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Title:
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Date:
2021-05-01

Citation:
Low, E. S. L., Gow, P. J., Testro, A. & Sinclair, M. (2021). Low participation in preventative health measures in a cohort of liver transplant recipients: A cross-sectional analysis. Clinical Transplantation, 35 (5), https://doi.org/10.1111/ctr.14257.

Persistent Link:
https://hdl.handle.net/11343/298297

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Article type : Brief Communication

Low participation in preventative health measures in a cohort of liver transplant recipients: a cross-sectional analysis

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Running Head: Low participation in health prevention in liver recipients

AUTHORSHIP

Dr Marie Sinclair conceived the study and created the survey with input from Associate Professor Adam Testro and Associate Professor Paul Gow. Data were collated and analysed by Dr Elizabeth Low. Manuscript was written by Dr Elizabeth Low in conjunction with review and editing by Dr Marie Sinclair, Associate Professor Adam Testro and Associate Professor Paul Gow.

FUNDING

No funding was received for this work.

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DISCLOSURES

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ABBREVIATIONS

AHF, acute hepatic failure
DEXA, dual-energy x-ray absorptiometry
FOBT, faecal occult blood test
HBV, hepatitis B virus
HCC, hepatocellular carcinoma
HCV, hepatitis C virus

ABSTRACT

Low ESL, Gow PJ, Testro A, Sinclair M. Low participation in preventative health measures in a cohort of liver transplant recipients: a cross-sectional analysis. Clin. Transplant.

Background:

Despite high rates of infection and malignancy post-solid organ transplant, there are little data on patient participation in preventative healthcare.

Methods:

We conducted a cross-sectional survey of post-liver transplant patients to evaluate insight into transplant-associated infective and neoplastic risks, and receipt of vaccination and cancer surveillance in accordance with Australian and local institution-specific guidelines. Descriptive analyses were used to assess characteristics potentially influencing adherence.

Results:

Of 219 patients surveyed, adherence to bowel cancer surveillance was significantly reduced in those distant from transplantation compared to those recently

transplanted (95.8% if transplanted ≤5 years ago vs. 68.3% if transplanted >5 years ago, p<0.001). Skin cancer surveillance participation with annual physician-directed examination was low (42.9%), particularly in younger patients (29.5% in <50yo vs. 48.1% in ≥50yo, p=0.01), who were also less adherent to vaccination recommendations (72.1% in <50yo vs. 87.3% in ≥50yo, p=0.008).

Conclusions:

This is the first analysis of preventative healthcare participation in a cohort of Australian liver transplant recipients, revealing concerning adherence to bowel and skin cancer surveillance recommendations. Major interventions to avoid preventable disease in this high-risk cohort are warranted.

KEYWORDS

Organ transplantation, population surveillance, neoplasms.

MAIN TEXT

Introduction

Liver transplantation remains the only curative option for end-stage cirrhosis and a subset of patients with hepatocellular carcinoma (HCC).[1-3] With 5-year survival exceeding 80%, preventative health is an increasingly important component of successful post-transplant care.[2,4,5] Both pre- and post-transplant factors contribute to the increased vulnerability of transplant recipients to non-liver disease, many of which can be targeted by established preventative healthcare.[6,7]

Australia conducts free screening programs for the early detection of breast, cervical and bowel cancers, for which evidence-based screening recommendations exist.[8] Nationwide vaccination recommendations also exist for the immunocompromised, and all aged 65 and above, including yearly influenza vaccines, and single-dose pneumococcal vaccination (three doses if immunocompromised).[9]

Preventative healthcare is vital post-transplant, where infections and cancers contribute considerably to morbidity and mortality.[2,10,11] Infections remain the leading

cause of hospitalization within 2 years of transplantation, while malignancies, purportedly more biologically aggressive in transplant recipients, account for approximately 20% of mortality.[2,10,11] In the post-liver transplant population, the incidence of de-novo cancer is reportedly double that of the general population.[2,12] This excess risk is likely driven by immunosuppressive agents, whose actions impairing immunosurveillance also increase susceptibility to infections in a population already rendered vulnerable by long-term chronic illness.[1,13]

Scant data have been published characterizing participation in preventative health strategies in solid organ recipients.[14,15] Recipient awareness of the elevated cancer and infection risks, which may influence participation in screening interventions, is unknown. This cross-sectional analysis aims to describe receipt of preventative healthcare recommendations, and evaluate transplant recipients' insight into the non-liver risks associated with transplantation.

