution to halt the progression of liver disease, there exist significant challenges in accessing this treatment. In order to optimize the care of these high-risk patients, we must work to remove modifiable barriers by incorporating existing resources at safety net hospitals with novel, patient-centered solutions to maximize this potential.

AIM 3

We hypothesize that DAA therapy administration after liver transplantation is associated with improved rates of SVR and improved RFS compared to those who receive DAA therapy prior to liver transplantation

METHODS

Study Design and Study Population

In this retrospective cohort study, patients were selected from the United States Hepatocellular Carcinoma Liver Transplantation Consortium (USHCCLTC), a multi-institutional collaborative of 19 high-volume liver transplant centers, including Emory University, the University of Cincinnati College of Medicine, David Geffen School of Medicine at University of California Los Angeles, Johns Hopkins, Indiana University Health, University of Alabama, Lahey Hospital and Medical Center, Keck School of Medicine of University of Southern California, Cleveland Clinic, University of Texas Southwestern Medical Center, Stanford University, Tampa General Hospital, University of Michigan, Piedmont Healthcare, Duke University School of Medicine, Henry Ford Health System, University of Pittsburgh Medical Center, University of Wisconsin-Madison, and Washington University School of Medicine in St. Louis. Patients who were older than 18 years of age with a diagnosis of HCC due to HCV etiology, completed DAA therapy, and underwent liver transplantation between 2015-2019 were included. HCC diagnosis was made according to the established Barcelona Clinic Liver Cancer Guidelines. HCV diagnosis was defined by the presence of HCV antibody or HCV RNA. Patients who previously received interferon therapy, who were transplanted outside of Milan criteria, who had missing DAA timing data, or who had a positive macroscopic margin during at the time of surgery (R2) were excluded. Institutional Review Board approval was obtained at each center prior to the initiation of data collection.

Study Variables and Outcomes

Demographic, preoperative, operative, post-operative, histopathologic, and long-term survival outcomes were collected via review of patient electronic medical records. Clinical and pathologic staging was based on the American Joint Committee on Cancer (AJCC) 8th edition. DAA therapy timing was categorized as the initiation of DAA therapy pre-LT, 0-3 months post-

LT, or ≥3 months post-LT. Liver-directed therapy was considered radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and/or Y-90. Primary outcomes were sustained virologic response (SVR) and recurrence-free survival (RFS).

Analytic Plan

Statistical analysis was conducted with SPSS 26.0 software (IBM Inc., Armonk, NY). Descriptive statistics for each variable was reported. A significance level (alpha) of 0.05 was specified for two-tailed tests. Comparative analysis was performed, including Chi-squared tests or Fisher's exact tests for discrete variables and Student's t-test or Mann-Whitney tests for continuous variables. Univariate binary and multivariable regression were performed to determine the association of clinicopathologic variables and outcomes of interest. Kaplan-Meier analysis, log-rank tests, and univariate Cox regression were performed to determine the association between timing of DAA therapy and survival.

RESULTS

Study Cohort Characteristics

Of the 857 patients in the USHCCLTC, 427 met the specified inclusion criteria. Baseline demographic, clinicopathologic, perioperative, and oncologic data are outlined in Table 2.1. Fifty-eight percent (n=258) of patients received DAAs pre-LT, 10% (n=45) received DAAs 0-3 months post-LT, and 27% (n=124) received DAAs ≥3 months post-LT. The median age at diagnosis was 61 years. The majority of patients received a ledipasivir/sofosbuvir regimen compared to sofosbuvir/velpatasvir or glecaprevir/pibrentasvir. While the majority of patients received liver-directed therapy, a higher proportion were offered liver-directed therapy if DAAs were administered pre-LT (93%, n=241), compared to those receiving DAAs 0-3 months post-LT (89%, n=40) or ≥3 months post-LT at (82%, n=102). A higher proportion of patients who underwent transplantation with an HCV+ donor liver received DAAs post-operatively, with 36% (n=16) of patients receiving HCV+ livers in the 0-3 months post-LT group and 33% (n=40) in the ≥3 months post-LT group, compared to 4% (n=9) in the pre-LT group. Notably, post-operative complication rates did not differ between the DAA timing groups (42% pre-LT, 53% 0-3 months post-LT, 48% ≥3 months post-LT, p=0.25). The median time on the waitlist was 7 months (IQR 3-12). Median follow-up was 36 months (IQR 21-52).

Sustained Virologic Response

Receiving DAA therapy ≥3 months post-LT was associated with a decreased odds of achieving SVR (OR 0.36, 95% CI 0.20-0.65, p<0.01) (Table 2.2). Patients within Milan criteria who were interferon-treatment naïve and received DAAs pre-LT, 0-3 months post-LT, and ≥3 months post-LT achieved SVR rates of 91%, 93%, and 78%, respectively. Notably, DAA therapy pre-LT or 0-3 months post-LT was associated with improved SVR rates greater than 13%.

Recurrence-Free Survival

Receiving DAA therapy ≥3 months post-LT was associated with worse RFS on univariate Cox regression (HR 2.34, 95% CI 0.14-4.82, p=0.02) (Table 2.3). A higher stage at diagnosis, specifically stage IV disease, was associated with worse RFS. Factors associated with improved RFS include achieving SVR (HR 0.28, 95% CI 0.13-0.62, p<0.01) and a DAA regimen of ledipadsivir/sofosbuvir (HR 0.33, 95% CI 0.13-0.84, p<0.01).

