Extrahepatic Manifestations of Hepatitis C Virus After Liver Transplantation

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KEYWORDS

• Diabetes mellitus • Lymphoproliferative disorders • Health-related quality of life
• Chronic kidney disease • Liver transplantation

KEY POINTS

- Extrahepatic manifestations of chronic hepatitis C virus (HCV) infection in the posttransplant setting are equally important than those seen in the absence of liver transplantation.
- Increased risks of metabolic abnormalities, especially diabetes mellitus, are compounded in the posttransplant setting.
- Although chronic HCV infection increases risk of lymphoproliferative disorders, these risks can be exacerbated by the increased risk of posttransplant Epstein–Barr virus–associated lymphoproliferative disorders.
- Understanding and addressing health-related quality of life impairments associated with chronic HCV is particularly important in the posttransplant setting.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection remains a leading cause of chronic liver disease and is one of the leading causes of cirrhosis and hepatocellular carcinoma

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requiring liver transplantation.[1–3] Although the emergence of highly effective antiviral therapies for the treatment of chronic HCV has revolutionized the treatment approach, leading to successful cure rates of greater than 90% to 95% associated with current available treatment regimens, there remains a large cohort of patients with HCV cirrhosis that will still progress to need for liver transplantation.[1,4] In addition, although highly effective therapies are available, barriers in access to these therapies will continue to contribute to HCV disease progression to cirrhosis and hepatocellular carcinoma.[5,6]

Several studies have reported on the beneficial effects of HCV cure, not only in terms of the benefits and improvements in hepatic disease, but improvements in extrahepatic and systemic manifestations of chronic HCV are also well-studied.[6,7] In particular, several recent studies have demonstrated significant improvements in patient-reported outcomes achieved with successful HCV treatment.[7–10] Despite these successes, disease progression to need for liver transplantation is not averted in all patients, and few studies have specifically evaluated extrahepatic manifestations of chronic HCV after liver transplantation. There is much debate on the optimal timing of HCV treatment among those awaiting liver transplantation. However, treatment of chronic HCV after liver transplantation is no longer a significant hurdle and the vast armamentarium of treatment options with short duration and high efficacy have made it much easier to achieve HCV cure in this population.[11–13]

The extrahepatic manifestations of chronic HCV in the posttransplant setting are similar to the manifestations exhibited in the pretransplant setting.[7,14–18] However, the overall milieu of the posttransplant state may interact with HCV such that certain extrahepatic manifestations become more relevant clinically and may impact the patient to a greater extent. As such, the current review focuses on the extrahepatic manifestations of chronic HCV that may be exacerbated in the posttransplant milieu (**Table 1**).

METABOLIC ABNORMALITIES

Significant metabolic abnormalities associated with chronic HCV infection are well-reported, with insulin resistance in the form of impaired glucose tolerance or diabetes mellitus having the greatest impact.[14,15,19–21] A recent metaanalysis evaluating the prevalence and burden of extrahepatic manifestations of chronic HCV included 31 studies evaluating the association of diabetes mellitus and chronic HCV.[15] Among these studies, which included 61,843 chronic HCV patients, the pooled prevalence of diabetes mellitus was 15% (95% confidence interval, 13–18) among chronic HCV patients compared with 10% (95% confidence interval, 6–15) among non-HCV controls. Furthermore, the authors calculated a pooled odds ratio of 1.58 (95% confidence interval, 1.30–1.86) for the association of DM in chronic HCV patients.[6] Despite being the second most common extrahepatic manifestation of chronic HCV, concurrent diabetes mellitus carries a much greater clinical burden given that it also increases risk of cardiovascular disease and chronic renal disease.[16,17,22,23] The prevalence of concurrent diabetes mellitus may also contribute to a higher risk of concurrent nonalcoholic fatty liver disease, which in the setting of chronic HCV contributes to more aggressive disease progression to cirrhosis and hepatocellular carcinoma. For example, 2 recent systematic reviews evaluated the impact of concurrent diabetes on the risk of disease progression and risk of hepatocellular carcinoma among chronic HCV patients.[24,25] Among a total of 20 observation studies included in the final analyses, the authors observed that concurrent obesity (odds ratio, 1.08–7.69), the presence of significant steatosis (odds ratio, 1.80–14.3), and concurrent diabetes mellitus (odds ratio,