Materials and Methods

A cross-sectional analysis was conducted on data collected from post-transplant patients attending outpatient consultations at the Victorian Liver Transplant Unit (Melbourne, Australia) from June to December 2018. All patients upon arrival were invited to participate by clinic nurses. Following informed consent, participants were given a paper-based, 14-item institution-formulated questionnaire (see Supplementary Materials). Completion occurred while awaiting appointments, and was collected prior to clinic exit. 219 responses were collected. This project was approved by the Austin Health Research Ethics Committee (RQ number 28333).

Outcome Measures

The primary aim was to describe participation in nationally recommended and local institution-specific preventative health measures. Australian recommendations included 2-yearly faecal occult blood test (FOBT) or 5-yearly colonoscopy if greater than 50 years old for bowel cancer, and in females, 5-yearly Pap smears for cervical cancer and 2-yearly mammography if greater than 50 years old for breast cancer.[8,16] Local institution guidelines, based on national or international practice guidelines, include annual physician-conducted full-skin examinations and 2-yearly dual-energy

X-ray absorptiometry (DEXA) scans, as well as yearly influenza and 5-yearly pneumococcal vaccination.[7,9]

We assessed participation in preventative health measures with 'yes'/'no' categories, and asked patients to document dates of last screening interventions. Individuals were classified as "adherent" or "non-adherent" if screening last occurred within the time interval specified by guidelines.

Participants responded to 'yes'/'no' categories to the statements, 'transplant patients are at higher risks of… cancer' and 'transplant patients are at higher risk of infection', to assess underlying awareness of elevated cancer and infection risks associated with transplantation, as detailed during pre-transplant evaluation education sessions and government-driven reminder letters.

To uncover potential factors associated with screening participation, time interval from transplantation, age, gender and underlying transplantation indications were retrieved from medical records. Time from transplantation was divided into two groups, those within and those greater than 5 years from transplantation, to assess for differences in participation between those with recent compared with distant transplantation. Acknowledging the margin of error with patient-reported outcomes, patient responses were compared with specific screening intervention dates recorded within the centre's database. For discrepancies that affected the binary outcome of adherence, the most recent date (patient-reported or database recorded) was accepted. If no corresponding database dates were found, the patient's reported date was accepted. If no patient-reported date was given, database dates were accepted. Language spoken, ethnicity and location of residence were also extracted, with postcode used to determine rurality according to the Australian Bureau of Statistics' Remoteness Area Codes.[17]

Statistical Analysis

Frequencies for dichotomous and polychotomous variables were generated. Descriptive statistics, including Chi-squared and Fisher's exact tests were used to evaluate for factors associated with screening participation. Analyses were performed using Statistical Analysis Software (SAS) v.9.4.

Results

219 of 730 patients attending post-transplant clinics during the recruitment period participated (response rate 30.0%). Respondents' characteristics are presented in Table 1. The median age of participants was 58.9 years (IQR 47.4-64.5 years). Most were male (68.5%), Caucasian (79.0%), English-speaking (93.6%) and of metropolitan residence (74.9%). The median time from transplantation was 3.7 years (IQR 1.2-9.7 years). Compared to survey non-respondent clinic attendees, survey respondents did not differ with respect to age (p=0.70), gender (p=0.31) or ethnicity (p=0.09), however English-speaking patients were significantly more likely to participate than non-English-speaking patients (30.5% vs. 16.7%, p=0.01).