Considering patients within Milan criteria who were interferon-treatment naïve, achieving SVR with DAAs was associated with improved 5-year RFS at 93%, compared to 76% in those who did not achieve SVR (Figure 2.1).

Receiving DAAs 0-3 months post-LT was associated with improved 5-year RFS of 100% compared to receipt of DAAs pre-LT at 94% and ≥3 months post-LT at 84% (Figure 2.2). Administering DAAs early in the post-operative period was associated with improved SVR and RFS.

DISCUSSION

For interferon treatment-naïve patients with HCV-associated HCC within Milan criteria undergoing liver transplantation, our analysis of a large multi-institutional collaborative of 19 high-volume centers in the U.S. suggests administering DAAs early in the post-operative period, within 3 months of liver transplantation, improves rates of viral clearance and recurrence-free survival.

Prior to 2011, treatment for HCV was severely limited, as the only available option was interferon-based therapy. Unfortunately, given the significant adverse drug reactions, interferon was poorly tolerated and SVR rates were abysmal, ranging from 29-56%.(3, 36) The emergence of DAAs fundamentally changed the HCV treatment landscape by offering a simple one pill per day dosing with minimal side effects, allowing patients to achieve SVR rates of 95-97%.(37) As a result, patients benefited from marked improvement in liver-associated morbidity and mortality. A 2017 retrospective review of 22,500 patients with HCV reported achieving SVR with DAAs resulted in a significantly reduced risk of developing HCC (HR 0.28, 95% CI 0.22-0.36).(38) In addition, a more recent study from our group demonstrated the association of HCV treatment and improved long-term outcomes in patients with HCC, regardless of clinical stage, HCC treatment modality, or treatment facility type.(39) With the considerable success of DAAs, interferon-based treatment strategies are no longer relevant to the modern management of HCV. Hence, we honed-in on an interferon treatment-naïve patient population. Furthermore, by excluding patients with prior interferon therapy, we removed a potential confounder for the immunologic interaction between HCV, HCC, and transplant immunosuppression, to better isolate the question of the optimal time to administer DAA therapy.

Considering the treatment approaches for HCC, complete tumor extirpation, specifically resection or liver transplantation, are the only two curative treatment options, with liver

transplant resulting in the most favorable long-term outcomes.(40) While the appropriate treatment strategy is dependent on the tumor burden, host liver function, and the future liver remanent, liver transplantation not only allows for clearance of the tumor, but also addresses any underlying liver disease. Other treatment modalities, including liver-directed therapy, radiation therapy, and systemic therapy, are often employed in combination with resection or as a bridge to liver transplant.(41) Given patients within Milan criteria are on the waitlist for an average of 8.4 months, many are offered bridging therapy to transplant with the goal of preventing disease progression beyond Milan criteria.(42) Predictably, liver-directed therapies are more frequently employed in liver transplant patients compared to other HCC patients.(43) Our data supports this trend. Nonetheless, compared to all other treatment approaches for unresectable disease, liver transplant offers superior oncologic outcomes in select patients, with 5-year overall survival exceeding 70%.(44)

There are data that describe the immunomodulatory effect of DAAs in the context of HCC and post-transplant immune suppression. HCV is implicated to induce hepatocyte apoptosis, oxidative stress, and steatosis, resulting in progressive liver damage, fibrosis, and ultimately end stage liver disease.(45) The 3 main classes of DAAs work by inhibiting specific HCV non-structural proteins involved in viral replication, namely NS3/4A, NS5A, and NS5B.(46) While many do not consider DAAs themselves tumorigenic, DAAs may increase the risk for HCC recurrence via an indirect mechanism. After eradication of the virus, DAA therapy evokes profound immunological changes. More specifically, DAAs rapidly decrease the cytotoxic function of natural killer (NK) cells and dampen intrahepatic activation of macrophages, while frequencies of suppressive regulatory T cells remain high.(47) The downstream effects of this are a diminished inflammatory response and cancer cell clearance mechanisms. Furthermore, in liver transplant patients, the immune system is suppressed pharmacologically to prevent graft rejection. This immunocompromised state inhibits tumor surveillance by the host, which may

result in an increased risk for HCC recurrence.(48, 49) When DAAs are offered prior to liver transplant, patients may have a prolonged state of sustained impairment of T cells.(50) These DAA-mediated changes in immune function may be the driver behind worse RFS seen in patients who received DAAs pre-LT compared to 0-3 months post-LT, and needs to be explored further. Bearing in mind the immunomodulatory impact of DAAs, clinicians should carefully consider the timing of HCV treatment, particularly in liver transplant patients.

