Original Article

A Multi-Institutional Comparison of Outcomes of Immunosuppressed and Immunocompetent Patients Treated With Surgery and Radiation Therapy for Cutaneous Squamous Cell Carcinoma of the Head and Neck

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BACKGROUND: Patients who are chronically immunosuppressed have higher rates of cutaneous squamous cell carcinoma of the head and neck (cSCC-HN). This is the largest multi-institutional study to date investigating the effect of immune status on disease outcomes in patients with cSCC-HN who underwent surgery and received postoperative radiation therapy (RT). **METHODS:** Patients from 3 institutions who underwent surgery and also received postoperative RT for primary or recurrent, stage I through IV cSCC-HN between 1995 and 2015 were included in this institutional review board-approved study. Patients categorized as immunosuppressed had chronic hematologic malignancy, human immunodeficiency/acquired immunodeficiency syndrome, or had received immunosuppressive therapy for organ transplantation $\geq$6 months before diagnosis. Overall survival, locoregional recurrence-free survival, and progression-free survival were calculated using the Kaplan-Meier method. Univariate and multivariate analyses were performed using Cox proportional-hazards regression. **RESULTS:** Of 205 patients, 138 (67.3%) were immunocompetent, and 67 (32.7%) were immunosuppressed. Locoregional recurrence-free survival (47.3% vs 86.1%; $P < .0001$) and progression-free survival (38.7% vs 71.6%; $P = .002$) were significantly lower in immunosuppressed patients at 2 years. The 2-year OS rate in immunosuppressed patients demonstrated a similar trend (60.9% vs 78.1%; $P = .135$) but did not meet significance. On multivariate analysis, immunosuppressed status (hazard ratio [HR], 3.79; $P < .0001$), recurrent disease (HR, 2.67; $P = .001$), poor differentiation (HR, 2.08; $P = .006$), and perineural invasion (HR, 2.05; $P = .009$) were significantly associated with locoregional recurrence. **CONCLUSIONS:** Immunosuppressed patients with cSCC-HN had dramatically lower outcomes compared with immunocompetent patients, despite receiving bimodality therapy. Immune status is a strong prognostic factor that should be accounted for in prognostic systems, treatment algorithms, and clinical trial design. ***Cancer*** **2017;123:2054-60**. © *2017 American Cancer Society.*

KEYWORDS: cutaneous squamous cell carcinoma, head and neck, immunosuppression, poor outcomes, postoperative radiation therapy.

INTRODUCTION

Approximately 700,000 individuals are diagnosed with cutaneous squamous cell carcinoma (cSCC) in the United States annually. The overwhelming majority have excellent outcomes with single-modality surgical clearance. However, there is a small, known subset of patients who demonstrate more aggressive behavior, including locoregional recurrence and even skin cancer-related death.[1,2] Their numbers are poorly understood because of their rarity and because skin cancer statistics are not collected by population-based registries in the United States. Consequently, these bad actors are frequently not recognized until they present with multiply recurrent or more advanced disease. Conversely, immunosuppressed patients are a demographic in which skin cancer incidence and morbidity is known to be more common. It has been demonstrated that patients with chronic lymphoid malignancies have an 8-fold to 13-fold increase in the incidence of cSCC compared with the immunocompetent (IC) population, whereas organ transplant recipients (OTRs) receiving chronic immunosuppressive therapies have up to a 65-fold to 100-fold increase in the incidence of cSCC, with up to 50% of Caucasian OTRs developing a cutaneous neoplasm in their post-transplantation lifetime.[3-10] Although the overwhelming majority of these

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cancers are also easily cured with surgery alone, there is a growing body of data to suggest that high-risk pathologic features, more aggressive phenotypes, and poorer outcomes are observed at higher rates in the immunosuppressed (IS) population.[6,11,12] Whereas locoregional recurrence (LRR) and distant metastasis are rare in the IC population, LRR rates ranging between 13% and 48% and distant metastatic rates ranging between 7% and 19% have been described in the IS population, especially after surgery monotherapy.[9,13,14]

