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Can Weather Be a Factor in Liver Transplant Waitlist and Posttransplant Outcomes? Analysis of United Network for Organ Sharing Registry

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ABSTRACT

Background. Cold climate is known to affect the frequency and attributable mortality of various illnesses. This study aims to evaluate the effect of climate among regions on liver transplant (LT) outcomes.

Methods. We analyzed data from the United Network for Organ Sharing registry for 98,517 adult patients (aged ≥ 18 years) who were listed for LT between 2010 and 2019. During this period, 51,571 patients underwent single-organ, deceased LT. States were categorized based on their mean winter temperature: warm states (45°F-70°F), intermediate states (30°F-45°F), and cold states (0°F-30°F). Post-LT outcomes at 1 month, 1 year, and 3 years were compared using Cox proportional hazard models. Ninety-day and 1-year waitlist outcomes were compared among climate regions using Fine-Gray hazard regression model.

Results. After adjusting risks for recipient and donor characteristics, LT candidates in cold states had a significantly higher waitlist (90-day: subdistribution hazard ratio (HR) 1.46; 1-year: subdistribution HR 1.41; $P < .001$) and posttransplant mortality (30-day: subdistribution HR 1.23; $P = .009$, 1-year: subdistribution HR 1.16; $P = .001$; 3-year: subdistribution HR 1.08; $P = .007$). LT recipients in cold states had a higher proportion of deaths due to infections than warm states (cold states: 2.3%; intermediate states: 2.1%; and warm states: 1.7%; $P < .001$).

Conclusions. Potential reasons include weather-related changes in the behavioral and physiological parameters of patients.

THE effect of climate differences in the frequency and attributable mortality on various medical illnesses is extensively reported in the literature [1−6]. The incidence of acute cardiovascular and cerebrovascular events such as myocardial infarction [7], ischemic/hemorrhagic strokes [8], and pulmonary embolism [9] are increased during cold weather compared to warmer temperatures. The underlying pathophysiology associated with cold weather seems to result from thrombosis due to hemoconcentration in the cold [10,11] and from other consequences of cardiovascular reflexes that are briefly induced by low temperatures [12−14]. In addition, the respiratory viral infections occur at a higher frequency during winter mainly because of outbreaks caused by influenza, respiratory syncytial virus, and rhinovirus [15−17].

The increased mortality of respiratory and cardiovascular diseases during winter is not only limited to healthy patients [18], but the effect is also seen in patients with end-stage renal disease and those who underwent liver or kidney transplant surgery [19,20]. In a study by Astor et al, the number of observed deaths in kidney transplant recipients exceeded the number expected by 8.9% in the winter. The pattern was strongest for deaths attributable to cardiovascular disease. Similarly, there was an excess of graft failures in winter [21]. A single-center retrospective study evaluated the outcomes of 190 consecutive liver transplant (LT) recipients who underwent transplantation over 10 years and reported increased frequency of deaths in the winter that was significantly greater than all other seasons [22]. The high wintertime mortality could not be explained by previously recognized risk factors of poor outcomes such as such as high Model for End-Stage Liver Disease (MELD) score, dialysis requirement,

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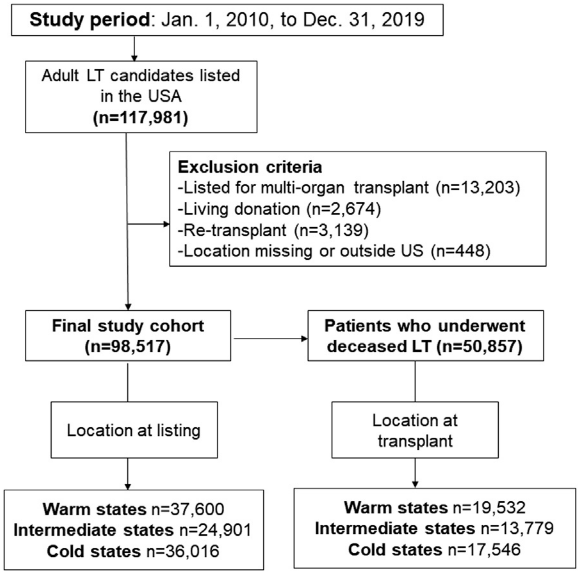

Fig 1. Flow chart of study population at listing/transplant. LT, liver transplant.

intraoperative large blood loss, infections, rejection, or increased immunosuppression [22].

Several studies have demonstrated seasonal variations in outcomes in different patient populations. Still, it is unknown whether such geographic climate differences exist for waitlist or posttransplant outcomes among LT recipients in the United States. We hypothesized that patients who were listed and transplanted in cold states had worse outcomes than patients in warmer states because of a higher cumulative exposure to cold weather. This study aims to evaluate climate effects on the waitlist and posttransplant outcomes for LT candidates/recipients.

MATERIALS AND METHODS

Patient Cohort

This study uses data from the Organ Procurement and Transplantation Network and United Network for Organ Sharing in the Standard Transplant Analysis and Research file, including de-identified waiting list and transplant data of all LT candidates registered since October 1, 1987 in the United States. For the analysis of waitlist outcomes, adult patients (aged ≥18 years old at listing) listed between January 1, 2010, and December 31, 2019, were evaluated. Patients with multi-organ listing, recipients of living donor transplant, and re-listing were excluded. For the analysis of posttransplant outcomes, adult transplant patients (aged >18 years old at LT) between January 1, 2010, and December 31, 2019, were evaluated. Patients who received a living donor transplant, re-transplant, and those who underwent LT combined with kidney, thoracic organs, intestine, and/or pancreas were excluded (Fig 1).