In relation to liver transplantation, there is considerable variability for when DAA therapy is administered. In our study, the timepoints for initiating DAAs pre-LT, 0-3 months post-LT, and ≥3 months post-LT were selected to reflect real-world practice patterns. Offering DAA therapy prior to liver transplant allows for the treatment of HCV while the patient is on the waitlist, which may halt the progression of liver disease, improve liver function, and avoid the need for liver transplant altogether.(51) Interestingly, improvements in liver function due to DAA therapy have not been shown to significantly impact waitlist priority or dropout rates.(52, 53) Importantly, disadvantages for administering DAA therapy prior to liver transplant include decreased rates of SVR, as active HCC tumors may serve as a reservoir for HCV.(54) This increases the risk for treatment failure and promotes resistance to re-treatment, which requires additional courses of DAAs, leading to an excess of $25,000-70,000 in costs compared to those who receive DAAs post-LT.(55, 56)

Conversely, reserving DAA therapy until after liver transplant may be preferred based on data demonstrating the improved efficacy of DAAs in inducing SVR, as well as a potential for a decreased risk of recurrence of HCC in previously treated patients.(57) Further, treating post-transplant increases access to HCV positive donors, which comprise 3-15% of donor pools across United Network for Organ Sharing (UNOS) regions.(58) Consistent with prior literature, in our study, we found initiating DAA therapy 0-3 months post-LT was associated with high rates

of SVR. Remarkably, among the 19 liver transplant centers included in this consortium, only a minority of patients (10%) received DAAs 0-3 months post-LT. While post-operative complications may lead to a delay in initiating DAA therapy, it is worth noting there was no significant difference in post-operative complication rates between the DAA timing groups. In fact, the post-operative complication rates were slightly higher in the 0-3 months post-LT group, compared to the pre-LT and ≥3 months post-LT groups.

With the widespread use of DAAs, controversial data have emerged describing an increased risk of HCC attributed to DAA therapy. Reig *et al*. reported a high rate of early HCC recurrence of 35% in 20 patients treated with DAAs who underwent resection or received liver-directed therapy.(16) Comparably, 19 patients receiving DAAs had an HCC recurrence rate of 42.1% in a study conducted by Conti and colleagues.(17) Though alarming, these findings should be carefully examined, and may be a result of small sample sizes, study designs without comparison groups, and short follow-up times of 5.7 months and 6 months, respectively. More recent studies have challenged these findings, concluding there was no association between DAA administration and HCC recurrence.(22, 59-64) A 2017 meta-analysis by Waziry *et al*. suggested there was no evidence for increased HCC recurrence after SVR was achieved from DAA or interferon-based therapy, however, the impact of timing of therapy as a variable was not taken into consideration.(65) The above conflicting literature highlight the significant heterogeneity of study inclusion criteria, HCC treatment modalities, and HCV treatments.

Currently, there is limited data regarding the optimal time to initiate DAAs in the liver transplant population.(66, 67) A study by Gorgen *et al*. sought to answer this question among 516 patients with underwent liver transplantation for HCV with HCC who received DAA therapy either pre or post-LT.(68) The investigators reported a SVR rate of 93.4% and a 5-year RFS of 93.4% for patients who received DAAs pre-LT and an SVR rate of 96.5% and a recurrence rate

of 2.9% for those who received DAAs post-LT. However, the study time period included patients from 2005-2015, while DAAs were widely disseminated in 2015. In addition, a number of patients were transplanted outside of Milan criteria (9.1% pre-LT, 17.2% post-LT) and the median time interval between administration of DAA and liver transplant was 2.4 months for pre-LT and 24 months post-LT. The comparison groups also included patients who received interferon, a now outdated form of treatment. Our study, in contrast, sought to determine the optimal timing of DAA therapy in the modern era in patients who did not previously receive interferon-based therapy.

CONCLUSIONS

In summary, the optimal timing of DAA therapy appears to be 0-3 months after liver transplant for HCV-associated HCC, given increased rates of sustained virologic response and improved recurrence-free survival. If feasible, we advocate for administration of DAAs early in the post-operative period, and delay of DAAs more than 3 months after liver transplant should be avoided. A randomized prospective trial is warranted to validate these results.

STRENGTHS AND LIMITATIONS: AIMS 1 & 2

Limitations of this study include its retrospective design. Second, the study time period was a limitation. With FDA approval of second-generation DAAs in late 2013 and its widespread dissemination in 2014-2015, it is likely we underestimate the extent of DAA use compared to current trends.(69) Third, data regarding HCV treatment start or end dates was not collected. As a result, we do not have access to time intervals between definitive HCC treatment and HCV therapy initiation, thus the optimal timing for HCV or DAA therapy is unclear. Though given the timeframe of our study, it is likely patients received DAAs after HCC treatment. In addition, principal investigators of the U.S. Safety Net Collaborative reported the general practice pattern at each center is to manage HCC prior to pursuing HCV treatment. Finally, details with respect to the specific DAA regimen and duration of therapy were not available.

Strengths of this study include the use of a multi-institutional collaborative database, which effectively eliminates single-institution bias and allows for generalizability. Moreover, to our knowledge, this is the first study to examine the impact of HCV treatment on survival outcomes in the highest volume safety net hospitals and their sister tertiary referral centers in the U.S.

STRENGTHS AND LIMITATIONS: AIM 3

Limitations of this study include those inherent to a retrospective design, specifically the exclusion of missing data. Second, the event rate for recurrence was zero for patients who received DAAs 0-3 months post-LT, limiting our ability to perform multivariable analysis. However, the fact there were no events is very striking and warrants further investigation. Third, as this study represents real-world practice patterns, there is variability between institutions regarding DAA regimen and surveillance protocols for HCC recurrence.