The majority of aggressive cSCCs that recur after standard surgical management are located in the head and neck region. Therefore, postoperative radiation therapy has been long used to treat patients with locally advanced disease (eg, T3/T4, lymph node-positive, perineural invasion) as a means of maximizing locoregional control and has demonstrated relatively high control rates in several retrospective series.[15-18] However, whether IS status is associated with inferior outcomes in patients with cSCC of the head and neck (cSCC-HN) who undergo surgery and receive postoperative radiotherapy (RT) has not been well studied and remains unknown. We recently performed a single-institution study comparing the outcomes of IS patients (primarily OTRs who were receiving iatrogenic immunosuppressive therapy) with IC patients and demonstrated inferior 2-year disease-free survival (45% vs 62%) and overall survival (36% vs 67%) in IS patients compared with IC patients, respectively.[19] The current study is an effort to validate these preliminary findings in a larger cohort from 3 institutions and to further elucidate the association between immune status and disease-related outcomes.

MATERIALS AND METHODS

Patients with cSCC-HN who underwent surgical resection and also received postoperative RT between 1995 and 2015 from The Cleveland Clinic, Washington University St. Louis, and University of California San Francisco were identified in each institution's respective institutional review board-approved registries. Patients were aged $\geq$18 years and had histologically confirmed cSCC-HN. Patients who had metastatic disease, had SCC in situ only, had received palliative doses of RT, or had inadequate medical records (lack of a tumor pathology record or a record of follow-up after completion of RT) were excluded. Patients with primary or recurrent, stage I through IV disease were included. All patients were restaged according to the American Joint Committee on Cancer (AJCC) seventh edition staging manual. All patients underwent surgical resection by wide local excision or Mohs micrographic surgery. The type of surgical resection was at the discretion of the treating surgeon.

Patients were categorized as IS if they were diagnosed with chronic hematologic malignancy, human immunodeficiency virus/acquired immunodeficiency syndrome, or had received immunosuppressive therapy for organ transplantation $\geq$6 months before diagnosis. Immunosuppressive agents included prednisone, cyclosporine, azathioprine, sirolimus, tacrolimus, and mycophenolate mofetil. OTRs included those receiving kidney, heart, lung, liver, pancreas, or bone marrow transplantation.

Postoperative RT was typically delivered with conventional electron-beam RT and 3-dimensional, conformal RT during the earlier years of the study, whereas intensity-modulated RT was used in more recent years of the study. Doses from 54 to 70 Gray (Gy) were typically used. RT targets typically included the tumor bed with generous clinical target volume margins. For patients who had multifocal perineural invasion (PNI), nerve roots were targeted to their origin at the skull base. For patients who had lymph node-positive disease, ipsilateral lymphatics also were included. Some patients received 2 or 3 cycles of concurrent cisplatin chemotherapy along with RT, most often in the setting of positive margins or extracapsular extension (ECE).

All patients were followed with postoperative treatment imaging using either computed tomography or positron emission tomography 3 months after RT. Patients were then continually followed in a multidisciplinary fashion. LRR was defined as recurrence at the primary site or margin of resection or in regional lymph nodes. Baseline characteristics were compared using the chi-square test for categorical variables, and the Student unpaired *t* test was used to compare continuous variables. Overall survival (OS), LRR-free survival, disease-free survival, and progression-free survival (PFS) were calculated using the Kaplan-Meier method. PFS was defined as freedom from any local, regional, or distant recurrence or death. Univariate and multivariate analyses were performed using Cox proportional hazards regression to identify variables associated with LRR. A P value $\leq .5$ was considered statistically significant. SAS software was used for statistical analysis.

RESULTS

In total, 205 patients (138 IC, 67 IS) were included in the study. The median age of the cohort was 70 years (range, 32-92 years), and the median Karnofsky performance status was 80 (range, 50-100). The median follow-up was 23.1 months (range, 2.8-156 months). Recurrent tumors

TABLE 1. Patient, Tumor, and Treatment Characteristics

Variable	No. of Patients (%)		P
	Immunocompetent, N = 138	Immunosuppressed, N = 67	
Age: Median [range], y	72 [31-92]	64 [39-88]	.003[a]
No. of men	116	64	—
Median KPS score	90	80	.076
Tumor type			.788
Primary	57 (41)	29 (43)	
Recurrent	81 (59)	38 (57)	
TNM stage			.045[a]
I	6 (4)	2 (3)	
II	47 (34)	34 (51)	
III	28 (20)	5 (7)	
IV	57 (41)	26 (39)	
Pathologic tumor classification[b]			.018[a,c]
pTx	23 (17)	5 (7)	
pT1/pT2	75 (54)	50 (51)	
pT3/pT4	40 (29)	12 (18)	
Pathologic lymph node status			.194[d]
pN0	85 (62)	45 (67)	
pN1-pN2a	23 (17)	5 (8)	
pN2b-pN3	30 (21)	17 (25)	
Mohs surgery	32 (23)	15 (22)	.960
Concurrent chemotherapy	18 (14)	10 (15)	.713

