Comorbid immunosuppression in Merkel cell carcinoma: A retrospective database study

To the Editor: Merkel cell carcinoma (MCC) is an aggressive neuroendocrine carcinoma associated with immunosuppression.[1] A better understanding of the outcomes of patients with comorbid immunosuppression is needed in light of excellent responses to immunotherapy, which generally requires immune competence.[2]

We performed an institutional review board-exempt cohort study using the National Cancer Database (NCDB) from 2004 to 2015. All *P* values were 2-sided, and we used survival analysis censored at 50 months of follow-up. We identified 3691 MCC patients with complete staging, immunologic, survival, and demographic data, of whom 423 (11%) were known to be immunosuppressed. Of these, 14 patients had a diagnosis of HIV/AIDS, 120 had a diagnosis of chronic lymphocytic leukemia, 114 were solid organ transplant recipients (SOTRs), 77 had non-Hodgkin's lymphoma, ≤ 10 had a combination of immunosuppressive diagnoses, and 94 had another or unspecified cause for immunosuppression. Immunosuppressed patients were more likely to present with node-positive disease (44% vs 34%; $P < .001$) and more advanced T stage (T2-4 in 41% vs 34%; $P = .018$) but not metastatic disease (6% vs 5%; $P = .83$) (Table I).

Table I. Patient characteristics

Clinical/demographic characteristic		Not immune suppressed*	Immunosuppressed*	*P* value†
Number of patients		3268 (88.5)	423 (11.5)	
Age, y	Median [IQR]	76.00 [67.00, 83.00]	72.00 [66.00, 79.00]	**<.001**
Female sex		1180 (36.1)	117 (27.7)	**.001**
Race	Asian	21 (0.6)	2 (0.5)	.119
	Black	29 (0.9)	9 (2.1)	
	Other	21 (0.6)	3 (0.7)	
	White	3197 (97.8)	409 (96.7)	
Regional income quartile	1	340 (10.4)	57 (13.5)	.1
	2	656 (20.1)	71 (16.8)	
	3	844 (25.8)	118 (27.9)	
	4	1428 (43.7)	177 (41.8)	
Regional high school Graduation quartile	1	374 (11.4)	60 (14.2)	.311
	2	733 (22.4)	95 (22.5)	
	3	995 (30.4)	131 (31.0)	
	4	1166 (35.7)	137 (32.4)	
Rural		62 (1.9)	11 (2.6)	.428
Charlson Comorbidity Index	0	2323 (71.1)	279 (66.0)	**.033**
	1	684 (20.9)	99 (23.4)	
	2	182 (5.6)	26 (6.1)	
	3	79 (2.4)	19 (4.5)	
T stage	0	187 (5.7)	18 (4.3)	**.018**
	1	1961 (60.0)	232 (54.8)	
	2	827 (25.3)	121 (28.6)	
	3	168 (5.1)	24 (5.7)	
	4	125 (3.8)	28 (6.6)	
N Stage	0	2171 (66.4)	238 (56.3)	**<.001**
	1	1001 (30.6)	160 (37.8)	
	2	96 (2.9)	25 (5.9)	
M Stage	1	173 (5.3)	24 (5.7)	.832

IQR, Interquartile range.
*Data are presented as number (%).
†Bold *P* values are statistically significant.