Similar to Aims 1 & 2, a consortium of 19 transplant centers in the U.S. eliminates single-institution or single-provider bias. Second, the isolation of our exposure of interest, the timing of DAA therapy, was improved as a result of our inclusion criteria for liver transplant patients with HCV-associated HCC who were interferon treatment-naïve and within Milan criteria. Thus, we were able to effectively remove potential biological confounders. Third, the rates of SVR and RFS represent real-world data from among the highest volume liver transplant centers in the U.S. Lastly, given this study is the first to answer the question of optimal timing of DAA therapy, the findings of this study can be readily applied to clinical practice.

CONCLUSIONS

HCV treatment for patients with HCC is associated with improved oncologic outcomes. Unfortunately, recognizing the fact that only a minority of patients received HCV treatment both at safety net hospitals and tertiary referral centers, efforts must be directed towards removing barriers to HCV treatment. For patients with HCV-associated HCC undergoing liver transplantation, DAAs should be offered 0-3 months after transplant, given increased rates of SVR and RFS. These compelling findings serve as a strong foundation for a prospective randomized clinical trial.

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TABLES

Table 1.1: baseline characteristics of HCC patients with HCV based on HCV treatment status

Variable	All Patients n=941 (%)	No HCV Treatment n=696 (74)	HCV Treatment n=245 (26)	p-value
Age median (median, IQR)	60 (56-64)	59 (55-64)	62 (58-65)	<0.01
Gender				
Female	207 (22)	154 (22)	53 (22)	0.87
Male	734 (78)	542 (78)	192 (78)	
Race				
White	448 (56)	296 (51)	152 (68)	
Black	297 (37)	242 (42)	55 (24)	<0.01
Asian	52 (7)	36 (6)	16 (7)	
Unknown	7 (1)	5 (1)	2 (1)	
Insurance status				
Uninsured	95 (11)	85 (14)	10 (4)	<0.01
Insured	769 (89)	539 (86)	23 (96)	
Mental health diagnosis				
No	814 (87)	589 (85)	225 (92)	<0.01
Yes	119 (13)	99 (14)	20 (8)	
Body Mass Index				
<18.49	23 (2)	20 (3)	3 (1)	
18.5-24.99	292 (32)	227 (34)	65 (27)	
25-29.99	336 (37)	231 (34)	105 (43)	0.11
30-34.99	175 (19)	127 (19)	48 (20)	
35-39.99	60 (7)	46 (7)	14 (6)	
≥40	30 (3)	22 (3)	8 (3)	
ASA class				
I	2	1 (1)	1 (1)	
II	36	23 (26)	13 (15)	<0.01
III	57	36 (40)	21 (25)	
IV	78	28 (32)	50 (59)	
V	1	1 (1)	0 (0)	
Cirrhosis				
No	50 (5.3)	34 (5)	16 (7)	0.34
Yes	887 (95)	658 (95)	229 (94)	
MELD (median, IQR)	10 (8-15)	11 (8-16)	10 (7-13)	0.03
Clinical stage				
I	428 (48)	290 (44)	138 (58)	
II	215 (24)	162 (25)	53 (22)	<0.01
III	163 (18)	129 (20)	34 (14)	
IVa	86 (10)	73 (11)	13 (6)	
Treatment facility				
Tertiary referral center	533 (57)	347 (50)	186 (76)	<0.01
Safety net hospital	408 (43)	349 (50)	59 (24)	
HCV treatment				
No	696 (74)	696 (74)	0	<0.01
Direct acting antiviral	46 (5)	0	46 (19)	

IFN	93 (10)	0	93 (38)	
Multiple treatment types	106 (11)	0	106 (43)	
HCC treatment				<0.01
No treatment	191 (20)	173 (25)	18 (7)	
Surgery	54 (6)	42 (6)	12 (5)	
Transplant	163 (17)	71 (10)	92 (38)	
Liver-directed therapy	473 (50)	354 (51)	119 (49)	
Chemotherapy	60 (6)	56 (8)	4 (2)	
Median follow-up (IQR)	18 (6-46)	14 (5-35)	39 (14-61)	<0.01

Abbreviations: IQR – interquartile range, CI – confidence interval, ASA – American Society of Anesthesiologists, MELD – Model for End-Stage Liver Disease

Table 1.2: univariate and multivariable Cox regression for overall survival for all HCC patients with HCV