Abbreviation: KPS, Karnofsky performance status.
[a] This *P* value indicates a statistically significant difference.
[b] For recurrent tumors, T-classification indicates the status of the recurrence immediately before surgery and radiation
[c] This *P* value is for the comparison between T1/T2 versus T3/T4 versus Tx.
[d] This *P* value is for the comparison between N0 versus N1-N2a versus N2b-N3.

TABLE 2. Characteristics of Immunosuppression, N = 67

Characteristic	No. of Patients
Organ transplantation recipient	41
Heart	1
Lung	6
Kidney	24
Liver	4
Other[a]	6
Single agent immunosuppression	8
Multiple agent immunosuppression	32
Hematologic malignancy	20
CLL	15
Non-Hodgkin lymphoma	5
HIV	6

Abbreviations: CLL, chronic lymphocytic leukemia; HIV, human immunodeficiency virus.
[a] Other indicates pancreas or bone marrow transplantation.

(58%), lymph node-negative (N0) disease (73%), and stage IV (nonmetastatic) disease (40%) were the most common presentations in the cohort. Baseline demographics are provided in Table 1. The median age of patients in the IS cohort was significantly younger ($P = .003$). Of the 67 patients who were characterized as IS, 41 were OTRs, 20 had a diagnosis of a hematologic malignancy, and 6 had a diagnosis of human immunodeficiency (Table 2). Of the OTRs, 78% received multiple-agent immunosuppression, and 22% received single-agent immunosuppression.

Treatment characteristics are outlined in Table 1. All patients completed RT (median dose, 60.5 grays). Postoperative RT and chemotherapy were received concurrently by 28 patients (14%), and there was no significant difference between the 2 groups regarding the receipt of chemotherapy. Of those patients who received chemotherapy, 15 patients (54%) received cetuximab, and 13 (46%) received cisplatin. Histopathologic features after surgical resection are listed in Table 3. IS patients presented more frequently with poorly differentiated tumors (37% vs 22%; $P = .010$). Those in the IS group also had higher rates of nodal ECE (77% vs 64%; $P = .664$) and PNI (54% vs 46%; $P = .323$), although he difference was not statistically significant.

Outcomes are outlined in Table 4, with locoregional failure as the predominant pattern of failure. Seventy-two patients (35%) experienced disease recurrence, including 24% with local recurrence, 11% with regional recurrence, and 15% with distant failure. LRR was significantly higher in the IS population compared with the IC population (54% vs 17%; $P < .0001$). The distant metastatic rate also was significantly higher in the IS population

TABLE 3. Histopathologic Findings After Primary Surgery

Variable	No. of Patients (%)		P
	Immunocompetent, N = 138	Immunosuppressed, N = 67	
Lymph node ECE, n = 75[a]	34 (45)	17 (38)	.664
Tumor differentiation			.010[b]
Well/moderate	88 (64)	30 (45)	
Poor	30 (22)	25 (37)	
Unknown	20 (14)	12 (18)	
PNI	64 (46)	36 (54)	.323
PNI named nerve	24 (17)	9 (13)	.470
Margin status			.812
Negative	85 (62)	43 (64)	
Involved	49 (36)	23 (34)	

Abbreviations: ECE, extracapsular extension; PNI, perineural invasion.
[a] ECE was evaluated only in patients who had lymph node-positive disease.
[b] This *P* value indicates a statistically significant difference.

