Title

Primary Care Utilization, Preventative Screening, and Control of Metabolic Syndrome in Metabolic Dysfunction-Associated Steatohepatitis Liver Transplant Recipients.

Authors

Flynn, Sarah
Saxena, Varun
Brandman, Danielle

Publication Date

2024

DOI

10.1177/21501319241247974

Peer reviewed

Journal of Primary Care & Community Health
Volume 15: 1–6

DOI: 10.1177/21501319241247974
journals.sagepub.com/home/jpc
Sage

Primary Care Utilization, Preventative Screening, and Control of Metabolic Syndrome in Metabolic Dysfunction-Associated Steatohepatitis Liver Transplant Recipients

Sarah J. Flynn, MD, MPhil[1], Varun Saxena, MD, MAS[2], and Danielle Brandman, MD, MAS[3]

Abstract

Objectives: Patients with pre-transplant metabolic dysfunction-associated steatohepatitis (MASH) are at high risk of metabolic syndrome (MetS) after liver transplant. While many patients are co-managed by a transplant team, most preventative screening and MetS management may occur in the primary care setting. We aimed to evaluate primary care utilization by MASH liver transplant recipients as well as MetS screening and control. **Methods:** We conducted a retrospective chart review that included adults who underwent liver transplant for MASH or cryptogenic cirrhosis at a single institution from January 2010 to December 2016, had available primary care data, and at least 36-months of follow-up post-transplant. Measures included primary care utilization, adherence to screening guidelines, and control of MetS. We used Fischer's exact test to explore the association of primary care utilization with screening and control. **Results:** A total of 37 patients met inclusion criteria with 366 visits reviewed. The median time to first visit was 68 days post-transplant and patients had a median of 9 total visits. Few patients met screening guidelines for diabetes (8.1%) or hyperlipidemia (10.8%). The percentage of patients with control of obesity, hypertension, diabetes, and hyperlipidemia decreased over the 36-month follow-up period. Primary care utilization was not associated with adherence to screening recommendations for diabetes ($P=.141$) or hyperlipidemia ($P=.103$). Higher primary care utilization was not associated with control of hypertension ($P=.107$), diabetes ($P=.871$), or hyperlipidemia ($P=.999$). **Conclusion:** More research is needed to investigate barriers to screening and management of MetS conditions in this high-risk patient population in the primary care setting as well as to optimize post-transplant care coordination.

Keywords

liver transplantation, metabolic syndrome, primary care

Introduction

Metabolic dysfunction-associated steatohepatitis (MASH) related cirrhosis is a leading indication for liver transplantation in the United States.[1,2] Metabolic syndrome (MetS), defined as the presence of 3 or more metabolic derangements: obesity, dyslipidemia, hypertension, or elevated fasting glucose levels, is a known risk factor for the development of non-alcoholic fatty liver disease and MASH.[3,4] While it is estimated that MetS affects 24% of the adult population in the United States, studies estimate that 64% to 71% of patients with MASH have MetS.[5-7]

[1]University of California, San Francisco, CA, USA
[2]Kaiser Permanente South San Francisco Medical Center, San Francisco, CA, USA
[3]Weill Cornell Medical College, New York, NY, USA

Dates received: 3 February 2024; revised: 25 March 2024; accepted: 29 March 2024

Corresponding Author:
Sarah J. Flynn, Division of Hospital Medicine, Department of Medicine, University of California, San Francisco, 521 Parnassus Avenue, San Francisco, CA 94143, USA.
Email: Sarah.Flynn2@ucsf.edu

Table 1. Screening Guidelines and Defined Control of MetS Conditions.

MetS condition	Screening guideline	Defined control
Obesity	No specific AASLD guideline for screening Evaluated number of primary care visits with body mass index (BMI) recorded	BMI < 30
Hypertension	No specific AASLD guideline for screening Evaluated number of primary care visits with blood pressure recorded	Blood pressure < 130/80
Diabetes	Hemoglobin A1c or fasting glucose every 3 months in the first-year post-liver transplant and then annually*	A1c < 7
Hyperlipidemia	Fasting lipids annually†	LDL < 100 Triglycerides < 150

*Unable to confirm fasting status of laboratory tests, utilized only hemoglobin A1c.
†Unable to confirm fasting status of laboratory tests.