	Univariate Cox Regression		Multivariable Cox Regression	
Variable	**HR (95% CI)**	**p-value**	**HR**	**p-value**
Age (median, IQR)	0.99 (0.97-0.99)	0.01	1.00 (0.99-1.01)	0.94
Gender				
Female	Reference			
Male	1.16 (0.93-1.44)	0.19		
Race				
White	Reference			
Black	1.14 (0.94-1.39)	0.18		
Asian	0.71 (0.43-1.18)	0.18		
Unknown	0.76 (0.24-2.37)	0.64		
Insurance status				
Uninsured	Reference		Reference	
Insured	0.54 (0.41-0.71)	<0.01	0.92 (0.66-1.28)	0.61
Cirrhosis				
No	Reference			
Yes	1.42 (0.93-2.16)	0.10		
MELD (median, IQR)	1.03 (1.02-1.03)	<0.01	1.02 (1.01-1.02)	<0.01
Clinical stage				
I	Reference		Reference	
II	1.54 (1.22-1.95)	<0.01	1.59 (1.24-2.07)	<0.01
III	3.4 (2.7-4.35)	<0.01	2.99 (2.29-3.89)	<0.01
IVa	4.1 (3.11-5.52)	<0.01	2.32 (1.69-3.18)	<0.01
Treatment facility				
Tertiary referral center	Reference		Reference	
Safety net hospital	1.44 (1.20-1.71)	<0.01	0.94 (0.75-1.16)	0.55
HCC treatment				
No treatment	Reference		Reference	
Surgery	0.08 (0.05-0.13)	<0.01	0.11 (0.07-0.19)	<0.01
Transplant	0.03 (0.02-0.05)	<0.01	0.04 (0.02-0.06)	<0.01
Liver-directed therapy	0.23 (0.19-0.29)	<0.01	0.38 (0.21-0.36)	<0.01
Chemotherapy	0.74 (0.53-1.02)	0.07	0.59 (0.39-0.87)	<0.01
HCV treated				
No	Reference		Reference	
Yes	0.41 (0.33-0.52)	<0.01	0.65 (0.51-0.83)	<0.01

Table 1.3: univariate and multivariable Cox regression for recurrence-free survival for all HCC patients with HCV

	Univariate Cox Regression		Multivariable Cox Regression	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age (median, IQR)	1.01 (0.96-1.05)	0.80		
Gender				
Female	Reference			
Male	1.08 (0.49-2.35)	0.85		
Race				
White	Reference		Reference	
Black	1.24 (0.58-2.67)	0.58	1.11 (0.51-2.41)	0.80
Asian	3.33 (1.39-7.97)	<0.01	2.51 (0.96-0.55)	0.06
Unknown	--	--	--	
Insurance status				
Uninsured	Reference			
Insured	--	--		
Cirrhosis				
No	Reference		Reference	
Yes	0.38 (0.18-0.81)	0.01	0.52 (0.22-1.23)	0.14
MELD (median, IQR)	0.99 (0.92-1.05)	0.64		
Clinical stage				
I	Reference			
II	1.19 (0.57-2.5)	0.63		
III	2.22 (0.95-5.18)	0.07		
IVa	--	0.98		
Treatment facility				
Tertiary referral center	Reference		Reference	
Safety net hospital	0.89 (0.46-1.70)	0.72	0.73 (0.35-1.54)	0.42
HCV treated				
No	Reference		Reference	
Yes	0.51 (0.27-0.95)	0.03	0.41 (0.20-0.83)	0.01
Final margin status				
R0	Reference			
R1	2.05 (0.49-8.54)	0.32		

Table 1.4: univariate and multivariable binary logistic regression for receipt of HCV treatment for all HCC patients with HCV

	Univariate Logistic Regression		Multivariable Logistic Regression	
Variable	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
All Patients				
Age (median, IQR)	1.04 (1.02-1.06)	<0.01	1.02 (0.99-1.05)	0.07
Gender				
Female	Reference			
Male	1.03 (0.72-1.47)	0.87		
Race				
White	Reference		Reference	
Black	0.44 (0.31-0.63)	<0.01	0.59 (0.39-0.88)	0.01
Asian	0.87 (0.47-1.61)	0.65	0.87 (0.43-1.75)	0.69
Unknown	0.78 (0.15-4.06)	0.77	1.08 (0.17-1.75)	0.94
Insurance status				
Uninsured	Reference		Reference	
Insured	3.63 (1.85-7.11)	<0.01	1.69 (0.76-3.78)	0.20
Cirrhosis				
No	Reference			
Yes	0.74 (0.40-1.37)	0.34		
MELD (median, IQR)	0.95 (0.92-0.97)	<0.01	0.96 (0.93-0.99)	0.04
Clinical stage				
I	Reference		Reference	
II	0.69 (0.48-0.99)	0.05	0.58 (0.37-0.92)	0.02
III	0.55 (0.36-0.85)	<0.01	1.09 (0.65-1.85)	0.73
IVa	0.37 (0.20-0.70)	<0.01	0.75 (0.37-1.52)	0.42
Treatment facility				
Tertiary referral center	Reference		Reference	
Safety net hospital	0.32 (0.23-0.44)	<0.01	0.76 (0.50-1.16)	0.21
HCC treatment				
No treatment	Reference		Reference	
Surgery	2.75 (1.23-6.14)	0.01	1.99 (0.75-5.28)	0.17
Transplant	12.45 (7.00-22.15)	<0.01	12.34 (5.79-26.33)	<0.01
Liver-directed therapy	3.23 (1.91-5.48)	<0.01	2.73 (1.36-5.50)	<0.01
Chemotherapy	0.69 (0.22-2.11)	0.51	1.22 (0.36-4.15)	0.76
Patients at Safety Net Hospitals				
Age (median, IQR)	1.02 (0.98-1.05)	0.32		
Gender				
Female	Reference			
Male	1.11 (0.58-2.15)	0.75		
Race				
White	Reference		Reference	
Black	0.46 (0.25-0.88)	0.02	0.61 (0.31-1.21)	0.16
Asian	0.89 (0.29-2.64)	0.83	1.05 (0.33-3.39)	0.93
Unknown	--	--	--	--
Insurance status				
Uninsured	Reference		Reference	
Insured	1.70 (0.66-4.38)	0.27	1.23 (0.40-3.79)	0.72