Patients were stratified based on the state they were listed/transplanted at into 3 groups according to the mean winter temperature in those states during the months of December, January and February (Fig 2): warm states (45°F-70°F): Alabama, California, Florida, Georgia, Hawaii, Louisiana, Mississippi, Puerto Rico, South Carolina, Texas and Virgin Islands; intermediate states (30°F-45°F): Arizona, Arkansas, Delaware, District of Columbia, Kansas, Kentucky, Maryland, Missouri, Nevada, New Jersey, New Mexico, North Carolina, Oklahoma, Oregon, Tennessee, Virginia, Washington, and West Virginia; and cold states (0°F-30°F): Alaska, Colorado, Connecticut, Illinois, Indiana, Maine, Massachusetts, Minnesota,

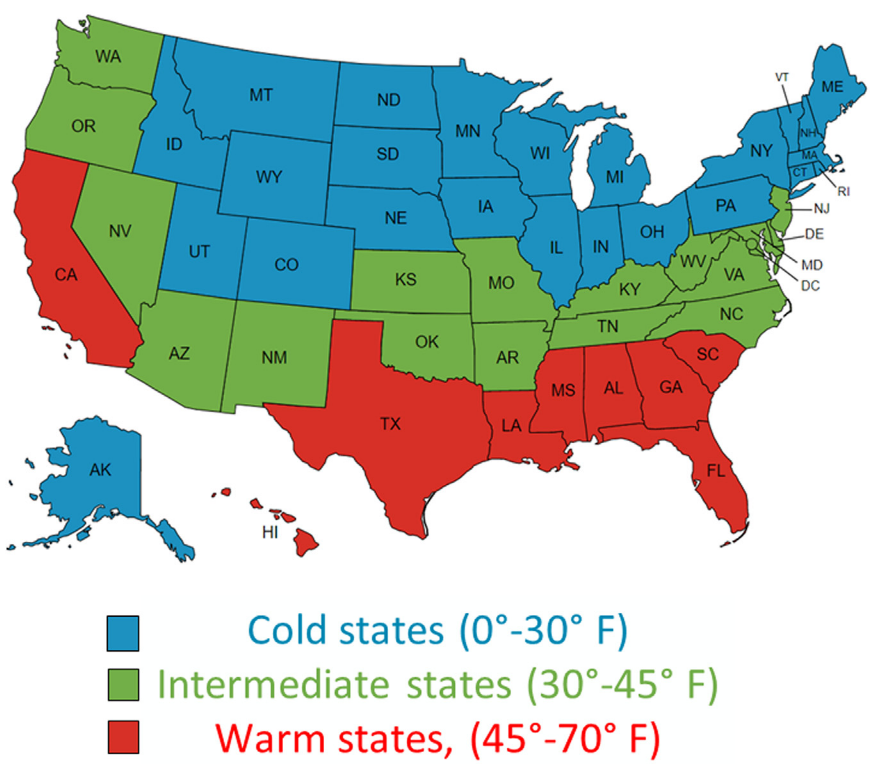

Fig 2. Map of state classification based on mean winter temperature.

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Table 1. Characteristics of the Study Population at Listing

Candidate Characteristics		Warm States (45°F-70°F) (n = 37,600)	Intermediate States (30°F-45°F) (n = 24,901)	Cold States (0°F -30°F) (n = 36,016)	*P*
Age (years), median (IQR)		57.0 (50.0, 63.0)	57.0 (50.0, 62.0)	57.0 (50.0, 63.0)	**< .001**
Sex, n (%)	Male	23733 (63.1)	16060 (64.5)	23787 (66.0)	**< .001**
	Female	13867 (36.9)	8841 (35.5)	12229 (34.0)	
BMI (kg/m^2), median (IQR)		28.1 (24.6, 32.3)	28.5 (24.9, 32.8)	28.2 (24.7, 32.6)	**< .001**
Ethnicity, n (%)	White	22642 (60.2)	19036 (76.4)	27494 (76.3)	**< .001**
	Black	2986 (7.9)	2484 (10.0)	2957 (8.2)	
	Hispanics	9434 (25.1)	1973 (7.9)	3674 (10.2)	
	Asians	2086 (5.5)	809 (3.2)	1396 (3.9)	
	Others	452 (1.2)	599 (2.4)	495 (1.4)	
Diabetes, n (%)		9705 (26.7)	6177 (25.5)	9087 (26.0)	**.004**
MELD score, median (IQR)		17.0 (11.0, 25.0)	17.0 (11.0, 24.0)	16.0 (11.0, 24.0)	**< .001**
Encephalopathy grade 3-4, n (%)		3304 (8.8)	2053 (8.2)	2735 (7.6)	**< .001**
Moderate ascites, n (%)		9279 (24.7)	5627 (22.6)	8662 (24.1)	**< .001**
Karnofsky score, n (%)	> 30	29287 (80.2)	20435 (83.3)	29506 (82.8)	**< .001**
	10-30	7231 (19.8)	4089 (16.7)	6120 (17.2)	
Candidate on life support, n (%)		1986 (5.3)	846 (3.4)	1436 (4.0)	**< .001**
Candidate on dialysis, n (%)		2916 (7.8)	1272 (5.1)	1928 (5.4)	**< .001**
Diagnosis, n (%)	HCV	8514 (23.4)	5861 (24.3)	7214 (20.7)	**< .001**
	NASH	4697 (12.9)	3604 (14.9)	4717 (13.5)	
	ALD	7497 (20.6)	4670 (19.4)	7795 (22.3)	
	CLD	1962 (5.4)	1721 (7.1)	2501 (7.2)	
	Others	13673 (37.6)	8260 (34.3)	12664 (36.3)	
Days on waitlist, median (IQR)		75.0 (12.0, 250.0)	81.0 (16.0, 234.0)	107.0 (20.0, 303.8)	**< .001**
Transplant center volume, n (%)	High-volume	15876 (42.2)	9699 (39.0)	6974 (19.4)	**< .001**
	Mid-volume	14232 (37.9)	11808 (47.4)	24779 (68.8)	
	Low-volume	7492 (19.9)	3394 (13.6)	4263 (11.8)	
Season at transplant, n (%)	Warm season	22416 (59.6)	14862 (59.7)	21230 (58.9)	.10
	Cold season	15184 (40.4)	10039 (40.3)	14786 (41.1)	
Era, n (%)	2015-2019	18248 (48.5)	12314 (49.5)	17047 (47.3)	**< .001**
	2010-2014	19352 (51.5)	12587 (50.5)	18969 (52.7)	

ALD, alcohol related liver disease; BMI, body mass index; CLD, cholestatic liver disease; DCD, donation after cardiac death; HCV, hepatitis C virus; IQR, interquartile range; MELD, Model for End-stage Liver Disease; NASH, nonalcoholic steatohepatitis. Bold type indicates statistically significant differences.