Table 1
Extrahepatic manifestations of chronic HCV that are exacerbated in the post-liver transplant setting

Extrahepatic Manifestations	Features of the Posttransplant Environment that Increase the Risk and Severity
Insulin resistance	Glucocorticoid-related insulin resistance Direct pancreatic islet cell injury by calcineurin inhibitors and cyclosporine have been reported
Cardiovascular events	Immunosuppression regimens may increase risk of cardiovascular risk factors, including hypertension and dyslipidemia Increased risk of insulin resistance may further affect cardiovascular risk Increased risk of posttransplant steatosis from immunosuppression regimens may increase cardiovascular disease risk
Lymphoproliferative diseases	Posttransplant immunosuppression may allow dysregulated lymphoproliferation Specifically, Epstein–Barr virus–associated lymphoproliferative disorders is propagated by immunosuppression
Renal diseases	Potential nephrotoxicity of posttransplant immunosuppression regimen, including calcineurin inhibitors Appropriate selection of direct acting antivirals for treatment of chronic HCV in the posttransplant setting must take into account presence of advanced renal dysfunction
Mixed cryoglobulinemia	Nephrotoxic risks in the posttransplant setting, including those related to HCV and immunosuppression may further exacerbate cryoglobulinemia associated renal dysfunction
Health-related quality of life	Postoperative complications and prolonged hospitalization can contribute to psychosocial impairments including depression

Abbreviation: HCV, hepatitis C virus.

2.25–9.24) were all associated with an increased risk of advanced fibrosis among chronic HCV patients.[25] In a subsequent analysis, the same group evaluated the impact of concurrent metabolic abnormalities on the risk of developing hepatocellular carcinoma among chronic HCV patients and only observed a significantly increased risk associated with concurrent diabetes mellitus.[24] Thus, the combined effects of metabolic derangements associated with chronic HCV are far reaching. Furthermore, the presence of metabolic abnormalities, whether coexisting or directly caused by chronic HCV infection, also affects posttransplant mortality.[26,27] Using the 2003 to 2013 United Network for Organ Sharing Organ Procurement and Transplant Network registry data, Aguilar and colleagues[26] demonstrated that concurrent diabetes mellitus was associated with a 22% higher posttransplant mortality when compared with patients without diabetes mellitus. In light of the multitude of negative effects associated with diabetes mellitus, the estimated economic burden of diabetes among chronic HCV patients is in excess of $440 million annually.[15]

Although it is clear that concurrent diabetes among chronic HCV patients contributes to increased morbidity and mortality, the risk of concurrent diabetes and the consequences of diabetes are perhaps even more significant in the posttransplant state.[26,28,29] Previous studies have reported on the increased risk of de novo diabetes mellitus and steatosis after liver transplantation.[19,30–32] The prevalence of posttransplant new-onset diabetes mellitus ranged from 13% to 28%.[19,32–34] Although there are several risk factors for de novo diabetes mellitus in the posttransplant setting, the immunosuppression regimen can contribute to significant metabolic

derangements, including diabetes mellitus.[34–36] It has been observed that calcineurin inhibitors may promote de novo development of diabetes mellitus through direct injury to the pancreatic islet cells. In addition, both tacrolimus and cyclosporine have been implicated in potential islet cell injury that may promote insulin resistance in the posttransplant setting.[35,36] The increased risk of concurrent diabetes associated with posttransplant risk factors is compounded further with the potential diabetogenic risks of chronic HCV infection in the posttransplant setting.[32,37]