Overall adherence to bowel cancer screening recommendations (FOBT or colonoscopy) was 85.3% (see Table 2). The proportion of recipients meeting bowel cancer screening recommendations significantly reduced as interval from transplantation increased, from 95.8% for those transplanted within 5 years, to 68.3% for those transplanted greater than 5 years ago (p<0.001). This difference remained on exclusion of patients within 5 years of transplant whose most recent screening occurred pre-transplant (transplant ≤ 5 years (88.1%) vs. transplant > 5 years (68.3%), p=0.02).

Overall participation with annual skin cancer surveillance was 42.9%, and was lower in non-Caucasians (29.6% in non-Caucasians vs. 46.2% in Caucasians, p=0.046), non-English-speaking compared with English-speaking patients (7.7% vs. 45.1%, p=0.008) and younger patients (Table 2, Supplementary Table 1). Sun protection use was not associated with increased skin cancer surveillance (p=0.24). Adherence of females (>50 years old) to biannual mammography was 74.4%, and 80.0% of all women reported up-to-date Pap smears. Era of transplantation did not significantly impact on female-specific cancer surveillance rates, even with exclusion of patients within two years of transplant with pre-transplant mammography (p=0.43).

Overall adherence to annual influenza vaccination was 83.0%. Younger patients (<50 years old) were less likely to comply with influenza vaccine recommendations (72.1% in <50 years old vs. 87.3% in ≥50 years old, p=0.008), as were metropolitan-

based patients compared to their rural counterparts (79.8% vs. 92.7%, p=0.03). Compliance to 5-yearly pneumococcal vaccination was 46.0%. Subgroup analysis of vaccination adherence in patients 65 years and over (for whom national recommendations exist) demonstrated 88.5% adherence to influenza and 64.7% adherence to pneumococcal vaccinations.

89.5% of participants reported DEXA scans within the last 2 years, occurring more frequently in Caucasians than non-Caucasians (93.6% vs. 73.9%, p<0.001) (Supplementary Table 2). Awareness of transplantation-associated increased cancer and infective risks (79.0% and 97.2% respectively), and underlying transplant indication, did not correlate with significant differences in screening behaviours (Supplementary Tables 3 and 4). Discrepancies between patient-reported and database recorded cancer screening occurred in 3.2% of patients.

Discussion

This is the first Australian study evaluating preventative healthcare participation in liver transplant recipients. Participation in bowel and skin cancer surveillance was concerningly low in population subsets, with 31.7% of patients more than 5 years post-transplant not meeting bowel cancer surveillance recommendations. Despite regular surveillance participation reviews with transplant clinicians encouraging screening, and free national screening programs, 73.1% of patients below 50 years old and 70.4% of non-Caucasians did not have appropriate skin cancer surveillance, concerning findings in patients with some of the highest rates of skin malignancies worldwide.[18] Clearly current strategies inadequately motivate participation in preventative healthcare.

Few prior studies have examined post-transplant cohort's participation in healthcare prevention.[14] A population-based Canadian study reported similar 5-year compliance to bowel cancer screening of 63.3% in solid organ transplant recipients, but lower participation in cervical (15.1%) and breast (17.2%) cancer screening than our cohort.[14] Comparable skin cancer surveillance rates of 40% were seen in an Australian-state prevalence study of high-risk kidney and liver transplant recipients.[18] Increasing awareness of white race and fair skin as risk factors for skin cancer may explain our Caucasian cohort's greater skin surveillance.[19,20] However, surveillance rates of only 29.6% in non-Caucasians and 7.7% in non-English-speaking patients

highlights a lack of participation in a group that, despite lower overall incidences of skin cancers, often present at a more advanced stage with poorer outcomes.[19,21]

Screening in our transplant population compared favourably to the general Australian population rates of breast (54.3%) and bowel (41.3%) screening, and paralleled international participation rates (81.3%, 71.7% and 61.9-63.4% adherence for cervical, breast and bowel screening in the United States).[22,23] Vaccination participation specifically in our cohort aged 65 years and over demonstrated higher participation with influenza (88.5% vs 74.8%) and pneumococcal (64.7% vs. 56.0%) vaccinations, compared to the general Australian population.[24] Notably in our cohort, rural address significantly increased participation in influenza vaccination. This may be driven by a perceived dilution of responsibility for such interventions amongst metropolitan physicians to their colleagues, in contrast to the more all-inclusive care of the sole rural practitioner.

