Delineation of clinical and biological factors associated with cutaneous squamous cell carcinoma among patients with chronic lymphocytic leukemia

Geffen Kleinstern, PhD,[a] Abdul Rishi, MBBS,[b] Sara J. Achenbach, MS,[a] Kari G. Rabe, MS,[a] Neil E. Kay, MD,[c] Tait D. Shanafelt, MD,[d] Wei Ding, MBBS,[c] Joe F. Leis, MD, PhD,[e] Aaron D. Norman, MPH,[a] Timothy G. Call, MD,[c] James R. Cerhan, MD, PhD,[a] Sameer A. Parikh, MBBS,[c] Christian L. Baum, MD,[f] and Susan L. Slager, PhD[a]

Rochester, Minnesota; Saint Louis, Missouri; Stanford, California; and Phoenix, Arizona

Background: The incidence of cutaneous squamous cell carcinoma (SCC) in patients with chronic lymphocytic leukemia (CLL) is significantly higher compared with age- and sex-matched controls.

Objective: To evaluate the association of factors associated with SCC risk.

Methods: Clinical CLL and SCC data were obtained from Mayo Clinic CLL Resource and self-reported questionnaires among patients with newly diagnosed CLL. We computed the CLL International Prognostic Index (CLL-IPI) from CLL prognostic factors, and a polygenic risk score from SCC susceptibility variants. We used Cox regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Among 1269 patients with CLL, the median follow-up was 7 years, and SCC subsequently developed in 124 patients. Significant associations with SCC risk were history of skin cancer (HR=4.80; 95% CI: 3.37-6.83), CLL-IPI (HR=1.42; 95% CI: 1.13-1.80), and polygenic risk score (HR=2.58; 95% CI: 1.50-4.43). In a multivariable model, these factors were independent predictors (C statistic = 0.69; 95% CI: 0.62-0.76). T-cell immunosuppressive treatments were also associated with SCC risk (HR=2.29; 95% CI: 1.47-3.55; adjusted for age, sex, and prior SCC).

From the Department of Health Sciences Research, Mayo Clinic, Rochester[a]; the Department of Internal Medicine, Mercy Hospital, Saint Louis[b]; the Division of Hematology, Mayo Clinic, Rochester[c]; the Division of Hematology, Department of Medicine, Stanford University[d]; the Department of Hematology and Oncology, Mayo Clinic, Phoenix[e]; and the Department of Dermatology, Mayo Clinic, Rochester.[f]

Authors Kleinstern and Rishi contributed equally.

Funding sources: Funding was provided by National Institutes of Health National Cancer Institute (CA-97274, CA-235026), Specialized Programs of Research Excellence (SPORE) in Human Cancer (P50-CA-97274), the Henry J. Predolin Foundation (R01-CA-92153), the National Center for Advancing Translational Science (UL1-TR-000135), and Mayo Clinic Cancer Center Support grant P30-CA-15083. Dr Kleinstern was supported by the National Institutes of Health National Cancer Institute grant R25-CA-92049 (Mayo Cancer Genetic Epidemiology Training Program). Dr Baum is supported by a Career Development Award through the Dermatology Foundation.

Conflicts of interest: Research funding has been provided to the institution from Pharmacyclics, MorphoSys, Janssen, AstraZeneca, and Ascentage Pharma for clinical studies in which Sameer A. Parikh is a principal investigator. Sameer A. Parikh has also participated in advisory board meetings of Pharmacyclics, AstraZeneca, Genentech, Gilead, and AbbVie (but was not personally compensated for his participation). Dr Kay has research funding from Acerta Pharm, Pharmacyclics, MEI Pharma, and Tolero; is on a data safety monitoring committee for Agios Pharm, Celgene, Sunesis, Cytomx Therapeutics, Morpho-Sys, Rigel Pharm, and Juno Therapeutics; and is on an advisory board for AstraZeneca, Cytomx Therapeutics, Pharmacyclics Dava Oncology, Acerta Pharma BV, and Juno Therapeutics. Wei Ding has research funding from Merck and is on an advisory board for Merck and Octapharma (no personal compensation). Authors Kleinstern, Rishi, Achenbach, Rabe, Shanafelt, Leis, Norman, Call, Cerhan, Baum, and Slager have no conflicts of interest to declare.

IRB approval status: The cohort protocol was approved by the Mayo Clinic Institutional Review Board.