Michigan, Montana, Nebraska, New York, New Hampshire, North Dakota, Ohio, Pennsylvania, Rhode Island, South Dakota, Utah, Vermont, Wisconsin, and Wyoming. In addition, deceased LT donors were stratified similarly based on their home states into cold, intermediate, and warm states. The state temperatures were based on data collected for 30 years and made available by the National Oceanic and Atmospheric Administration National Climatic Data Center of the United States [23]. This study was approved for an institutional review board waiver after review.

Analysis of Waitlist Outcomes

In adult LT candidates, 90-day and 1-year waitlist mortality and transplant probability were compared among the state groups. Patients removed from the waitlist because of deterioration in their medical condition (i.e., too sick to transplant) were considered as waitlist mortalities. We examined 2 era groups with a 5-year range: Era 1 included listings between 2010 to 2014, and Era 2 between 2015 to 2019. Eras were defined according to the availability and wide-spread use of antiviral therapy for hepatitis C virus, which was more common in Era 2 [24]. Risks were adjusted for the following recipient characteristics at listing based on a previous methodology: age (Categories: ≤ 50, 50-59, and > 60 years); ethnicity (Categories: white, black, Hispanic, and others), body mass index (Categories: 18.5-24.9, 25.0-29.9, and ≥ 30 kg/m^2); sex (Categories: male and female); history of diabetes (Binary: yes or no); Karnofsky performance status score (Categories: >30 and 10-30); dialysis or life support requirement (Binary: yes and no); MELD score (Categories: 6-14, 15-25, and ≥ 26); presence of ascites (Categories: none/mild, and moderate/severe) or encephalopathy (Categories: none/Grade 1-2, and Grade 3-4); diagnosis of end-stage liver disease (hepatitis C, non-alcoholic steatohepatitis, alcohol-related liver disease, cholestatic liver disease, and others); season; and listing center transplant volume and era of listing (Eras 1-2) [25]. The seasons were stratified into either warm (April to October) or cold (November to March). To evaluate the effects of transplant center experience on outcomes, transplant centers were classified into 3 groups: Group 1: centers that performed 62 or more cases of LT per year during the study period (high-volume center group); Group 2: centers that performed between 62 and 30 LT per year during the study period (mid-volume center group); and Group 3: centers that performed less than 30 LT per year during the study period (low-volume center group). We used the 75th percentile value (62 transplants/year) and 50th percentile value (30 transplants/year) of the number of LTs in each center as the threshold.

Analysis of Posttransplant Outcomes

In adult deceased LT recipients, 30-day, 1-year, and 3-year posttransplant liver graft and patient survival were compared among state groups.

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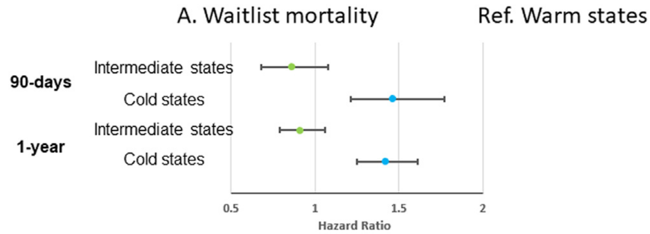
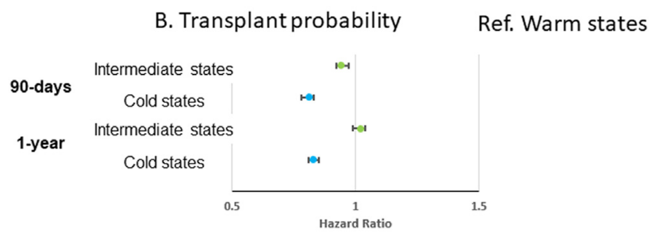


	States	sHR	95% CI Lower	Upper	P values
90-days	Intermediate	0.86	0.68	1.08	0.13
	Cold	1.46	1.21	1.77	**<0.001**
1-year	Intermediate	0.91	0.79	1.06	0.12
	Cold	1.42	1.25	1.61	**<0.001**



	States	sHR	95% CI Lower	Upper	P values
90-days	Intermediate	0.94	0.92	0.97	**<0.001**
	Cold	0.81	0.78	0.83	**<0.001**
1-year	Intermediate	1.02	0.99	1.04	0.44
	Cold	0.94	0.90	0.99	**<0.001**

Fig 3. Comparison of 1-year waitlist outcomes between different states according to their winter temperature: cold (0°F-30°F) and intermediate (30°F-45°F) (reference warm states (45°F-70°F) for entire cohort.