Cirrhosis				
No	Reference			
Yes	2.99 (0.40-22.29)	0.28		
MELD (median, IQR)	0.97 (0.92-1.01)	0.14	0.98 (0.92-1.03)	0.39
Clinical stage				
I	Reference		Reference	
II	0.79 (0.42-1.49)	0.47	0.72 (0.35-1.49)	0.38
III	0.53 (0.24-1.17)	0.12	0.91 (0.37-2.21)	0.83
IVa	0.12 (0.02-0.87)	0.04	0.18 (0.02-1.42)	0.10
HCC treatment				
No treatment	Reference		Reference	
Surgery	4.12 (1.14-14.88)	0.03	1.71 (0.39-7.37)	0.38
Transplant	11.69 (4.29-31.87)	<0.01	7.29 (2.36-22.51)	<0.01
Liver-directed therapy	2.25 (0.84-6.01)	0.11	1.35 (0.45-4.06)	0.59
Chemotherapy	1.24 (0.23-6.55)	0.80	1.57 (0.28-8.91)	0.61
Patients at Tertiary Referral Centers				
Age (median, IQR)	1.04 (1.02-1.07)	<0.01	1.03 (1.01-1.06)	0.02
Gender				
Female	Reference			
Male	1.00 (0.68-1.48)	0.98		
Race				
White	Reference		Reference	
Black	0.44 (0.29-0.65)	<0.01	0.53 (0.34-0.83)	<0.01
Asian	0.86 (0.43-1.71)	0.66	0.79 (0.37-0.83)	0.57
Unknown	1.03 (0.19-5.38)	0.97	1.42 (0.23-8.78)	0.70
Insurance status				
Uninsured	Reference		Reference	
Insured	5.55 (2.22-13.89)	<0.01	2.46 (0.89-6.79)	0.08
Cirrhosis				
No				
Yes				
MELD (median, IQR)	0.59 (0.31-1.11)	0.10	0.95 (0.91-0.99)	0.02
Clinical stage				
I	Reference		Reference	
II	0.65 (0.43-0.99)	0.05	0.52 (0.31-0.88)	0.01
III	0.56 (0.35-0.91)	0.02	1.21 (0.67-2.18)	0.52
IVa	0.46 (0.24-0.88)	0.02	1.07 (0.50-2.27)	0.87
HCC treatment				
No treatment	Reference		Reference	
Surgery	2.22 (0.83-5.90)	0.11	2.18 (0.66-7.29)	0.20
Transplant	12.75 (6.62-24.52)	<0.01	18.56 (7.37-46.76)	<0.01
Liver-directed therapy	3.61 (1.97-6.62)	<0.01	3.89 (1.65-9.23)	<0.01
Chemotherapy	0.48 (0.10-217)	0.34	0.99 (0.19-5.18)	0.99

Table 2.1: baseline characteristics for interferon-naïve patients with HCV-associated HCC within Milan criteria who underwent liver transplantation

Variable	All Patients n=427 (%)	Pre-LT n=258 (58)	0-3 months Post-LT n=45 (10)	≥3 months Post-LT n=124 (27)	p-value
Age at diagnosis (median, IQR)	61 (57-65)	61 (57-66)	62 (60-66)	61 (57-64)	0.60
Gender					
Female	85 (20)	54 (21)	7 (16)	24 (19)	0.70
Male	342 (80)	204 (79)	38 (84)	100 (81)	
Race					
White	273 (64)	160 (62)	27 (61)	86 (69)	0.47
Black	72 (17)	45 (17)	10 (22)	17 (14)	
Asian	14 (3)	11 (4)	0 (0)	3 (2)	
Latino	64 (15)	41 (16)	7 (16)	16 (13)	
Other	4 (1)	1 (1)	1 (1)	2 (2)	
ASA					
I	1 (1)	1 (1)	0 (0)	0 (0)	0.10
II	21 (5)	19 (8)	0 (0)	2 (2)	
III	141 (33)	79 (31)	19 (42)	43 (35)	
IV	256 (61)	151 (60)	26 (58)	79 (63)	
Functional status					
Independent	304 (75)	185 (76)	23 (62)	96 (78)	0.17
Partially dependent	91 (23)	55 (23)	12 (33)	24 (19)	
Totally dependent	9 (2)	3 (1)	2 (5)	4 (3)	
Stage at diagnosis					
I	132 (34)	91 (38)	12 (33)	29 (24)	0.21
II	120 (30)	67 (29)	13 (36)	40 (34)	
III	136 (35)	76 (32)	11 (31)	49 (41)	
IV	4 (1)	3 (1)	0 (0)	1 (1)	
DAA regimen					
Sofosbuvir/velpatasvir	32 (8)	17 (7)	2 (4)	13 (11)	<0.01
Ledipasivir/sofosbuvir	240 (57)	155 (62)	22 (49)	63 (51)	
Glecaprevir/pibrentasvir	44 (10)	0 (0)	14 (31)	30 (24)	
Other	104 (25)	79 (31)	7 (16)	18 (14)	
SVR achieved					
No	54 (13)	24 (9)	3 (7)	27 (23)	<0.01
Yes	365 (87)	231 (91)	41 (93)	93 (77)	
Received liver-directed therapy					<0.01
No	44 (10)	17 (7)	5 (11)	22 (18)	
Yes	383 (90)	241 (93)	40 (89)	102 (82)	
Deceased donor					
Deceased donor	424 (99)	256 (99)	45 (100)	123 (99)	0.76
Living donor	2 (1)	1 (1)	0 (0)	1 (1)	
HCV+ donor liver					
No	351 (84)	242 (96)	28 (64)	81 (67)	<0.01
Yes	65 (16)	9 (4)	16 (36)	40 (33)	
Any post-op complication					0.25