Accepted for publication June 29, 2020.

Reprints not available from the authors.

Correspondence to: Susan L. Slager, PhD, Mayo Clinic, 200 1st St SW, Rochester, MN, 55905. E-mail: slager@mayo.edu.

Published online July 16, 2020.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.06.1024

Limitations: The sample size decreases when combining all risk factors in a single model.

Conclusion: SCC risk includes history of skin cancer, an aggressive disease at time of CLL diagnosis, receiving T-cell immunosuppressive treatments, and high polygenic risk score. Future studies should develop prediction models that include these factors to improved screening guidelines. (J Am Acad Dermatol 2020;83:1581-9.)

Key words: chronic lymphocytic leukemia; cutaneous squamous cell carcinoma.

CAPSULE SUMMARY

- Squamous cell carcinoma risk among patients with chronic lymphocytic leukemia was associated with squamous cell carcinoma-specific risk factors: history of skin cancer and squamous cell carcinoma polygenic risk score; and chronic lymphocytic leukemia prognostic factors: international prognostic index, and T-cell immunosuppressive treatments.
- These factors predict squamous cell carcinoma risk among patients with chronic lymphocytic leukemia and may improve screening guidelines.

Chronic lymphocytic leukemia (CLL) is a B-cell lymphoproliferative disorder and the most prevalent adult leukemia in the Western world.[1,2] Nonmelanoma skin cancer (NMSC) is the most common group of malignant neoplasms in White-skinned population and practically refers to keratinocyte carcinomas, such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), where they account for 99% of the tumors in this group.[3-5]

The risk of NMSC is increased in immunosuppressed conditions, such as in patients with a history of a solid organ transplant, autoimmune disorders, HIV infection, and non-Hodgkin lymphoma, including CLL.[6-10] CLL-associated NMSC is a common phenomenon that has been described for decades in the literature.[11-13] The incidence of skin cancers in patients with CLL is significantly higher compared with age- and sex-matched controls, with an 8-fold increased risk.[11,14] Moreover, NMSCs are the most common secondary cancers in patients who are survivors of CLL.[9,15]

CLL treatments, such as chemotherapeutic regimens and radiations, can be mutagenic and may increase the risk of NMSC; however, conflicting data make this hypothesis controversial.[10,16]

In recent years, genome-wide association studies have identified single nucleotide polymorphisms (SNPs) that are associated with BCC and SCC.[17-19] We recently reported an association between the genetic burden for risk of NMSC and CLL, highlighting the pleiotropic effect of genes in the pathogenesis of these cancers and suggesting that they have a partially shared genetic etiology.[20]

Although almost all SCC are cured with surgery, nodal metastasis develops in a subset of approximately 2% to 5%,[21-23] and it is estimated that 4000 to 8000 patients die of SCC in the United States each year.[24] Moreover, patients with CLL who develop SCC are more likely to experience locally aggressive SCC disease or metastatic SCC disease compared with those without CLL.[25,26] A recent study of 18,407 patients with CLL found the relative risks of *in situ* and invasive SCC were 24.6 and 7.6, respectively, which were the largest relative risks observed compared with those from other secondary cancers.[27]

The etiology of SCC risk among patients with CLL is not well established. Herein, we evaluate factors associated with the risk of SCC among patients with CLL, including CLL-specific factors (ie, clinical characteristics, prognostic CLL biomarkers, and CLL treatment), as well as known SCC factors (ie, genetic risk score of inherited SCC susceptibility SNPs, prior history of skin cancer, age, and sex).

METHODS

Study population

Patients with newly diagnosed CLL (defined here as consented ≤9 months from diagnosis) from 2002 to 2015, age 18 years or older, and no prior history of lymphoma were enrolled and systematically monitored by the Mayo Clinic/University of Iowa Lymphoma Specialized Program of Research Excellence. The Mayo Clinic Institutional Review Board approved the cohort protocol, and all participants provided written informed consent.