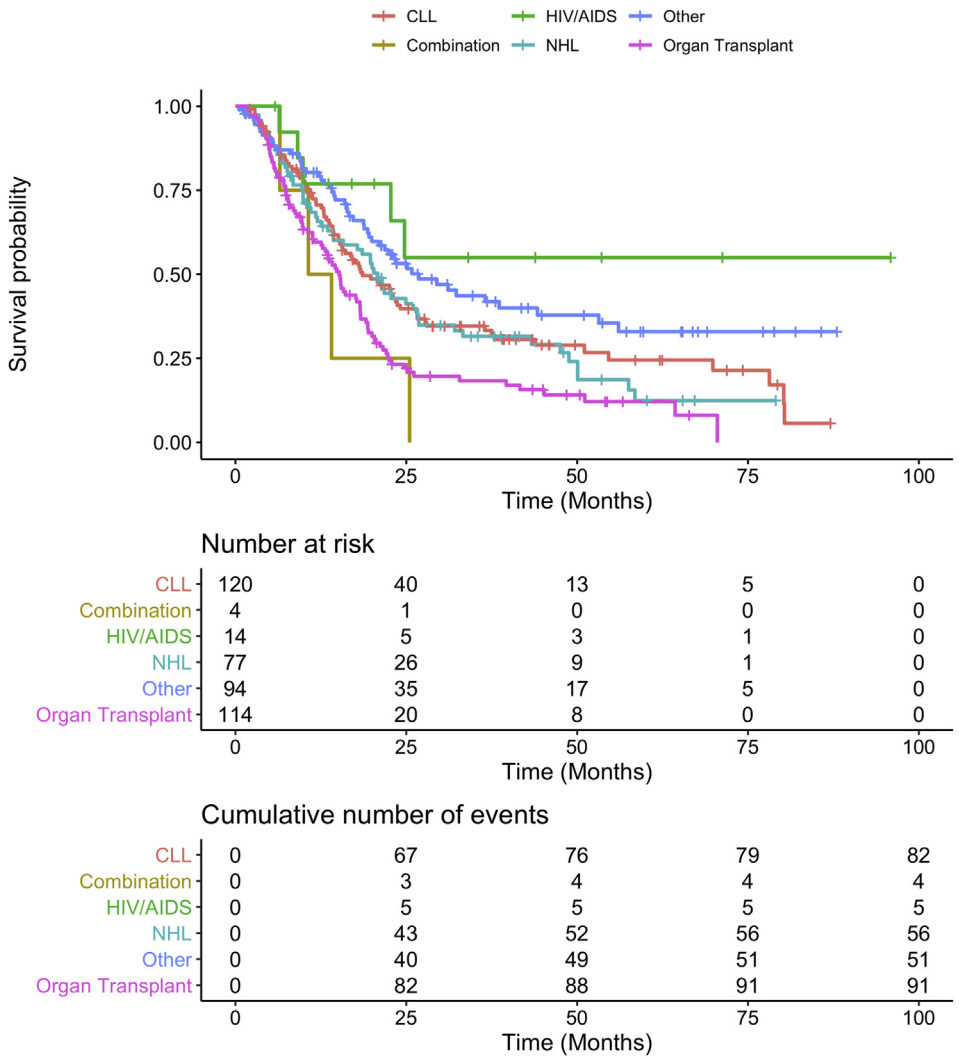

Fig 1. Survival by types of immune suppression.

The vast majority of patients diagnosed with MCC underwent local therapy with some form of surgical intervention (91% of nonimmunosuppressed patients and 92% of immunosuppressed patients; $P = .75$). Patients with immunosuppression were more likely to receive external beam radiation therapy than immune competent patients (60% vs 55%, respectively; $P = .012$), but there was no significant difference in the use of systemic therapy or immunotherapy ($P = .214$, $P = .878$, respectively).

Overall, immunosuppression was associated with significantly reduced overall survival (univariable hazard ratio [HR], 2.34 [2.06-2.65]; $P < .001$; multivariable HR, 2.37 [2.17-2.81]; $P < .001$ with adjustments for stage, age, sex, comorbidity, and socioeconomic factors). Compared to chronic lymphocytic leukemia, immunosuppression related to being a SOTR was associated with significantly worse outcomes (HR, 1.57 [1.17-2.13]; $P = .003$), and HIV/AIDS trended toward better outcomes (HR, 0.42 [0.17-1.04]; $P = .062$) (Fig 1).

Our findings provide additional detail on prior work, suggesting inferior oncologic outcomes for patients with immunosuppression, with the largest differences seen with SOTRs.[1,3,4] SOTRs, generally require long-term immunosuppressive therapy and are commonly excluded from therapeutic advances as the field naturally moves toward immunotherapy, such as in the ongoing phase III STAMP study of adjuvant pembrolizumab (NCT03712605).[2] This problem is expected to grow, as the number of patients with solid organ transplants is rising.[5]

There are several limitations to using a hospital-based cancer registry, including errors in coding, bias in missing data, lack of complete clinical data (including details on other or combined causes of immunosuppression), selection bias, and residual confounding. Additionally, the lack of laboratory

values limits our ability to quantify the degree of immunosuppression in conditions like HIV (eg, viral load, CD4 count). Finally, the Charlson Comorbidity Index includes several conditions related to immunosuppression, which significantly limits correction for medical comorbidity between immunosuppressed and competent immune patients.

Overall, our findings highlight the gap in outcomes among patients with MCC and comorbid immunosuppression. Therapeutic advances are needed for these patients as the treatment landscape shifts toward immunotherapy.

The data used in the study are derived from a deidentified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Paul Riviere, MD,[a,b] Danielle Brazel, MD,[c] Khodayar Goshtasbi, MD,[d] Edward C. Kuan, MD,[d] Ling Gao, MD PhD,[e,f,g] and Jeremy Harris, MD, MPhil[a]

From the Department of Radiation Oncology, University of California Irvine, Orange, California,[a] the Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, California,[b] the Department of Internal Medicine, University of California Irvine, Orange, California,[c] the Department of Otolaryngology-Head and Neck Surgery, University of California Irvine, Orange, California,[d] the Department of Dermatology, University of California Irvine, Orange, California,[e] Veterans Affairs Long Beach Healthcare System, Long Beach, California[f] and Southern California Institute for Research and Education, Long Beach, California.[g]

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Correspondence to: Jeremy Harris, MD, MPhil, Department of Radiation Oncology, University of California, Irvine School of Medicine, Orange, CA

E-mail: jeremy.harris@uci.edu

Conflicts of interest

Dr Riviere discloses consulting fees from Peptide Logic, LLC. Dr Gao was a consultant for EMD Serono (2015) and received research support from Gilead (2015-2017). Drs Brazel, Goshtasbi, Kuan, and Harris have no conflicts of interest to declare.

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