The prevalence of developing conditions associated with MetS is even higher in all liver transplant recipients: hypertension 40% to −85%; diabetes 10% to 64%, obesity 24% to 64%; dyslipidemia 40% to 66%.[8] This is multifactorial with contributions from immunosuppressive medication regimens which can influence glucose and lipid metabolism, restoration of health and appetite, and pre-existing genetic disposition.[9-11] Patients transplanted due to MASH cirrhosis are at even higher risk of developing MetS post-transplant due to pre-transplant risk factors including obesity, genetic, and environmental factors.[12,13] Importantly, the clinical features of MetS contribute to post-liver transplant morbidity and mortality, specifically increasing the risk of cardiovascular disease and cardiac mortality.[13-16] Cardiovascular disease is one of the leading non-hepatic causes of death post-transplant.[17-19]

The American Association for the Study of Liver Diseases (AASLD) provides practice recommendations for the management of adult patients who have successfully undergone liver transplantation which include guidelines for the screening and treatment of obesity, hypertriglyceridemia, hypertension, and diabetes in liver transplant recipients.[8] Prevention, early recognition, and treatment of MetS post-transplant may impact long-term survival.[19] Despite initial involvement from transplant centers and hepatologists post-transplant, most preventative screening and MetS management in liver transplant recipients may occur in the primary care setting.[20-23]

This study aimed to evaluate primary care utilization by patients who received a liver transplant due to MASH or cryptogenic cirrhosis, adherence to screening guidelines and control of MetS comorbidities, and the association of primary care utilization with screening and control of MetS conditions.

Methods

We conducted a retrospective chart review that included adults who underwent liver transplant for MASH or cryptogenic cirrhosis at a single institution in Northern California from January 2010 to December 2016. Given the strong epidemiological relationship between MASH and cryptogenic cirrhosis as well as similarities in post-operative clinical courses of patients undergoing liver transplantation for each indication, we included both in our sample.[24,25] Additional eligibility criteria included that patients received their primary care exclusively through a specific staff model health maintenance organization in which patients receive services within a closed healthcare system and had at least 36-months of documented follow-up post-transplant available in the electronic medical record (EMR). We identified the sample using data from the United Network for Organ Sharing and confirmed inclusion criteria through detailed review of the EMR.

Measures of interest included primary care utilization, adherence to screening guidelines, and control of MetS conditions. Primary care utilization was defined as office visits to Internal Medicine and/or Family Medicine healthcare providers including physicians, nurse practitioners, and physician assistants. We recorded the total number of office visits and timing of each in-person visit post-transplant. Adherence to screening guidelines as well as control of MetS conditions were evaluated based on standards set by the AASLD (Table 1). Control was evaluated yearly for each MetS condition during the first 36-months of follow-up, using the average values for body mass index (BMI), blood pressure measurements, hemoglobin A1c, low-density lipoprotein (LDL) level, and triglyceride level during each 12-month period of follow-up for each patient.

For each eligible patient, we conducted a detailed review of the EMR noting basic demographic information, primary care utilization, adherence to screening guidelines, and control of MetS conditions according to these definitions. All recorded information was de-identified and stored on a HIPAA compliant secured server. We performed descriptive statistics for each measure including frequency counts and calculating the percentage of patients meeting guidelines for screening and control of MetS conditions. When evaluating control of MetS comorbidities, patients were included in descriptive statistics if they had the relevant screening

test documented during each 12-month period of follow-up. Using Fischer's exact test, we explored the association of primary care utilization (classified as low, moderate, or high) with meeting screening guidelines and control of MetS conditions over the 36-month period. SPSS was utilized for statistical analyses. The University of California, San Francisco Institutional Review Board approved this study.

Results

A total of 760 liver transplants were completed at the institution from January 2010 to December 2016. 37 patients met defined inclusion criteria and among this cohort a total of 366 primary care visits were reviewed (Table 2). Patients had a median of 9 in-person primary care visits in the 36-month period post-liver transplant with a median time to first visit of 68 days.

While BMI and blood pressure were consistently measured and recorded during primary care visits, few patients met AASLD guidelines for diabetes using hemoglobin A1c measurement (3/37, 8.1%) or hyperlipidemia (6/37, 16.2%) screening post-transplant (Table 2). 8 patients (21.6%) had no record of measured hemoglobin A1c and 5 patients (13.5%) had no record of hyperlipidemia screening in the first 36 months of follow-up.