CLL clinical and prognostic data

Clinical and prognostic CLL data were obtained from the Mayo Clinic CLL Resource. We computed the CLL International Prognostic Index (CLL-IPI) for each patient using a weighted average of 5 independent CLL prognostic factors: *IGHV* mutational status, serum β_2-microglobulin, Rai stage, age

Abbreviations used:

BCC: basal cell carcinoma
CI: confidence interval
CLL: chronic lymphocytic leukemia
HR: hazard ratio
IPI: International Prognostic Index
NMSC: nonmelanoma skin cancer
PRS: polygenic risk score
SCC: squamous cell carcinoma
SNP: single nucleotide polymorphism

at CLL diagnosis and fluorescence in situ hybridization 17p deletion/*TP53* status.[28] As previously done, we then categorized the CLL-IPI into 4 risk groups: low, intermediate, high, and very high risk.[28]

CLL treatment regimens were collected and classified as positive if a patient received T-cell immunosuppressive treatments that we designated as purine analogue-, alemtuzumab-, or bendamustine-based treatments, or a combination of these. All other therapies that did not contain purine analogues were combined into an "other" category.

Data on newly diagnosed SCCs were abstracted from medical records, including date and diagnosis of other skin cancer subtypes, such as BCC, Merkel cell carcinoma, other NMSC, and melanoma. Prior history of any skin cancers before CLL diagnosis was ascertained from patient-reported questionnaires completed at the time of consent.

Genetic data

Patients with CLL were genotyped using the Illumina OmniExpress (Illumina, Inc, San Diego, CA) or Affymetrix 6.0 (Affymetrix/Thermo Fisher Scientific, Santa Clara, CA) arrarys.[29,30] Each genotyping array underwent rigorous quality control metrics, as previously done.[29,30] We computed the SCC polygenic risk score (SCC-PRS) for the 545 patients with CLL with available genetic data. The PRS is a weighted average of the number of risk alleles across the SNPs that have been validated to be associated with SCC. The weights for each SNP were the log of the odds ratio reported from prior studies,[19] and 9 SNPs were available for calculating the PRS for analysis (Supplemental Table I, available via Mendeley at https://doi.org/10.17632/3r4sdppf59.2).

Statistical analysis

We calculated time from the date of the CLL diagnosis to the date of the first SCC event or the last date of follow-up. Survival curves presenting the incidence of first SCC after the CLL diagnosis were calculated using the Kaplan-Meier method, and the log-rank test was used to test statistical differences. Cox regression analysis was used for multivariate analyses and to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). SCC risk factors included sex, history of skin cancer before the CLL diagnosis, and SCC-PRS, both as a continuous variable per SD and as a categorical variable by tertiles, using the first tertile as the reference category. CLL factors included age at CLL diagnosis, CLL-IPI as a continuous variable per category and as a categorical variable, and CLL treatment. Specifically for CLL treatment, we evaluated its effect on the risk of SCC by modeling treatment as a time-dependent covariate, both in a univariate and a multivariate analysis adjusted for age, sex, and prior history of SCC. We did not include CLL-IPI in this model because CLL-IPI and treatment are highly correlated. In a sensitivity analysis, we censored cases at the date of onset of CLL treatment regimens to remove the effect of treatment in the risk of SCC. Descriptions of the available data for each factor evaluated in our models are presented in Supplemental Fig 1.

To evaluate model discriminatory ability, we computed a C statistic and 95% CIs[31] for the adjusted Cox regression models. The C statistic is equivalent to the area under the receiver operating

Table I. Clinical characteristics of patients with chronic lymphocytic leukemia (*CLL*)

Characteristics	Total (N = 1269)
Age at CLL diagnosis, median (range), y	63 (24-91)
Male sex, No. (%)	858 (68)
Rai stage, No. (%)	
0	676 (54)
I/II	511 (41)
III/IV	71 (6)
Missing	11
Serum β_2-microglobulin, median (range), μg/mL	2.4 (0.2-16.2)
Missing, No.	206
IGHV mutation status, No. (%)	
Unmutated	486 (45)
Mutated	602 (55)
Missing	181
FISH: Del 17p-positive or *TP53* mutation, No. (%)	60 (6)
Missing	202
CLL-IPI risk score, No. (%)	
0-1: low risk	403 (44)
2-3: intermediate	307 (34)
4-6: high	164 (18)
7-10: very-high	39 (4)
Missing	356

IPI, International Prognostic Index; *FISH*, fluorescence in situ hybridization; *No.*, number; *SCC* squamous cell carcinoma.