Possible risk factors for posttransplant graft loss and mortality were investigated for each state group. We examined 2 era groups with 5-year range: Era 1 included patients transplanted between 2010 to 2014, and Era 2 between 2015 to 2019. The hazards of mortality were adjusted for the following variables based on previous methodology [25]. Recipient variables at transplant included the following based on a previous methodology: age (Categories: ≤ 50, 50-59, and > 60 years); sex (Categories: male and female); ethnicity (Categories: White, Black, Hispanic, and other); body mass index (Categories: 18.5-24.9, 25.0-29.9, and ≥ 30 kg/m^2); MELD score (Categories: 6-14, 15-25, and ≥ 26); diabetes (Binary: yes or no); Karnofsky performance status score (Categories: >30, and 10-30); hepatocellular carcinoma (Binary: yes and no); diagnosis of end-stage liver disease (hepatitis C, non-alcoholic steatohepatitis, alcohol-related liver disease, cholestatic liver disease, and others); dialysis (Binary: yes and no) or life support requirement (Binary: yes and no); presence of ascites (Categories: none/mild, and moderate/severe) or encephalopathy (Categories: none/Grade 1-2, and Grade 3-4); season; transplant center volume (Categories: low-, mid-, and high-volume centers); and Era of transplant (Eras 1-2) [25]. Donor variables included split liver graft (Binary: yes and no); type of donation (Categories: donation after cardiac death and donation after brain death), organ share type (Categories: local, regional, and national); age (continuous); sex (Categories: male and female); ethnicity (Categories: white, black, Hispanic, and other); cold ischemia time (Categories: ≤ 8 and > 8); and cause of death (Categories: anoxia, cerebrovascular accident, and head trauma) [26].

Statistical Analysis

Data were analyzed using the median with interquartile range for continuous variables and using percentages for discrete variables. Comparisons of continuous variables and discrete variables were performed using the Mann-Whitney test and χ^2 test. Waitlist outcomes were compared by the Gray test to estimate the cumulative incidence of competing events, including death, transplantation, removal from waitlist due to clinical improvement, and removal from the waitlist for other reasons. The Fine-Gray proportional hazard regression for competing events was used to perform casual evaluation of the subdistribution hazards of waitlist outcomes after adjusting for candidate variables at listing. Patient survival and liver graft survival rates were estimated by a Kaplan-Meier method with log-rank tests. Casual evaluation of risk factors for posttransplant mortality and the subdistribution hazard risk (sHR) were analyzed using Cox proportional hazards models and compared among state groups. The hazards of patient death were adjusted for recipient and donor variables described. P value < .05 was considered statistically significant. All statistical analyses were completed using SPSS version 25 (IBM, Armonk, New York, USA) and EZR version 1.37 (Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics at Listing

A total of 117,981 adult patients were registered for LT during the study period. The following populations were excluded: 3,139 listed for a re-transplant; 2,674 received a living donor transplant; 448 with a location of listing that is missing or outside of the United States; and 13,203 listed for LT combined with thoracic organs, intestine, or pancreas. A total of 98,517 adult LT candidates were identified for the analysis of the waitlist outcomes: 37,600 (38.2%) patients listed in warm states; 24,901 (25.2%) listed in intermediate states; and 36,016 (36.6%) listed in cold states (Fig 1). The number of patients listed with the diagnosis of alcohol-related liver disease was

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Table 2. Characteristics of the Study Population at Transplant

		Warm States (45-70°F) (n = 19,532)	Intermediate States (30-45°F) (n = 13,779)	Cold States (0-30°F) (n = 17,546)	P
Recipient characteristics					
Age (y), median (IQR)		58.0 (51.0, 63.0)	57.0 (51.0, 63.0)	58.0 (51.0, 63.0)	**< .001**
Age (y), n (%)	< 50	4326 (22.1)	3127 (22.7)	3882 (22.1)	**.005**
	50-59	7094 (36.3)	5108 (37.1)	6231 (35.5)	
	≥ 60	8112 (41.5)	5544 (40.2)	7433 (42.4)	
Sex, n (%)	Male	12658 (64.8)	9232 (67.0)	11981 (68.3)	**< .001**
	Female	6874 (35.2)	4547 (33.0)	5565 (31.7)	
BMI (kg/m^2), median (IQR)		28.4 (24.5, 32.5)	28.8 (25.3, 33.0)	28.7 (25.1, 32.9)	**< .001**
Ethnicity, n (%)	White	12115 (62.0)	10543 (76.5)	13599 (77.5)	**< .001**
	Black	1629 (8.3)	1411 (10.2)	1398 (8.0)	
	Hispanics	4469 (22.9)	1067 (7.7)	1626 (9.3)	
	Asians	1087 (5.6)	425 (3.1)	690 (3.9)	
	Others	232 (1.2)	333 (2.4)	233 (1.3)	
Diabetes, n (%)		4877 (25.7)	3359 (25.0)	4392 (25.6)	.48
MELD score, median (IQR)		22.0 (14.0, 32.0)	21.0 (13.0, 30.0)	21.0 (13.0, 31.0)	**< .001**
Encephalopathy grade 3-4, n (%)		2253 (11.5)	1582 (11.5)	2110 (12.0)	.23
Moderate ascites, n (%)		6038 (30.9)	3963 (28.8)	5417 (30.9)	**< .001**
Karnofsky score, n (%)	> 30	13374 (69.0)	10151 (74.2)	12329 (71.0)	**< .001**
	10-30	6015 (31.0)	3535 (25.8)	5034 (29.0)	
Recipient on life support, n (%)		2251 (11.5)	724 (5.3)	1104 (6.3)	**< .001**
Recipient on dialysis, n (%)		2657 (13.6)	1176 (8.6)	1600 (9.1)	**< .001**
Diagnosis, n (%)	HCV	4196 (21.9)	3279 (24.3)	3562 (20.6)	
	NASH	2608 (13.6)	1979 (14.6)	2419 (14.0)	
	ALD	4055 (21.2)	2630 (19.5)	3739 (21.7)	
	CLD	1060 (5.4)	895 (6.5)	1241 (7.1)	
	Others	7613 (37.9)	4996 (35.1)	6585 (36.6)	
Transplant center volume, n (%)	High-volume ≥ 62 Tx/year	8654 (44.3)	5786 (42.0)	3892 (22.2)	**< .001**
	Mid-volume 30-62 Tx/year	3753 (19.2)	1678 (12.2)	2219 (12.6)	
	Low-volume < 30 Tx/year	7125 (36.5)	6315 (45.8)	11435 (65.2)	
Season at transplant, n (%)	Warm season	11436 (58.6)	8164 (59.2)	10367 (59.1)	.29
	Cold season	8096 (41.4)	5615 (40.8)	7179 (40.9)	
Era, n (%)	2015-2019	11522 (59.0)	8094 (58.7)	10340 (58.9)	.70
	2010-2014	8010 (41.0)	5685 (41.3)	7206 (41.1)	
Donor characteristics					
Age (y), median (IQR)		43.0 (28.0, 55.0)	41.0 (27.0, 54.0)	43.0 (29.0, 55.0)	**< .001**
Sex, n (%)	Male	11554 (60.8)	8558 (59.0)	10299 (59.3)	**.001**
	Female	7458 (39.2)	5955 (41.0)	7068 (40.7)	
BMI (kg/m^2), median (IQR)		26.8 (23.4, 31.1)	26.9 (23.5, 31.5)	27.1 (23.6, 31.6)	**< .001**
Ethnicity, n (%)	White	9969 (52.4)	10146 (69.9)	12865 (74.1)	**< .001**
	Black	3924 (20.6)	2702 (18.6)	2647 (15.2)	
	Hispanics	3792 (19.9)	1188 (8.2)	1438 (8.3)	
	Asians	703 (3.4)	318 (2.0)	300 (1.6)	
	Others	689 (3.6)	184 (1.3)	141 (0.8)	
History of diabetes, n (%)		2515 (13.3)	1774 (12.3)	2160 (12.5)	**.012**
History of MI, n (%)		729 (3.9)	693 (4.8)	667 (3.9)	**< .001**
History of hypertension, n (%)		7273 (38.5)	5267 (36.5)	6192 (35.9)	**< .001**
History of cocaine use, n (%)		3224 (17.2)	2784 (19.6)	3795 (22.2)	**< .001**
History of heavy alcohol use, n (%)		2861 (15.4)	2226 (15.7)	2969 (17.5)	**< .001**
History of heavy cigarette use, n (%)		3581 (19.2)	3393 (23.8)	4239 (24.9)	**< .001**
Cause of death, n (%)	Trauma	6175 (33.2)	4283 (30.3)	4529 (26.5)	**< .001**
	Anoxia	5438 (29.2)	5281 (37.4)	7202 (42.2)	
	Cerebrovascular	6924 (37.2)	4511 (31.9)	5296 (31.0)	
	Others	84 (0.5)	63 (0.4)	48 (0.3)	
DCD donor, n (%)		1062 (5.6)	1011 (7.0)	1404 (8.1)	**< .001**
Allocation type, n (%)	Local	14163 (69.1)	9939 (63.8)	13752 (72.9)	**< .001**
	Regional	5620 (27.4)	4770 (30.6)	4336 (23.0)	
	National	713 (3.5)	872 (5.6)	778 (4.1)	
Split graft, n (%)	Yes	168 (0.9)	153 (1.1)	308 (1.8)	**< .001**
DRI, median (IQR)		1.54 (1.32, 1.84)	1.52 (1.30, 1.83)	1.54 (1.29, 1.84)	**< .001**
CIT (hours), median (IQR)		5.93 (4.60, 7.45)	5.75 (4.45, 7.23)	5.87 (4.70, 7.18)	**< .001**