The percentage of patients with an average BMI <30 decreased each year, with only 38.2% of patients recording an average non-obese BMI during the third year of follow-up (Table 2). The percentage of patients with LDL and triglyceride levels at goal also decreased each year with 52.6% of patients with LDL at goal at year 3 and 50% of patients with triglycerides at goal at year 3. The percentage of patients with blood pressure control decreased from year 1 to year 2 from 61.1% to 42.9% with improvement in year 3 to 54.9%. While the percentage of patients with diabetic control decreased from year 1 to year 3, more patients in our cohort were screened for diabetes in year 3 post-transplant with an increase in the absolute number of patients with diabetic control (17 patients at year 3 from 15 patients in year 1).

In the first 36 months of follow-up, primary care utilization was not significantly associated with adherence to screening recommendations for diabetes ($P=.356$) or hyperlipidemia ($P=.103$). Higher primary care utilization was not associated with control of obesity ($P=.317$), hypertension ($P=.107$), diabetes ($P=.871$), or LDL levels ($P=.999$). There was a statistically significant association between uncontrolled triglyceride levels and high primary care utilization ($P=.002$).

Discussion

Few liver transplant recipients with MASH met guideline-based recommendations for preventative screening post-transplant for diabetes or hyperlipidemia. The percentage of patients in this cohort with control of obesity, hypertension, diabetes, and hyperlipidemia decreased post-transplant. While primary care utilization was high, it was not associated with meeting screening recommendations or control of conditions associated with MetS.

The worsened control of MetS comorbidities over time seen within our patient cohort is consistent with past literature showing high prevalence of hypertension, diabetes, obesity, and dyslipidemia post-transplant.[8,12,13] While not directly evaluated in our study, MetS comorbidities are known to contribute to post-liver transplant morbidity and mortality.[13-16] Further supporting the clinical importance of screening for and controlling MetS comorbidities post-transplant, a recent cohort study showed blood pressure control according to clinical practice guidelines among liver transplant recipients was associated with decreased mortality and cardiovascular events.[26]

To our knowledge this is the first study to look at the association of primary care utilization with meeting screening recommendations and control of MetS comorbidities in patients who received a liver transplant secondary to MASH or cryptogenic cirrhosis. In our cohort, more office visits with primary care providers were not associated with patients meeting screening recommendations or control of MetS conditions. Although recommendations for the care of post-transplant patients are published, primary care providers may not be aware of these guidelines.[8,22,23,27,28] Additionally, a recent study found that providers may not recognize the increased risk of cardiovascular disease in liver transplant recipients and may have low confidence in their ability to provide cardiovascular care to this patient population.[29]

Furthermore, best practices for care coordination between primary care and transplant hepatologists post-transplant are unknown and only minimal research efforts have been devoted to this. In a small postal survey to transplant hepatologists conducted over a decade ago, the majority of hepatologists indicated that primary care providers should be managing MetS related conditions including hypertension, diabetes, and dyslipidemia.[20] In a telephone survey to transplant centers throughout the United States conducted over 20 years ago, there was significant variability in the expectations and roles of primary care providers in the post-transplant care of patients.[21] In a recent study involving focus groups, providers identified unclear care team roles and responsibilities as well as perceived complexities of communication and coordination with transplant teams as barriers for managing cardiovascular disease in liver transplant recipients.[29] While some centers may have developed explicit clinical pathways, including protocols for post-transplant follow-up, these are not universally adopted by all transplant centers.[30]

There are multiple limitations with this study. To allow for a comprehensive retrospective chart review, we needed to utilize a small convenience sample of patients meeting

Table 2. Demographic Characteristics, Primary Care Utilization, MetS Screening, and Comorbidity Control in MASH Liver Transplant Recipients.