The increased risk of diabetes associated with chronic HCV and the posttransplant setting also contribute to increased risks of cardiovascular disease.[22,23] This is particularly important given that chronic HCV infection itself has been shown to increase the risk of cardiovascular disease and stroke.[6,23] Although several studies have evaluated this association, a recent metaanalysis demonstrated a 20% increased odds of cardiovascular disease associated with chronic HCV infection and a 35% increased odds of developing stroke.[15] This extrahepatic manifestation of chronic HCV is especially relevant in the posttransplant setting, because many additional factors contribute to an environment that increases the risks of cardiovascular events. The increased risks of metabolic derangements in the posttransplant setting including hypertension, dyslipidemia, and diabetes mellitus further compound the risk of cardiovascular events.[19,38–40] Furthermore, there is an increased risk of concurrent nonalcoholic fatty liver disease in posttransplant patients, even when the initial etiology of chronic liver disease was not related to nonalcoholic fatty liver disease.[41–44] This further complicates the clinical scenario given that nonalcoholic fatty liver disease itself is well-correlated with an increased risk of cardiovascular disease, such that one of the leading causes of morbidity and mortality among nonalcoholic fatty liver disease patients is cardiovascular related.[45–49] A recent metaanalysis by Targher and colleagues[49] included a total of 16 observational studies evaluating the association of nonalcoholic fatty liver disease with the incidence cardiovascular disease. Over a mean period of 6.9 years in the pooled analysis, patients with nonalcoholic fatty liver disease had a 64% increased risk of fatal and/or nonfatal cardiovascular disease. Thus, the risk of cardiovascular disease is affected by multiple factors, and the convergence of these factors among chronic HCV patients in the posttransplant setting highlights the importance of better understanding disease prevalence and risk factors.

Although the increased cardiovascular disease risk in the posttransplant setting is likely multifactorial, reflecting the combined effects of immunosuppression-related effects on hypertension, dyslipidemia, and insulin resistance, the etiology of the increased risk of cardiovascular disease associated with chronic HCV is not well-defined.[14,23] Previous studies have suggested that HCV itself may have proatherogenic effects.[50–52] Specifically, prior observational studies report an increased risk of carotid atherosclerosis associated with chronic HCV infection, and this increased risk persisted even after correcting for the potential confounding effect of hepatic steatosis.[53] However, other studies suggest that HCV promotes cardiovascular risk through proinflammatory pathways, such that increased systemic inflammatory cascade contributes to increased atherosclerosis development.[53,54] Nevertheless, regardless of the mechanism of action, the increased risk of cardiovascular disease among chronic HCV patients is real, and this may be especially significant in the posttransplant setting.

LYMPHOPROLIFERATIVE DISORDERS

The risks of lymphoproliferative disorders among chronic HCV patients have been well-reported. Several studies in various cohorts have demonstrated an increased risk of non-Hodgkin lymphoma among patients chronically infected with HCV.[55–58]

Most recently, the results of a large metaanalysis identified 16 studies that investigated the association between chronic HCV and lymphoproliferative disorders.[6] Among these pooled studies, the risk of lymphoma was 60% higher among patients with chronic HCV when compared with non-HCV controls. Although the exact mechanism of this increased risk is poorly understood, several hypotheses have been raised. One thought purports that chronic stimulation of lymphocytes via persistent untreated HCV over time leads to dysregulated proliferation that contributes to a pathogenic lymphoproliferative state.[59–61] Another theory suggests that viral replication of HCV within B cells may have a direct oncogenic effect such that it also contributes to a dysregulated growth and replication leading to uncontrolled proliferation.[62,63]

The increased risk of lymphoproliferative disorders associated with chronic HCV is particularly important in the posttransplant setting, given that the certain immunosuppression regimens in the posttransplant setting may also contribute to increased risk of lymphoproliferative disorders.[64] The overall prevalence of posttransplant lymphoproliferative disorders is as high as 20% in some studies.[64,65] However, the risk is relatively lower among post-liver transplant patients compared with patients who receive lung and heart transplants. However, despite the relative lower risk of posttransplant lymphoproliferative disorders in renal and liver transplant recipients, given that the majority of solid organ transplants in the United States are those involving kidney and liver, the overall burden of posttransplant lymphoproliferative disorders among post-liver transplant patients is much greater. The overall incidence of posttransplant lymphoproliferative disorders among liver transplant recipients has ranged from 0.8% to 3.6% in some studies.[64,65] Lymphoproliferative disorders in the posttransplant setting are thought to be propagated through Epstein–Barr virus (EBV) infection.[66] The immunosuppressed state in the posttransplant patient allows uncontrolled EBV-associated promotion of lymphoproliferation. Although difficult to manage in the posttransplant setting, with the need to balance the importance of immunosuppression for the prevention of solid organ rejection and the need to balance pulling back on immunosuppression to better control the EBV-associated consequences, the concurrence of chronic HCV infection can pose an even more difficult dilemma. As such, the combined risk of lymphoproliferative disorders in the posttransplant setting is an important extrahepatic manifestation of chronic HCV to be particularly cognizant of.