ALD, alcoholic liver disease; BMI, body mass index; CIT, cold ischemia time; CLD, cholestatic liver disease; DCD, donation after cardiac death; DRI, donor risk index; HCV, hepatitis C virus; IQR, interquartile range; MELD, Model for End-stage Liver Disease; MI, myocardial infarction; NASH, nonalcoholic steatohepatitis; Tx: Transplant. Bold type indicates statistically significant differences.

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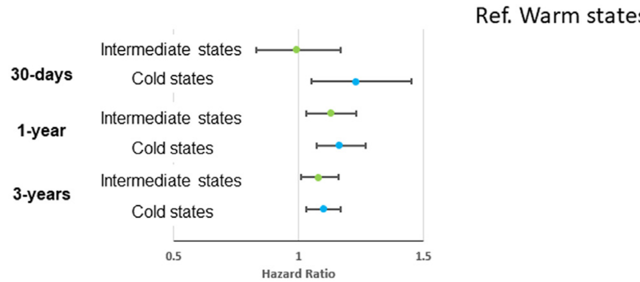

	States	sHR	95% CI Lower	Upper	P values
30-days	Intermediate	0.99	0.83	1.17	0.88
	Cold	1.23	1.05	1.45	**0.010**
1-year	Intermediate	1.13	1.03	1.23	**0.010**
	Cold	1.16	1.07	1.27	**0.009**
3-years	Intermediate	1.08	1.01	1.16	**0.028**
	Cold	1.10	1.03	1.17	**0.007**

Fig 4. Comparison of Cox regression patient survival for cold states (0°F-30°F), intermediate states (30°F-45°F), and warm states (45°F-70°F) for entire cohort.

higher in cold states (7795 (22.3%)) compared to intermediate (4670 (19.4%)) and warm states (7497 (20.6%)). The days on the waitlist (cold states: 107 days; intermediate states: 81 days; and warm states: 75 days; $P < .001$) were significantly higher, and the MELD score at listing (cold states: 16.0; intermediate states: 17.0; and warm states 17.0; $P < .001$) was lower in cold states than in other groups (Table 1). The proportion of patients listed at high-volume transplant centers were the lowest in cold states 6974 (19.4%) compared to intermediate 9699 (39.0%), and warm states 15,876 (42.2%) (Table 1).

Waitlist Outcomes Among the Climate Groups

Patients listed in cold states had significantly higher risk of 90-day and 1-year waitlist mortality than those listed in warm states (90-day: sHR 1.46, 95% CI 1.21-1.77; $P < .001$; and 1-year: sHR 1.41, 95% CI 1.24-1.60; $P < .001$). The risk of 90-day and 1-year waitlist mortality was similar between intermediate and warm states (Fig 3). Listings in cold states were associated with a statistically significantly lower transplant probability than listings in intermediate states at 90 days (reference: warm states, 90 days; intermediate states: sHR 0.94, 95% CI 0.92-0.97; $P < .001$; cold states: sHR 0.81, 95% CI 0.78-0.83; $P < .001$; see Figure 3).