Demographic information	
Male (%)	20 (54)
Median age in years (range)	62 (38-75)
Race/Ethnicity	
Caucasian/White (%)	19 (51.4)
African American/Black (%)	0
Hispanic (%)	13 (35.1)
Asian (%)	1 (2.7)
Other or missing (%)	4 (10.8)
Primary indication for liver transplant	
MASH cirrhosis (%)	31 (83.8)
Cryptogenic cirrhosis (%)	6 (16.2)
Primary care utilization	
Total visits	366
Median number of visits per patient (range)	9 (1-27)
Median time to first visit in days (range)	68 (10-760)
MetS screening	
Obesity	
% of visits with BMI recorded (n)	92.1 (337/366)
Hypertension	
% of visits with blood pressure recorded (n)	98.4 (360/366)
Diabetes	
% of patients meeting AASLD diabetes screening recommendations (n)	8.1 (3/37)
% of patients with yearly monitoring of hemoglobin A1c (n)	48.6 (18/37)
Hyperlipidemia	
% of patients meeting AASLD cholesterol screening recommendations[a]	16.2 (6/37)
MetS control	
Obesity	
% of patients with average BMI $<$ 30, year 1 (n)	61.1 (22/36)
% of patients with average BMI $<$ 30, year 2 (n)	44.1(15/34)
% of patients with average BMI $<$ 30, year 3 (n)	38.2 (13/34)
Hypertension	
% of patients with blood pressure control, year 1 (n)	61.1 (22/36)
% of patients with blood pressure control, year 2 (n)	42.9 (15/35)
% of patients with blood pressure control, year 3 (n)	54.9 (19/35)
Diabetes	
% of patients with diabetic control, year 1 (n)	68.2 (15/22)
% of patients with diabetic control, year 2 (n)	60.9 (14/23)
% of patients with diabetic control, year 3 (n)	65.4 (17/26)
Hyperlipidemia[a]	
% of patients with LDL at goal, year 1 (n)	69.6 (16/23)
% of patients with LDL at goal, year 2 (n)	52.9 (9/17)
% of patients with LDL at goal, year 3 (n)	52.6 (10/19)
% of patients with triglycerides at goal, year 1 (n)	63.6 (14/22)
% of patients with triglycerides at goal, year 2 (n)	53.3 (8/15)
% of patients with triglycerides at goal, year 3 (n)	50.0 (9/18)

[a]Unable to confirm fasting status of laboratory tests.

inclusion criteria which limited our sample size and study power. When evaluating primary care utilization, we included only in-person office-visits given the low rates of telehealth during the study period. We were unable to assess the main purpose of visits and if patients saw their assigned longitudinal primary care provider or another provider within the practice. Our sample only included patients who received care through a closed healthcare system, and it is possible that patients may have concurrently received care elsewhere with data not linked to the EMR to allow for inclusion in this review. The study did not specifically evaluate or control for pre-transplant factors including patient's engagement with primary care or the presence of MetS conditions prior to liver transplant. We also did not evaluate if patients were on treatment for MetS conditions either pre- or post-transplant. As this study was focused on primary care utilization, it did not quantify the involvement of liver transplant providers for each patient throughout the study period, but it is standard practice that beyond 1 year post-transplant liver transplant recipients are seen by the transplant team only annually.

Conclusion

This retrospective rechart review adds to the literature showing increased rates of conditions associated with MetS in patients who have undergone a liver transplant secondary to MASH or cryptogenic cirrhosis. In our patient cohort, primary care utilization was not associated with meeting screening recommendations or control of conditions associated with MetS. More research is needed to assess primary care providers' knowledge of screening guidelines and to further investigate patient-level, provider-level, and system-level barriers to screening and management of MetS in this high-risk patient population. The optimal strategy to provide education and support to primary care providers caring for liver transplant recipients, as well as models of transitions in care also warrant further exploration.

Author Contributions

SF and DB collaboratively contributed to the project concept and research design. SF primarily extracted data from the electronic medical records and analyzed the data. All authors aided in interpretation of the results. SF drafted the manuscript with input from all authors. All authors offered critical revisions and provided final approval of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Sarah J. Flynn https://orcid.org/0000-0001-9938-1752