RENAL DISORDERS

The risk of kidney injury associated with chronic HCV infection is a particularly complex extrahepatic manifestation, given that HCV contributes to renal dysfunction through a variety of mechanisms.[67] One of the more prevalent extrahepatic manifestations of chronic HCV, mixed cryoglobulinemia, is a vasculitis that contributes directly to renal dysfunction.[7,16,17] The presence of mixed cryoglobulinemia further exacerbates the risk of HCV-related renal disease. Even in the absence of cryoglobulinemia, HCV-associated glomerulonephritis has been well-documented. Furthermore, as previously mentioned, HCV contributes to increased risk of diabetes mellitus, and the negative impact of chronic insulin resistance on the development of chronic renal dysfunction is also well-establised.[20,37] In a recent metaanalysis that included 14 studies specifically evaluating the association of chronic HCV infection with development of chronic renal disease, the authors demonstrated a 26% increased risk of having renal disease progression among chronic HCV patients compared with non-HCV controls.[6] A multicenter study using data from the Multinational Observational Study in Transplantation (MOST) evaluated predictors

of post-liver transplantation renal dysfunction. On multivariate analysis, positivity for chronic HCV was an independent predictor of posttransplant renal dysfunction even after correcting for baseline serum creatinine levels before liver transplantation.[68] The increased risk of chronic kidney disease associated with HCV is particularly important in the posttransplant setting given that immunosuppression with calcineurin inhibitors have also been reported to contribute to nephrotoxicity. Other immunosuppressive regimens including cyclosporine also need to be monitored closely in the setting of renal dysfunction.

Although renal disease is an important extrahepatic manifestation of chronic HCV, an equally important consideration is the management of chronic HCV in the post-kidney transplant setting. The significant burden of chronic HCV in the kidney transplant setting is demonstrated in a recent systematic review reporting up to a 10% chronic HCV prevalence among kidney transplant recipients.[69] Furthermore, the presence of concurrent chronic HCV in kidney transplant recipients is also associated with increased graft loss and overall posttransplant mortality.[70,71] Thus, the need for safe and effective therapies for eradicating HCV after kidney transplant are paramount to improve long-term outcomes. Before the availability of current direct-acting antiviral therapies, treatment of chronic HCV in the post-kidney transplant setting presented a dilemma given the high risk, including allograft rejection and loss together with the low effectiveness of antiviral therapies.[72,73] However, the current era of interferon-free and ribavirin-free regimens have demonstrated high efficacy and an acceptable safety profile in treating chronic HCV in the post-kidney transplant setting.[74–76]