TABLE 4. Patterns of Failure for All Patients Stratified by Immune Status

Pattern of Failure	No. of Patients (%)		P
	Immunocompetent, n = 138	Immunosuppressed, n = 67	
Local recurrence	20 (15)	30 (45)	< .0001
Regional recurrence	10 (7)	13 (19)	.007
Locoregional recurrence	24 (17)	36 (54)	< .0001
Distant failure	14 (10)	17 (25)	.005

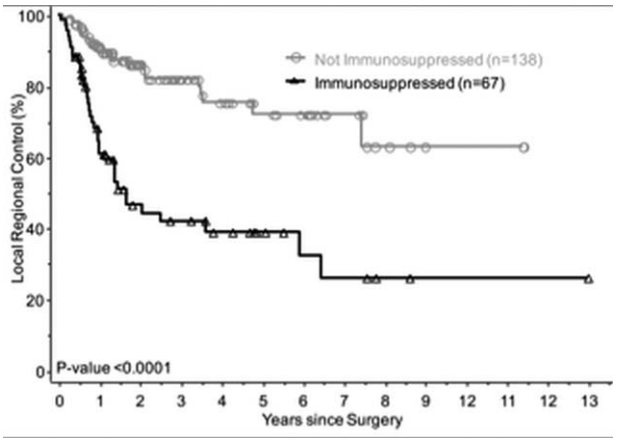

Figure 1. Locoregional recurrence-free survival is illustrated according to immune status (n = 205).

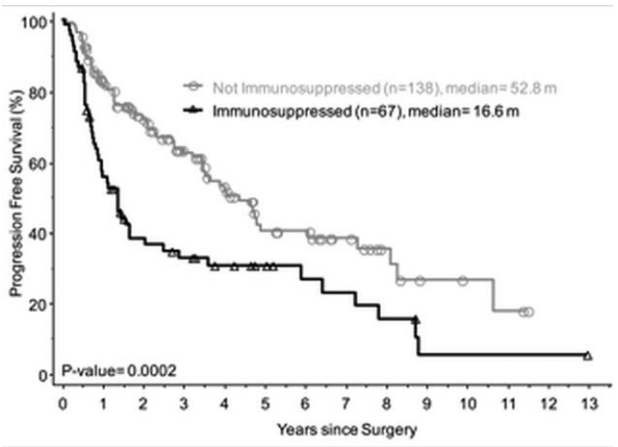

Figure 2. Progression-free survival is illustrated according to immune status (n = 205).

compared with the IC population (25% vs 10%; $P = .005$). The 2-year LRR-free survival rate (47% vs 86%; $P < .0001$) and the 2-year PFS rate (38.7% vs 71.6%; $P = .002$) were lower for IS patients (Figs. 1 and 2). The 2-year OS rate (61% vs 78%) demonstrated a similar trend, although OS was not significantly different ($P = .135$) between the 2 groups (Fig. 3).

Univariate analysis demonstrated that IS status (hazard ratio [HR], 3.80; $P < .0001$), recurrent tumor (HR, 1.90; $P = .025$), poorly differentiated tumor (HR, 2.30; $P = .002$), and PNI (HR, 1.78; $P = .030$) were the only variables significantly associated with higher rates of LRR. Multivariate analysis demonstrated that IS status (HR,

3.79; $P < .0001$), recurrent tumor (HR, 2.67; $P = .001$), poorly differentiated tumor (HR, 2.08; $P = .006$), and PNI (HR, 2.05; $P = .009$) were significantly associated with increased LRR (Table 5). Tumor (T)-classification, group stage, etiology of immunosuppression, degree of immunosuppression, margin status, and nodal ECE were not significantly associated with increased LRR. In a subsequent analysis of the 86 patients who had de novo disease, excluding those with recurrent cancer, only immune status was significantly associated with LRR (HR, 5.0; $P = .0025$).

DISCUSSION

It is well known that chronically IS patients have a higher rate of developing cutaneous malignancies, which are often associated with more aggressive histologic features.

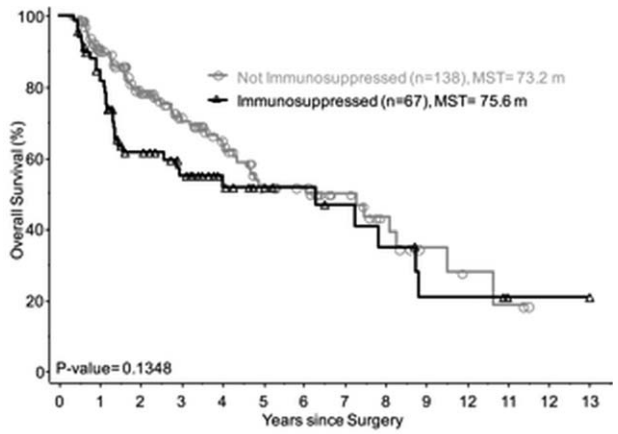

Figure 3. Overall survival is illustrated according to immune status (n = 205). MST indicates median survival time.