No Yes	236 (55) 190 (45)	150 (58) 107 (42)	21 (47) 24 (53)	65 (52) 59 (48)	
Re-transplant No Yes	 420 (99) 6 (1)	 253 (98) 4 (2)	 44 (98) 1 (2)	 123 (99) 1 (1)	0.75
Months on waitlist (median, IQR)	7 (3-12)	8 (4-14)	7 (2-8)	8 (4-7)	<0.01
Follow-up in months (median)	36 (21-52)	34 (18-51)	30 (19-44)	41 (28-54)	<0.01

Table 2.2: univariate binary logistic regression for achieving SVR for interferon-naïve patients with HCV-associated HCC within Milan criteria who underwent liver transplantation

	Univariate Regression		**Multivariable Regression**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age at diagnosis (median, IQR)	1.03 (0.98-1.07)	0.31		
Gender				
Female	Reference			
Male	0.46 (0.19-1.11)	0.08		
Race				
White	Reference			
Black	0.55 (0.27-2.09)	0.55		
Asian	1.74 (0.22-13.75)	1.74		
Latino	1.05 (0.44-2.51)	1.05		
Functional status				
Independent	Reference			
Partially dependent	1.18 (0.58-2.40)	0.65		
Totally dependent	1.14 (0.14-9.46)	0.91		
Stage at diagnosis				
I	Reference			
II	0.75 (0.37-1.54)	0.44		
III	1.33 (0.61-2.89)	0.47		
IV	0.43 (0.04-4.34)	0.47		
DAA regimen				
Sofosbuvir/velpatasvir	Reference			
Ledipasivir/sofosbuvir	0.48 (0.11-2.11)	0.33		
Glecaprevir/pibrentasvir	0.24 (0.05-1.18)	0.08		
Other	0.38 (0.08-1.77)	0.22		
Timing of DAA therapy				
Pre-LT	Reference			
0-3mo post-LT	1.42 (0.41-4.93)	0.58		
≥3mo post LT	0.36 (0.20-0.65)	<0.01		
Received liver-directed therapy	Reference			
No	1.33 (0.56-3.16)	0.52		
Yes				
HCV+ donor liver				
No	Reference			
Yes	0.65. (0.31-1.34)	0.24		
Any post-op complication				
No	Reference			
Yes	0.60 (0.34-1.07)	0.08		
Re-transplant				
No	Reference			
Yes	--			
Months on waitlist	1.01 (0.99-1.03)	0.38		

Table 2.3: univariate Cox regression for recurrence-free survival for interferon-naïve patients with HCV-associated HCC within Milan criteria who underwent liver transplantation

	Univariate Regression		**Multivariable Regression**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age at diagnosis (median, IQR)	0.99 (0.94-1.05)	0.83		
Gender				
Female	Reference			
Male	2.43 (0.74-7.96)	0.14		
Race				
White	Reference			
Black	1.13 (0.46-2.78)	0.80		
Asian	--	--		
Latino	1.11 (0.41-2.89)	0.86		
Other	--	--		
ASA				
I	Reference			
II	1.38 (0.17-10.86)	0.76		
III	2.13 (0.29-15.80)	0.46		
IV	--	--		
Functional status				
Independent	Reference			
Partially dependent	0.36 (0.11-1.19)	0.09		
Totally dependent	1.83 (0.44-7.71)	0.41		
Stage at diagnosis				
I	Reference			
II	0.97 (0.35-2.68)	0.96		
III	1.98 (0.85-4.62)	0.12		
IV	9.72 (2.05-46.05)	<0.01		
DAA regimen				
Sofosbuvir/velpatasvir	Reference			
Ledipasivir/sofosbuvir	0.33 (0.13-0.84)	<0.01		
Glecaprevir/pibrentasvir	0.26 (0.05-1.29)	0.10		
Other	0.21 (0.07-0.71)	<0.01		
Timing of DAA therapy				
Pre-LT	Reference			
0-3mo post-LT	--	--		
≥3mo post LT	2.34 (0.14-4.82)	0.02		
SVR achieved				
No	Reference			
Yes	0.28 (0.13-0.62)	<0.01		
Received liver-directed therapy				
No	Reference	0.51		
Yes	1.49 (0.46-4.90)			
Deceased donor				
Deceased donor	Reference			

Living donor	--	--		
HCV+ donor liver				
No	Reference			
Yes	0.82 (0.32-2.14)	0.69		
Any post-op complication				
No	Reference			
Yes	1.50 (0.76-2.98)	0.25		
Re-transplant				
No	Reference			
Yes	2.89 (0.39-21.19)	0.29		
Months on waitlist	0.97 (0.93-1.02)	0.19		