Patient Characteristics at Transplant

A total of 50,857 transplant patients were evaluated. Among them, 19,532 (38.4%) were transplanted in warm states, 13,779 (27.1%) were transplanted in intermediate states and 17,546 (34.5%) were transplanted in cold states (Fig 1). Regarding recipient characteristics, patients who underwent LT in warm states were sicker compared to the remaining states with a higher median MELD score (median (interquartile range): 22.0 (14.0-32.0); $P < .001$), and higher proportions of life support requirement 2251 (11.5%; $P < .001$) (Table 2). Although the donor risk index was similar between cold and warm states (median [(interquartile range): cold 1.54 (1.29-1.84); warm 1.54 (1.32-1.84); $P < .001$), the donors in warm states had more favorable features compared to the remaining states as evident by the lower body mass index (median (interquartile range) 26.8 kg/m^2 (28.0-55.0); $P < .001$), lower proportions of donation after circulatory death donors 1062 (5.6%; $P < .001$), and lower proportions of donors with a history of heavy alcohol use 2861 (17.1%; $P < .001$) and heavy cigarettes use 3581 (19.2%; $P < .001$) (Table 2). The proportion of LT occurring at high-volume transplant centers was significantly higher in the warm states group than in the intermediate and cold states respectively (warm 44.3%, intermediate 42.0%, and cold 22.2%; $P < .001$**.**

Mortality Analysis of Adult LT Recipients According to State Groups

When assessing the risk of mortality according to the state temperature groups, multivariable Cox regression analysis revealed that undergoing LT surgery in cold states was associated with higher risk for mortality at 30-days (sHR 1.23, 95% CI 1.05-1.45; $P = .009$ (reference warm states)), 1-year (sHR 1.16, 95% CI 1.07-1.27; $P = .001$ (reference warm states)) and 3-year (sHR 1.08, 95% CI 1.03-1.17; $P = .007$ (reference warm states)). Moreover, LT recipients in intermediate states had a higher risk of mortality at 1-year (intermediate states: sHR 1.13, 95% CI 1.03-1.23; $P = .01$) and 3-year (intermediate states: sHR 1.08, 95% CI 1.01-1.16; $P = .03$) compared to warm states but lower than that for cold states (reference warm states) (Fig 4 and Supplemental Table 1). In terms of the causes of death, patients in cold states had a higher proportion of deaths due to infections (2.3%) compared to intermediate (2.1%) and warm states (1.7%; $P < .001$). There was no statistically significant difference in the cardiovascular and cerebrovascular causes of death for LT recipients among the temperature regions (Table 3).

Subgroup Analysis of Waitlist and Posttransplant Outcomes in Each Center Volume Group

Transplant centers were categorized into 3 groups based on their transplant volume. Cold states had a lower proportion of high-volume transplant centers. The interaction between center

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Table 3. Causes of Death for Liver Transplant Recipients

	Warm States (45°F-70°F)	Intermediate States (30°F-45°F)	Cold States (0°F-30°F)	*P*
Cardiovascular, n (%)	430 (2.2)	321 (2.3)	443 (2.5)	.45
Cerebrovascular, n (%)	80 (0.4)	65 (0.5)	64 (0.4)	.36
Infection, n (%)	332 (1.7)	294 (2.1)	395 (2.3)	< **.001**
Others, n (%)	1715 (8.8)	1195 (8.7)	1619 (9.2)	< **.001**

volume groups and posttransplant outcomes was examined to address possible concerns about effects of center volume on outcomes. There was no statistically significant interaction between low- or mid-volume transplant centers and cold states for short-term and long-term patient survival (30-day, $P = .34$; 1-year, $P = .57$; and 3-year, $P = .88$). The significant association among the climate groups and waitlist and posttransplant outcomes was independent of the center volume group. To further examine this, the waitlist and posttransplant outcomes were evaluated within each group. Patients listed at low-volume centers in cold states had worse 90-day and 1-year waitlist mortality compared to warm states (90-day: sHR 1.58, 95% CI 1.18-2.01; $P = .002$; and 1-year: sHR 1.60, 95% CI 1.33-1.93; $P < .001$) and lower transplant probability at 90-day and 1-year compared to warm states (90-day: sHR 0.76, 95% CI 0.73-0.80; $P < .001$; and 1-year: sHR 0.74, 95% CI 0.71-0.76; $P < .001$). Patients listed at high-volume centers in cold states had worse 90-day waitlist mortality compared to warm states (90-day: sHR 1.46, 95% CI 1.05-2.03; $P = .023$) and lower transplant probability at 1-year compared to warm states (1-year: sHR 0.94, 95% CI 0.90-0.99; $P = .010$) (Supplemental Figs 1 and 2).

In terms of posttransplant outcomes, patients transplanted at low-volume centers in cold states had a higher risk of mortality at 1 year and 3 years compared to warm states (30-day: sHR 1.32, 95% CI 1.06-1.65; $P = .012$; 1-year: sHR 1.19, 95% CI 1.05-1.35; $P = .008$; and 3-year: sHR 1.18, 95% CI 1.01-1.23; $P = .025$). Patients transplanted at high-volume centers in cold states had similar risk of mortality at 30 days, 1 year, and 3 years (Supplemental Fig 3).

DISCUSSION

Using 10 years of national data, we observed a significantly higher waitlist and posttransplant mortality risk for LT candidates and recipients in cold states. LT patients in cold states were more likely to be less sick at listing with lower MELD scores and were less likely to require life support or dialysis. After adjusting risks for those characteristics, a significantly higher risk of waitlist and posttransplant mortality in cold states remained observed and LT recipients in cold states had a higher proportion of deaths due to infections than warm states, which might have contributed to the findings observed. There are no previous studies looking at the relationship between climate regions and LT waitlist/posttransplant outcomes using a national database.