References

1. Wong RJ, Singal AK. Trends in liver disease etiology among adults awaiting liver transplantation in the United States, 2014–2019. *JAMA Netw Open*. 2020;3:e1920294.
2. Goldberg D, Ditah IC, Saeian K, et al. Changes in the prevalence of Hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. *Gastroenterology*. 2017;152:1090-1099.
3. Hamaguchi M, Kojina T, Takeda N, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med*. 2005;143:722-728.
4. Almeda-Valdes P, Cuevas-Ramos D, Aquilar-Salinas CA. Metabolic syndrome and nonalcoholic fatty liver disease. *Ann Hepatol*. 2009;8:18-24.
5. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287:356-359.
6. Marchesini G, Bugianesi E, Forlani G, et al. Non-alcoholic steatohepatitis in patients cared in metabolic units. *Diabetes Res Clin Pract*. 2004;63:143-151.
7. Kotronen A, Westerbacka J, Bergholm R, et al. Liver fat in the metabolic syndrome. *J Clin Endocrinol Metab*. 2007;92:3490-3497.
8. Lucey MR, Terrault N, Ojo L, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl*. 2013;19(1):3-26.
9. Bianchi G, Marchesini G, Marzocchi R, Pinna AD, Zoli M. Metabolic. syndrome in liver transplantation: relation to etiology and immunosuppression. *Liver Transpl*. 2008;4:1648-1654.
10. Pagadala M, Dasarathy S, Eghtesad B, McCullough AJ. Posttransplant metabolic syndrome: an epidemic waiting to happen. *Liver Transpl*. 2009;15:1662.
11. Ruiz-Rebollo ML, Sanchez-Antolin G, Garcia-Pajares F, et al. Risk of development of the metabolic syndrome after orthotopic liver transplantation. *Transplant Proc*. 2010;42:663.
12. Sookoian S, Pirola CJ. The genetic epidemiology of nonalcoholic fatty liver disease: toward a personalized medicine. *Clin Liver Dis*. 2012;16:467-485.
13. Laryea M, Watt KD, Molinari M, et al. Metabolic syndrome in liver transplant recipients: prevalence and association with major vascular events. *Liver Transpl*. 2007;13:1109-1114.
14. Madhwal S, Atreja A, Albeldawi M, et al. Is liver transplantation a risk factor for cardiovascular disease? A meta-analysis of observational studies. *Liver Transpl*. 2012;18:1140-1146.
15. Gami A, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. 2007;49:403-414.
16. Laish I, Braun M, Mor E, Sulkes J, Harif Y, Ari ZB. Metabolic syndrome in liver transplant recipients: prevalence,

risk factors, and association with cardiovascular events. *Liver Transpl*. 2011;17(1):15-22.
17. Rossetto A, Bitetto D, Bresadola V, et al. Cardiovascular risk factors and immunosuppressive regimen after liver transplantation. *Transplant Proc*. 2010;42:2576-2578.
18. Vogt D, Henderson JM, Carey WD, Barnes D. The long-term survival and causes of death in patients who survive at least 1 year after liver transplantation. *Surgery*. 2002;132:775-780.
19. Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. *Am J Transplant*. 2010;10:1420-1427.
20. Heller JC, Prochazka AV, Everson GT, Forman LM. Long-term management after liver transplantation: primary care physician versus hepatologist. *Liver Transpl*. 2009;15(10):1330-1335.
21. McCashland TM. Post transplantation care: role of the primary care physician versus transplant center. *Liver Transpl*. 2001;7:S2-S12.
22. McGuire BM, Rosenthal P, Brown CC, et al. Long-term management of the liver transplant patient: recommendations for the primary care doctor. *Am J Transplant*. 2009;9(9):1988-2003.
23. Singh S, Watt KD. Long-term medical management of the liver transplant recipient: what the primary care physician needs to know. *Mayo Clin Proc*. 2012;87(8):779-790.
24. Caldwell SH, Lee VD, Kleiner DE, et al. NASH and cryptogenic cirrhosis: a histological analysis. *Ann Hepatol*. 2009;8(4):346-352.
25. Maheshwari A, Thuluvath PJ. Cryptogenic cirrhosis and NAFLD: are they related? *Am J Gastroenterol*. 2006;101(3):664-668.
26. VanWagner LB, Holl JL, Montag S, et al. Blood pressure control according to clinical practice guidelines is associated with decreased mortality and cardiovascular events among liver transplant recipients. *Am J Transplant*. 2020;20(3):797-807.
27. Neuberger J. Follow-up of liver transplant recipients. *Best Pract Res Clin Gastroenterol*. 2020;46:101682.
28. Durand F. How to improve long-term outcome after liver transplantation? *Liver Int*. 2018;38(S1):134-138.
29. VanWagner LB, Gordon E, Adamski L, et al. Liver transplant recipient, caregiver, and provider perceptions of cardiovascular disease and related risk factors after transplant. *Liver Transplant*. 2021;27(5):668-683.
30. Pavlaki M, Hanto DW. Clinical pathways in transplantation: a review and examples from Beth Israel Deaconess Medical Center. *Clin Transplant*. 2012;26(3):382-386.