FIGURES

Figure 1: overall survival by HCV treatment for all HCC patients (Panel A), recurrence-free survival by HVC treatment for surgical patients (Panel B) overall survival by HCV treatment at safety net hospitals (Panel C), overall survival by HCV treatment at tertiary referral centers (Panel D)

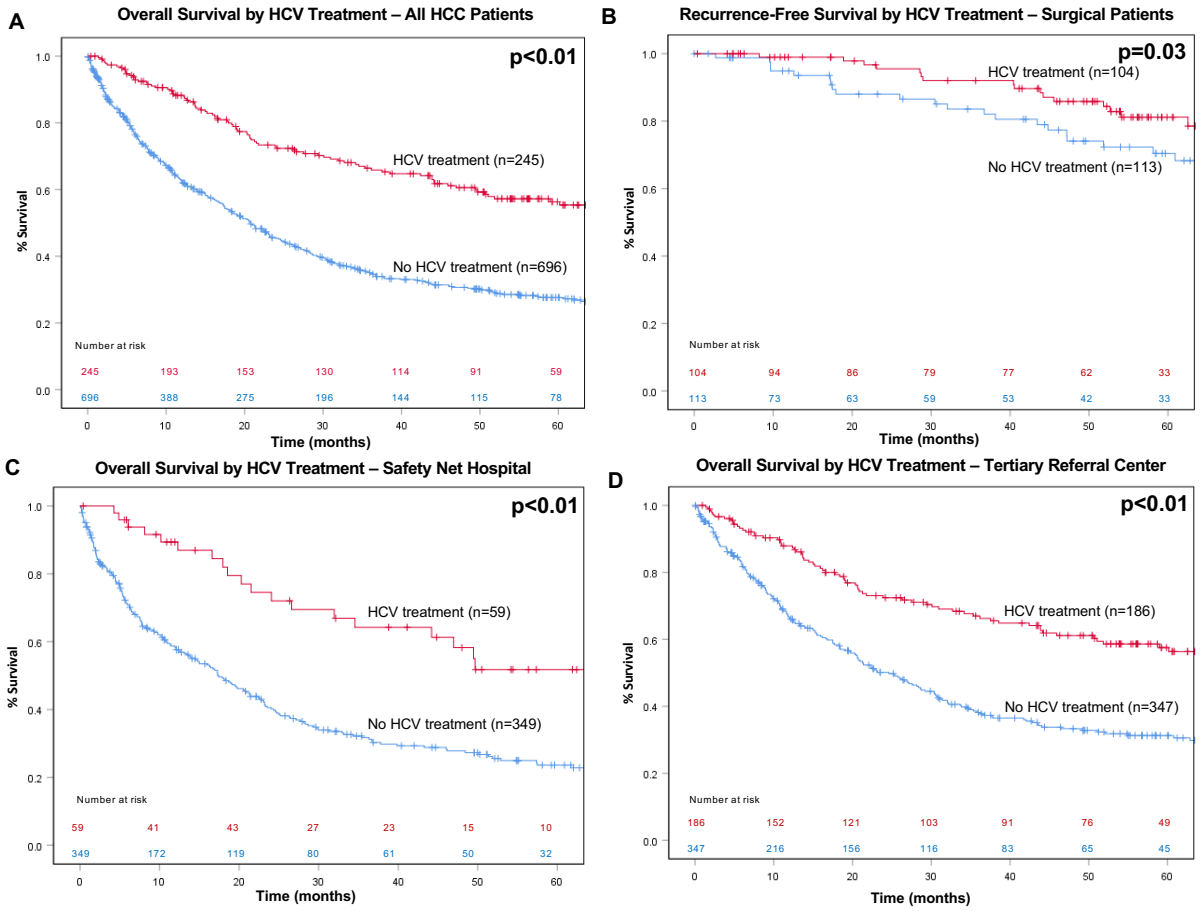

Figure 2.1: recurrence-free survival by SVR for interferon-naïve patients with HCV-associated HCC within Milan criteria who underwent liver transplantation

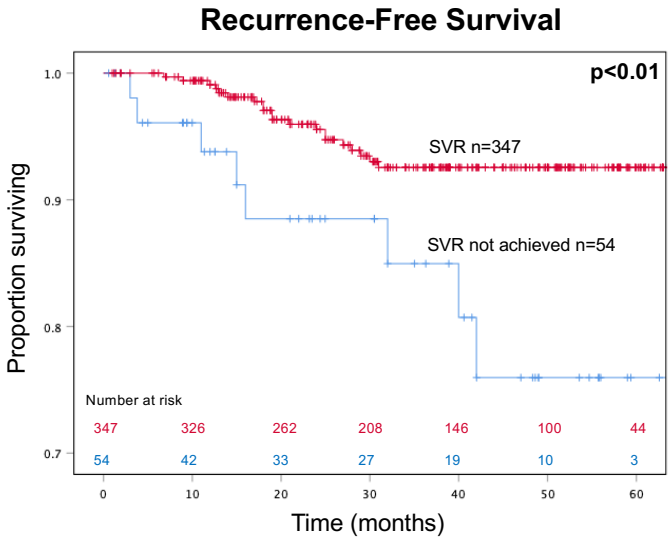

Figure 2.2: recurrence-free survival by timing of DAA therapy initiation for interferon-naïve patients with HCV-associated HCC within Milan criteria who underwent liver transplantation