Several studies have evaluated the effect of weather on the overall health and susceptibility to disease for the general population and patients with end-stage organ disease. A study by Lin et al identified low temperature and high humidity as risk factors for acute on chronic liver failure [27]. The effect of climate on alcohol consumption and alcohol-related liver disease in the United States was explored in a study by Williams et al, who showed a negative correlation between the age-standardized prevalence of heavy drinking, liters of alcohol consumption, and state temperatures [28]. Patients in cold states had a higher proportion of patients with alcohol-related liver disease (22.3%; $P < .001$) compared to intermediate (19.4%) and warm states (20.6%). It has been reported that patients with alcohol-related liver disease had better waitlist and posttransplant outcomes compared to patients with other major liver disease etiologies [25]. Despite this, patients transplanted in cold states had worse posttransplant outcomes compared to warm states. Cold weather leads to an increase in respiratory disease secondary to cross-infection from indoor crowding, the adverse effects of cold on the immune system's resistance to respiratory infection, and the fact that low temperatures improves the survival of bacteria in droplets [29]. The increase in the frequency of acute respiratory infections in the winter predisposes patients to cardiovascular disease because infections increase the risk for arterial thrombosis through endothelial dysfunction and activation of the inflammatory and coagulation system [14,30−33]. This was reinforced by the findings in our study that LT recipients in cold states had a higher proportion of mortality due to infections than other regions (cold states: 2.3%, intermediate states 2.1%, and warm states: 1.7%; $P < .001$). Other possible reasons for the findings of this study would include the increased risk of cardiovascular diseases during cold weather. Cold weather can trigger an excess cardiac sympathetic activity, hypercoagulopathy, and excess inflammatory response that may have contributed to the excess of cardiovascular diseases mortality during winter months. However, the data from our study could not support this finding as there was no statistical difference in the cardiovascular and cerebrovascular causes of death for LT recipients in our cohort. It is unclear the exact mechanisms underlying these meteorologic factors; however, this can be partly attributed to changes in temperature.

The transplant center volume is a well-known risk factor for worse outcomes [34,35]. The effect of low-center volume on waitlist outcomes has been demonstrated in a previous study by Wong et al in which waitlist mortality for patients with acute liver failure was highest at low-volume centers [36]. We noticed a higher proportion of patients being transplanted at low-volume centers in cold states (65.2%; $P < .001$) compared to intermediate states (45.8%) and warm states (36.5%). While the variation in organ acceptance practices based on the transplant center experience at low-volume centers would have been a reason for the worse waitlist and posttransplant outcomes in cold states, the subgroup analysis evaluating only low-volume centers showed that the waitlist mortality remained the highest in

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cold-states compared to warm states at 90 days, and patients transplanted in cold states had higher risk for mortality compared to warm states at 30 days. These highlight the potential effect of cold weather on outcomes in LT patients. Varying clinical practice patterns between sites, socioeconomic status, and patient-level characteristics such as the presence and severity of comorbidities, all of which may have modified the association between climate and outcomes. The effect of the weather may be an important factor to consider as transplant centers undergo regular review process to ensure high-quality care if their outcomes are significantly worse than expected.

Relevant strengths of this study include a large number of LT patients assessed using the national transplant registry over 10 years. There are several limitations to our study that deserve to be acknowledged. The advantage of using a large registry database is at the expense of a lack of granularity in the collected data. The exact causes of death and graft failure cannot be verified or entirely captured during the follow-up period. We could not obtain information about the recipient's cardiovascular disease prior to transplant as this is not recorded by the United Network for Organ Sharing registry. Data linkage of registry data to other databases can allow the collection of additional information, such as the type and nature of cause-specific mortality, which could improve the findings of our study. In addition, validating this association in other population registry cohorts outside of the United States may provide greater confidence in the robustness of the estimates between seasonality and outcomes.

CONCLUSIONS

This study revealed that patients in cold states had worse waitlist and posttransplant outcomes than other climate regions after adjusting risks for the recipient, donor factors and center volume. Our results highlight the need for further studies to understand better the pathologic mechanisms resulting in worse waitlist and posttransplant outcomes in colder states. These findings would have important implications for research and clinical care, including the need for closer monitoring of LT patients in cold areas, especially for risk of infection.

DATA AVAILABILITY

Data will be made available on request.

ACKNOWLEDGMENTS

The United Network for Organ Sharing has supplied the data reported here as the contractor for the Organ Procurement and Transplantation Network. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the Organ Procurement and Transplantation Network or the United States government.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.transproceed.2022.08.018.

REFERENCES

[1] Phillips DP, Christenfeld N, Ryan NM. An increase in the number of deaths in the United States in the first week of the month−an association with substance abuse and other causes of death. N Engl J Med 1999;341:93–8.

[2] Battle YL, Martin BC, Dorfman JH, et al. Seasonality and infectious disease in schizophrenia: the birth hypothesis revisited. J Psychiatr Res 1999;33:501–9.

[3] Peters RW, Brooks MM, Zoble RG, et al. Chronobiology of acute myocardial infarction: cardiac arrhythmia suppression trial (CAST) experience. Am J Cardiol 1996;78:1198–201.

[4] Hauksdottir GS, Love A, Sigurdardottir V, et al. Seasonal variation of mycoplasma infections in Iceland and Israel: different associations with meteorological variables. Eur Respir J 1997;10:2432–3.

[5] Tilles SA, Bardana Jr EJ. Seasonal variation in bronchial hyperreactivity (BHR) in allergic patients. Clin Rev Allergy Immunol 1997;15:169–85.

[6] Loeb M, McGeer A, McArthur M, et al. Surveillance for outbreaks of respiratory tract infections in nursing homes. CMAJ 2000;162:1133–7.