There are notable limitations of our single-centre study. Our 30.0% response rate raises the concern of sampling bias, although as survey respondents are generally more likely to engage with healthcare than non-responders, true preventative healthcare participation may be even lower than reported. Reasons for participation refusal were not collected, but observation suggests that excessive effort required and inability to recall intervention dates may have contributed. While comparison of age, gender and ethnicity did not yield notable differences between survey responders and non-responders, English speakers were significantly more likely to participate, and the lower representation of non-English speakers is an important limitation. Data limitations prevented more comprehensive assessment of socioeconomic factors, which remains a potential confounder, although the cost-free nature of preventative healthcare interventions in Australia likely alleviates some financial burden. We also acknowledge that the phrasing used to determine infection and cancer risk awareness may have biased towards a positive response.

The selection bias associated with respondent-based surveys lends to potential over-reporting. In attempt to mitigate this, we compared reported cancer screening and vaccinations rates with their occurrence dates in the centre's transplant database, with discrepancies in only 3.2% of patients. We acknowledge that

accepting patient-reported dates from externally performed tests may falsely elevate screening rates. However, this potential for over-reporting, together with the likely contribution of pre-transplant assessment interventions in recently transplanted respondents to falsely elevating preventative healthcare participation rates, suggests that true participation for this cohort may be even lower than reported in this study. Analysis excluding recently transplanted participants with pre-transplant date cancer surveillance maintained the difference in bowel cancer screening participation between time-from-transplantation intervals. As new reports suggest relatively low diagnostic yield of cancer screening during the transplant assessment, ongoing malignancy surveillance becomes increasingly critical as time from transplantation and cumulative exposure to immunosuppressants increase.[25,26]

With rising numbers of transplants occurring (transplantation rates have increased 124% in Australia over the last 10 years)[27], nuanced analysis into factors contributing to poor participation in preventative health measures and formulation of evidence-based, transplant recipient-specific recommendations is required.

In conclusion, this study highlights concerningly low participation in preventative health measures in a cohort of liver transplant recipients. This was predominantly evident in those further from transplantation, and in younger recipients. There is a major need for interventions to engage this vulnerable population in preventative healthcare to avoid preventable diseases.

References

1. 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.
2. Seree O, Altieri M, Guillaume E, et al. Longterm Risk of Solid Organ De Novo Malignancies After Liver Transplantation: A French National Study on 11,226 Patients. *Liver Transpl.* 2018;24(10):1425-1436.
3. 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.