We previously published the first-single institution comparison of patients treated with surgery and postoperative RT for high-risk cSCC-HN, which demonstrated significantly higher rates of LRR (48% vs 24%; $P = .01$) and inferior disease-free survival at 2 years (45% vs 62%; $P = .04$) in IS patients compared with IC patients. The current study confirms those preliminary findings in a large, multi-institutional cohort and is the largest comparative study to date to demonstrate inferior outcomes for IS patients with cSCC-HN, despite similar, aggressive, multimodality therapy. There are several important implications to this observation.

First, the patterns of failure in the IS population have significant implications for treatment intensification and future clinical trial design. The observation that more than one-half of patients recurred locoregionally despite receiving RT underscores the importance of trying to identify these patients at earlier stages of disease, when adjuvant therapy may be more effective, as well as the need for intensification strategies when disease presents at a more advanced stage. The companion finding that IS patients have a 25% distant metastatic failure rate is also quite surprising and points toward the addition of systemic therapy as the ideal method of intensification that requires study. The Trans-Tasman Radiation Oncology Group recently completed the 0501 POST randomized trial (clinicaltrials.gov identifier NCT00193895) investigating the addition of weekly carboplatin to postoperative RT compared with RT alone in patients with cSCC in an effort to intensify treatment for high-risk patients, the results of which should be available in early 2017.[20] Notably, immunosuppressed patients were excluded from that trial. Epidermal growth factor receptor inhibitors have

TABLE 5. Univariate and Multivariate Analyses for Locoregional Recurrence

	Univariate Analysis		Multivariate Analysis	
Prognostic Factor	HR (95% CI)	*P*	HR (95% CI)	*P*
Immunosuppression status: IS vs IC	3.802 (2.27-6.37)	< .0001[a]	3.788 (2.24-6.41)	< .0001[a]
Recurrent vs primary tumor	1.898 (1.08-3.33)	.025[a]	2.667 (1.49-4.79)	.001[a]
Cell differentiation: Poor vs well/moderate	2.304 (1.37-3.86)	.002[a]	2.079 (1.23-3.52)	.006[a]
PNI: Yes vs no	1.178 (1.06-2.99)	.030[a]	2.049 (1.20-3.50)	.009[a]
TNM stage: IV vs I-III	1.123 (0.67-1.88)	.658		
Type of immunosuppression: Heme Malig/HIV vs OTR	1.422 (0.73-2.79)	.306		
Tumor classification: T3/T4 vs T1/T2	1.577 (0.95-2.72)	.101		
Immunosuppressive agents: Single agent vs multiagent	2.331 (0.87-6.25)	.092		
Margin status: Close/positive vs negative	1.276 (0.76-2.13)	.354		
Neck lymph node ECE: Yes vs no, n = 75[a]	2.268 (0.65-7.94)	.200		

Abbreviations: CI, confidence interval; ECE, extracapsular extension HIV, human immunodeficiency virus; HR, hazard ratio; IC, immunocompetent; IS, immunosuppressed; Heme Malig, hematologic malignancy; OTR, organ transplantation recipient; PNI, perineural invasion.
[a] This *P* value indicates a statistically significant difference.
[b] ECE was evaluated only in patients who had lymph node-positive disease.