[7] Pell JP, Cobbe SM. Seasonal variations in coronary heart disease. QJM 1999;92:689–96.

[8] Gallerani M, Manfredini R, Ricci L, et al. Chronobiological aspects of acute cerebrovascular diseases. Acta Neurol Scand 1993;87:482–7.

[9] Gallerani M, Manfredini R, Ricci L, et al. Sudden death from pulmonary thromboembolism: chronobiological aspects. Eur Heart J 1992;13:661–5.

[10] Keatinge WR, Coleshaw SR, Cotter F, et al. Increases in platelet and red cell counts, blood viscosity, and arterial pressure during mild surface cooling: factors in mortality from coronary and cerebral thrombosis in winter. Br Med J (Clin Res Ed) 1984;289:1405–8.

[11] Neild PJ, Syndercombe-Court D, Keatinge WR, et al. Cold-induced increases in erythrocyte count, plasma cholesterol and plasma fibrinogen of elderly people without a comparable rise in protein C or factor X. Clin Sci (Lond) 1994;86:43–8.

[12] Collins KJ, Easton JC, Belfield-Smith H, et al. Effects of age on body temperature and blood pressure in cold environments. Clin Sci (Lond) 1985;69:465–70.

[13] Woodhouse PR, Khaw KT, Plummer M. Seasonal variation of blood pressure and its relationship to ambient temperature in an elderly population. J Hypertens 1993;11:1267–74.

[14] Mudge Jr. GH, Grossman W, Mills Jr. RM, et al. Reflex increase in coronary vascular resistance in patients with ischemic heart disease. N Engl J Med 1976;295:1333–7.

[15] Mackenbach JP, Looman CW, Kunst AE. Air pollution, lagged effects of temperature, and mortality: The Netherlands 1979-87. J Epidemiol Community Health 1993;47:121–6.

[16] Katsouyanni K, Zmirou D, Spix C, et al. Short-term effects of air pollution on health: a European approach using epidemiological time-series data. The APHEA project: background, objectives, design. Eur Respir J 1995;8:1030–8.

[17] Farb A, Tang AL, Burke AP, et al. Sudden coronary death. Frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. Circulation 1995;92:1701–9.

[18] Broers NJ, Usvyat LA, Marcelli D, et al. Season affects body composition and estimation of fluid overload in haemodialysis patients: variations in body composition; a survey from the European MONDO database. Nephrol Dial Transplant 2015;30:676–81.

[19] Guinsburg AM, Usvyat LA, Etter M, et al. Seasonal variations in mortality and clinical indicators in international hemodialysis populations from the MONDO registry. BMC Nephrol 2015;16:139.

[20] Usvyat LA, Carter M, Thijssen S, et al. Seasonal variations in mortality, clinical, and laboratory parameters in hemodialysis patients: a 5-year cohort study. Clin J Am Soc Nephrol 2012;7:108–15.

[21] Astor BC, Melamed ML, Mandelbrot DA, et al. Seasonality of mortality and graft failure among kidney transplant recipients in the US - a retrospective study. Transpl Int 2018;31:293–301.

[22] Singh N, Wagener MM, Gayowski T. Seasonal pattern of early mortality and infectious complications in liver transplant recipients. Liver Transpl 2001;7:884–9.

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[23] Current Results. Winter temperature averages for every state. https://www.currentresults.com/Weather/US/average-state-temperatures-in-winter.php; 2021 [accessed 13.08.21].

[24] Flemming JA, Kim WR, Brosgart CL, et al. Reduction in liver transplant wait-listing in the era of direct-acting antiviral therapy. Hepatology 2017;65:804–12.

[25] Nagai S, Collins K, Chau LC, et al. Increased risk of death in first year after liver transplantation among patients with nonalcoholic steatohepatitis vs liver disease of other etiologies. Clin Gastroenterol Hepatol 2019;17:2759–68 e5.

[26] Feng S, Goodrich NP, Bragg-Gresham JL, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am J Transplant 2006;6:783–90.

[27] Lin S, Han L, Li D, Wang T, Wu Z, Zhang H, et al. The association betweenmeteorological factors and the prevalence of acute-on chronic liver failure: Apopulation-based study, 2007−2016. J Clin Transl Hepatol 2019;7:341–5.

[28] Williams R, Alexander G, Armstrong I, et al. Disease burden and costs from excess alcohol consumption, obesity, and viral hepatitis: fourth report of the Lancet Standing Commission on Liver Disease in the UK. Lancet 2018;391:1097–107.

[29] Handley BA, Webster AJ. Some factors affecting the airborne survival of bacteria outdoors. J Appl Bacteriol 1995;79:368–78.

[30] Marshall RJ, Scragg R, Bourke P. An analysis of the seasonal variation of coronary heart disease and respiratory disease mortality in New Zealand. Int J Epidemiol 1988;17:325–31.

[31] Chin MH, Goldman L. Factors contributing to the hospitalization of patients with congestive heart failure. Am J Public Health 1997;87:643–8.

[32] Nguyen JL, Yang W, Ito K, et al. Seasonal influenza infections and cardiovascular disease mortality. JAMA Cardiol 2016;1:274–81.

[33] Stewart S, McIntyre K, Capewell S, et al. Heart failure in a cold climate. Seasonal variation in heart failure-related morbidity and mortality. J Am Coll Cardiol 2002;39:760–6.

[34] Axelrod DA, Guidinger MK, McCullough KP, et al. Association of center volume with outcome after liver and kidney transplantation. Am J Transplant 2004;4:920–7.

[35] Ozhathil DK, Li YF, Smith JK, et al. Impact of center volume on outcomes of increased-risk liver transplants. Liver Transplant 2011;17:1191–9.

[36] Wong NZ, Schaubel DE, Reddy KR, et al. Transplant center experience influences spontaneous survival and waitlist mortality in acute liver failure: an analysis of the UNOS database. Am J Transplant 2021;21:1092–9.

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