4. Compston JE. Osteoporosis after liver transplantation. *Liver Transpl.* 2003;9(4):321-330.
5. McCaughan GW, Munn SR. Liver transplantation in Australia and New Zealand. *Liver Transpl.* 2016;22(6):830-838.
6. Royal Australian College of General Practitioners. National P, Community Medicine C. Guidelines for preventive activities in general practice. *Aust Fam Physician.* 2001;Spec No:S1i-xvi, S1-1-61.
7. Acuna SA, Huang JW, Scott AL, et al. Cancer Screening Recommendations for Solid Organ Transplant Recipients: A Systematic Review of Clinical Practice Guidelines. *Am J Transplant.* 2017;17(1):103-114.
8. Cancer Council. Screening programs. *About cancer* 2016; https://www.cancer.org.au/about-cancer/early-detection/screening-programs/, 2020.
9. Australian Technical Advisory Group on Immunisation (ATAGI). Australian Immunisation Handbook. In. Canberra: Australian Government Department of Health; 2018.
10. Dharnidharka VR, Stablein DM, Harmon WE. Post-transplant infections now exceed acute rejection as cause for hospitalization: a report of the NAPRTCS. *Am J Transplant.* 2004;4(3):384-389.
11. Miao Y, Everly JJ, Gross TG, et al. De novo cancers arising in organ transplant recipients are associated with adverse outcomes compared with the general population. *Transplantation.* 2009;87(9):1347-1359.
12. Finkenstedt A, Graziadei IW, Oberaigner W, et al. Extensive surveillance promotes early diagnosis and improved survival of de novo malignancies in liver transplant recipients. *Am J Transplant.* 2009;9(10):2355-2361.
13. Chak E, Saab S. Risk factors and incidence of de novo malignancy in liver transplant recipients: a systematic review. *Liver Int.* 2010;30(9):1247-1258.
14. Acuna SA, Sutradhar R, Camacho X, et al. Uptake of Cancer Screening Tests Among Recipients of Solid Organ Transplantation. *Am J Transplant.* 2017;17(9):2434-2443.
15. Courtney AE, Leonard N, O'Neill CJ, McNamee PT, Maxwell AP. The uptake of cervical cancer screening by renal transplant recipients. *Nephrol Dial Transplant.* 2009;24(2):647-652.

16. Party CCACCGW. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer. In: Cancer Council Australia Sydney; 2017.
17. Statistics ABo. Australian Statistical Geography Standard (ASGS): Volume 5– Remoteness Structure, Australia July 2011 (ABS Catalogue No. 1270.0. 55.005). In: Commonwealth of Australia Canberra; 2013.
18. Iannacone MR, Sinnya S, Pandeya N, et al. Prevalence of Skin Cancer and Related Skin Tumors in High-Risk Kidney and Liver Transplant Recipients in Queensland, Australia. *J Invest Dermatol.* 2016;136(7):1382-1386.
19. Jambusaria-Pahlajani A, Crow LD, Lowenstein S, et al. Predicting skin cancer in organ transplant recipients: development of the SUNTRAC screening tool using data from a multicenter cohort study. *Transpl Int.* 2019;32(12):1259-1267.
20. Iannacone MR, Pandeya N, Isbel N, et al. Sun Protection Behavior in Organ Transplant Recipients in Queensland, Australia. *Dermatology.* 2015;231(4):360-366.
21. Pritchett EN, Doyle A, Shaver CM, et al. Nonmelanoma Skin Cancer in Nonwhite Organ Transplant Recipients. *JAMA Dermatol.* 2016;152(12):1348-1353.
22. National cancer screening programs participation data. Australian Institute of Health and Welfare; 2019. https://www.aihw.gov.au/reports/cancer-screening/national-cancer-screening-programs-participation/contents/breastscreen-australia. Accessed May 2019.
23. Hall IJ, Tangka FKL, Sabatino SA, Thompson TD, Graubard BI, Breen N. Patterns and Trends in Cancer Screening in the United States. *Prev Chronic Dis.* 2018;15:E97.
24. Dyda A, Karki S, Hayen A, et al. Influenza and pneumococcal vaccination in Australian adults: a systematic review of coverage and factors associated with uptake. *BMC Infect Dis.* 2016;16(1):515.
25. Haagsma EB, Hagens VE, Schaapveld M, et al. Increased cancer risk after liver transplantation: a population-based study. *J Hepatol.* 2001;34(1):84-91.
26. Oey RC, van Tilburg L, Erler NS, et al. The Yield and Safety of Screening Colonoscopy in Patients Evaluated for Liver Transplantation. *Hepatology.* 2019;69(6):2598-2607.

27. Donate Life. *Australian Donation and Transplantation Activity Report 2018.* Canberra, Australia: Organ Tissue Authority; 14 February 2019.