MIXED CRYOGLOBULINEMIA

Another common extrahepatic manifestation of chronic HCV, mixed cryoglobulinemia has a reported prevalence ranging from 10% to nearly 50% among chronic HCV patients.[58] In addition to renal disease in the form of membranoproliferative glomerulonephritis, the clinical manifestations of mixed cryoglobulinemia reflect the systemic nature of this disease, ranging from mild symptoms of palpable purpura, weakness, and arthralgias to severe manifestations, such as pulmonary hemorrhage and central nervous system involvement.[16,18,58,77] Most commonly, though, skin, joints, and renal involvement are the primary manifestations of cryoglobulinemia. A recent metaanalysis that included 21 studies reported a pooled prevalence of 30.1% among chronic HCV patients compared with 1.9% among non-HCV populations.[15] However, this high prevalence of mixed cryoglobulinemia included both symptomatic and asymptomatic patients. The prevalence of symptomatic cryoglobulinemia is much lower at approximately 5% of chronic HCV patients.[15,58] Although the exact pathogenesis is not well-described, it has been hypothesized that chronic antigenic stimulation by the HCV contributes to risk of cryoglobulinemia in the same manner as the increased risk of HCV-related autoimmune and lymphoproliferative disorders.[58] In the post-liver transplant setting, the prevalence of mixed cryoglobulinemia is also similarly high, with some studies reporting prevalence of nearly 50%, with 20% of those patients reporting symptomatic cryoglobulinemia.[77–79] Furthermore, concurrent cryoglobulinemia in the posttransplant setting can further complicate the risk of acute kidney injury associated with HCV itself and concurrent immunosuppression therapies. However, the current era of highly effective direct acting antivirals have demonstrated success in treatment HCV-associated mixed cryoglobulinemia, thus emphasizing the importance of early recognition of this extrahepatic manifestation to that timely therapy can be initiated.[80]

HEALTH-RELATED QUALITY OF LIFE

The importance of health-related quality of life assessment among patients with chronic HCV is becoming more important as we realize the encompassing negative impact of untreated HCV infection.[6,7,81] The emphasis on health-related quality of life assessment reflects the perceived impact on patients' overall well-being, including both physical and mental health.

Understanding and addressing the impact of disease processes on health-related quality of life is not only important to consider the holistic approach to improving patient outcomes, but also that impairments in health-related quality of life has been demonstrated to contribute to significant economic deficits resulting from decreased productivity or increased use of health care resources.[6,81–83] A recent metaanalysis evaluating the impact of HCV on health-related quality of life demonstrated that, among the physical health domains, the lowest scores were seen among the general health categories.[6] Among the mental health domains, HCV patients scored the lowest in those categories assessing social functioning. Overall scores were lower in HCV patients when compared with their non-HCV counterparts.[6] Furthermore, fatigue, also an important factor that affects health-related quality of life, was found to be significantly more prominent among HCV patients compared with healthy controls.[81,82,84] The prevalence of concurrent depression as a potential manifestation of chronic HCV has also been evaluated, and the pooled risk assessment observed that chronic HCV patients were more than twice as likely as non-HCV controls to have significant depression.[6] Assessment of health-related quality of life is equally important in the posttransplant setting and the interplay between impaired quality of life associated with chronic HCV can be compounded by the quality of life impairments seen after liver transplantation.[85–89] The concurrence of chronic HCV in this posttransplant setting may further contribute to decreased quality of life.

The economic burden of extrahepatic manifestations is particularly significant in the post-liver transplant setting. Among all chronic HCV patients, the total direct medical costs associated with management of extrahepatic manifestations of chronic HCV was estimated at $1.5 billion in 2014, with HCV-associated diabetes mellitus ($443.4 million) and HCV-related depression ($430.7 million) account for the leading comorbidities in terms of direct medical costs.[15] The negative impact of extrahepatic manifestations in posttransplant patients can further exacerbate this economic burden, leading to prolonged hospitalization, increased use of outpatient resources, and overall worse posttransplant outcomes.

SUMMARY

It has become more apparent that the detrimental effects of untreated chronic HCV infection extend beyond the hepatic manifestations and extrahepatic manifestations impart significant health consequences for patients. These extrahepatic manifestations in the posttransplant setting are particularly important given that the posttransplant setting itself contributes to and potentially compounds the detrimental effects. Furthermore, the highly immunosuppressed environment of the posttransplant setting not only contributes to increased metabolic abnormalities, but increases the risk for EBV-associated lymphoproliferative disorders. Chronic kidney disease and mixed-type cryoglobulinemia is also important to consider in the posttransplant setting, given the multitude of factors contributing to renal dysfunction, both HCV related and non–HCV related. This is particularly important in its effect on appropriate adjustments to immunosuppressive regimens. Finally, the impact of chronic HCV infection on

health-related quality of life is particularly important in the posttransplant setting given the tenuous physical and mental health affected by the stressors of undergoing successful liver transplantation.

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