demonstrated activity in cSCC in both definitive and recurrent/metastatic settings and is an attractive potential target for high-risk patients.[21,22] The NRG Oncology group is currently designing a randomized study comparing RT alone versus RT plus epidermal growth factor receptor inhibition in patients with high-risk cutaneous skin cancer and is planning to stratify patients based on their immune status. Finally, a new class of immunotherapy drugs, including antagonists of the programmed death receptor 1 (PD-1), programmed death receptor ligand 1 (PDL-1), and cutaneous T-cell lymphoma antigen 4 (CTLA-4) targets, have all proven highly effective in melanoma; and the former has recently demonstrated a survival advantage and obtained US Food and Drug Administration approval in second-line treatment for recurrent/metastatic, mucosal, squamous carcinoma of the head and neck.[23-25] Early case reports have also demonstrated significant activity in metastatic cSCC.[26,27] All of these agents are attractive candidates for study in this space. Data regarding the efficacy of immunotherapy in the IS population are limited. A recent study indicated that PD-1 inhibitors produced an impressive response in a renal transplantation recipient who had metastatic cSCC; however, an acute rejection of her graft was also precipitated. Conversely, several case series have demonstrated that CTLA-4 inhibitors are safe in IS transplantation recipients who have cutaneous malignancies and may be a safer strategy for checkpoint inhibition in these patients. Additional studies are needed to clarify the safety and efficacy of immune-oncologic approaches in this patient population.

This study may also help refine prognostication systems in this disease. Our findings are consistent with other studies reporting that immunosuppression is independently associated with inferior outcomes.[28,29] Both the AJCC seventh edition staging system and the more powerfully prognostic Brigham and Women's Hospital staging systems fail to include IS status as a risk factor.[30] Although poorly differentiated histology and recurrent disease are factors that upstage patients with smaller tumors to T2 status in the AJCC system, immune status is not currently included. Also, although T-classification is the primary driver in the current AJCC system, it was not significantly associated with outcome in this study. Perhaps including IS status as an important host-related, high-risk factor in these systems may enhance their prognostic capability.

Finally, the inferior outcomes in IS patients highlight the need for increased multidisciplinary management of these patients and enhanced preventive measures to reduce their risk of developing these high-risk cancers. Dermatologists, Mohs surgeons, head and neck surgeons, radiation and medical oncologists, transplantation physicians, and pathologists all have a significant role to play in helping to optimize outcomes in this high-risk subpopulation of patients with cSCC-HN.[31] Proactive steps can also be taken to prevent these cancers, including more frequent visits with dermatologists who have expertise in this area, aggressive treatment of actinic keratosis and other premalignant lesions, oral retinoic acid therapy, and optimizing transplantation regimens to include the lowest doses and the least mitogenic immunosuppressive agents.[32] Educational efforts aimed at increasing the awareness of community dermatologists and oncologists about this population of high-risk patients would be of great service as well.

Limitations to our study are characteristic of a retrospective analysis. Our cohort consists of high-risk patients with cSCC-HN who were treated with multimodality therapy, which includes referral bias for those recommended for adjuvant RT. This may limit the generalizability of our findings, especially to patients who undergo surgery alone. Although institutional variation is inherent in this data set, indications and techniques of adjuvant RT were fairly consistent at all participating centers. This data set was also limited to patients with cSCC-HN and may not apply to those with SCC deriving from nonhead and neck primary sites. These limitations notwithstanding, this is a large, multi-institutional data set to confirm higher than expected rates of both locoregional failure and distant metastases in IS patients who received bimodality therapy and has important implications for patient counseling, clinical decision making, and clinical trial design.

Conclusion

IS status is strongly associated with inferior locoregional control and progression-free survival in patients with high-risk cSCC-HN who undergo surgery and receive postoperative RT. This finding underscores the need for improved prognostic systems, increased multidisciplinary management, and clinical trials investigating methods of intensified therapies for these patients.

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AUTHOR CONTRIBUTIONS

Bindu V. Manyam; Conceptualization, methodology, investigation, data curation, writing–original draft, writing–review and editing, and visualization. **Adam A. Garsa:** Investigation, data curation, and writing–review and editing. **Re-I Chin:** Investigation, data curation, writing–original draft, and writing–review and editing. **Chandana A. Reddy:** Formal analysis, resources, writing–review and editing, and visualization. **Brian Gastman:** Writing–review and editing. **Wade Thorstad:** Conceptualization, writing–review and editing, and supervision. **Sue S. Yom:** Conceptualization, writing–original draft, writing–review and editing, and supervision. **Brian Nussenbaum:** Writing–review and editing. **Steven J. Wang:** Writing–review and editing. **Allison T. Vidimos:** Writing–review and editing. **Shlomo A. Koyfman:** Conceptualization, methodology, validation, resources, writing–original draft, writing–review and editing, visualization, supervision, and project administration.

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