Table 1: Characteristics of the 219 Respondents of the Austin Health 'Liver Transplant Unit Preventative Health Survey', 2018

Patient Factor		Frequency	Relative Frequency (%)	Median (IQR)
Age (years)				58.9 (47.4-64.5)
Median Time from Transplant (years)				3.7 (1.2-9.7)
Sex	Male	150	68.5	
	Female	69	31.5	
Language Spoken	English	205	93.6	
	Other	14	6.4	
Race	Caucasian	173	79.0	
	Other	46	21.0	
Location of Residence	Metropolitan	164	74.9	
	Rural/Remote	55	25.1	
Year of First Liver Transplantation	2014-2018	127	58.0	
	Pre-2014	92	42.0	
Reason for Transplantation	HCC	62	28.3	
	Autoimmune[1]	45	20.5	
	Alcohol	28	12.8	
	Other[2]	27	12.3	
	Viral hepatitis	20	9.1	
	AHF	16	7.3	
	NASH	11	5.0	
	Congenital	10	4.6	
Underlying Aetiology of HCC	HCV	21	33.9	
	HBV	18	29.0	
	Alcohol	10	16.1	

	Other	9	14.5
	NASH	4	6.5
Current Smoker		11	5.0

[1] inclusive of autoimmune hepatitis, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), lupoid cirrhosis

[2] inclusive of cryptogenic cirrhosis, sarcoidosis, Wilson's disease, other metabolic disorders

HCC = hepatocellular carcinoma, NASH = non-alcoholic steatohepatitis, AHF = acute hepatic failure, HBV = hepatitis B virus, HCV = hepatitis C virus

Table 2: Awareness of increased transplant-associated risks, rates of participation with screening and their association with age, gender and time from transplantation.

	Participation n (%)	By Gender n (%)			By Age n (%)			By Time from Transplantation n (%)		
		Male	Female	P	Age < 50 years	Age ≥50 years	P	≤ 5 years	> 5 years	P
Awareness of Increased Cancer Risk n=219	173 (79.0)	116 (77.3)	57 (82.6)	0.37	48 (78.7)	125 (79.1)	0.95	101 (79.5)	72 (78.3)	0.82
Awareness of Increased Infection Risk n=218	212 (97.2)	146 (97.3)	66 (97.1)	1.00	59 (96.7)	153 (97.5)	0.67	126 (99.2)	86 (94.5)	0.08
Bowel Cancer Screening[1] n=156 (patients ≥50yo)	133 (85.3)	98 (83.8)	35 (89.7)	0.44				**92 (95.8)**	**41 (68.3)**	**<0.001**
Annual Skin Check n=217	93 (42.9)	63 (42.3)	30 (44.1)	0.80	**18 (29.5)**	**75 (48.1)**	**0.01**	52 (41.3)	41 (45.1)	0.57
Mammography[2] n=39 (women ≥50yo)	29 (74.4)							15 (68.2)	14 (82.4)	0.46

Pap Smears[3] n=65 (women)	52 (80.0)				23 (79.3)	29 (80.6)	0.90	26 (74.3)	26 (86.7)	0.35
DEXA Scan n=219	196 (89.5)	138 (92.0)	58 (84.1)	0.07	51 (83.6)	145 (91.8)	0.08	115 (90.6)	81 (88.0)	0.55
Vaccination – Annual Influenza n=218	181 (83.0)	126 (84.0)	55 (80.9)	0.57	**44 (72.1)**	**137 (87.3)**	**0.008**	103 (81.1)	78 (85.7)	0.37
Vaccination – 5-yearly Pneumococcal n=200	92 (46.0)	**55 (40.7)**	**37 (56.9)**	**0.03**	20 (35.1)	72 (50.4)	0.05	58 (48.7)	34 (42.0)	0.35

[1] FOBT within 2 years or colonoscopy within 5 years

[2] Mammography within 2 years

[3] Pap smear within 5 years