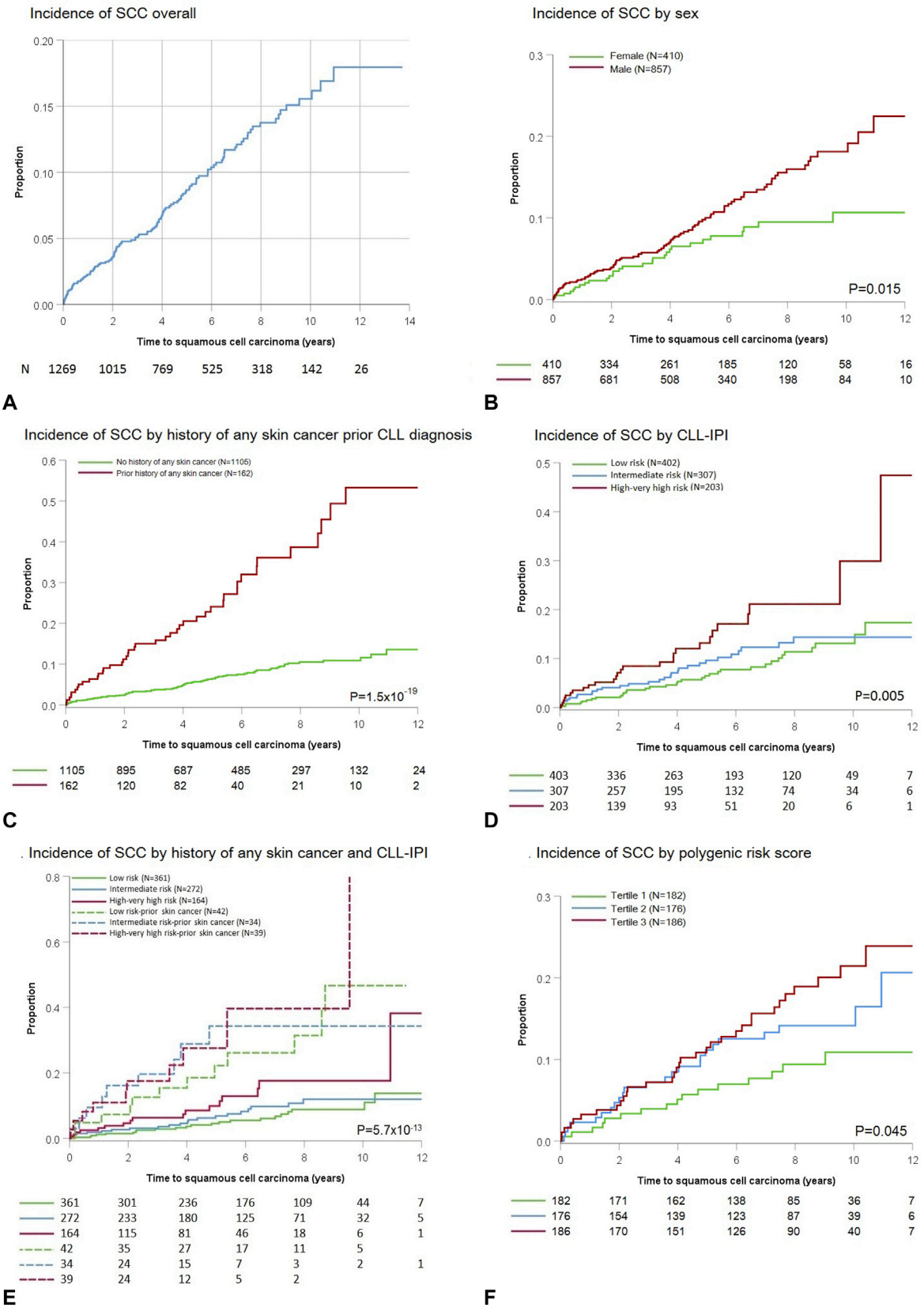

Fig 1. Kaplan-Meier survival curves indicate the time to the first squamous cell carcinoma (*SCC*) after the chronic lymphocytic leukemia (*CLL*) diagnosis. (**A**) Incidence of SCC among patients with CLL. (**B**) Incidence of SCC by male (*red*) and female (*green*) sex. (**C**) Incidence of

characteristic curve and is the probability that the measure or predicted risk is higher for a patient who experienced the outcome of interest (in our case, SCC) and a patient who did not.[32] A C statistic = 0.5 is equivalent to chance, C statistic >0.7 is considered a good discrimination, C statistic >0.8 is a strong discrimination, and a C statistic = 1 indicates perfect discrimination.[33]

RESULTS

Among 1269 patients with CLL, the median age at diagnosis was 63 years (range, 24-91 years), all were White, 68% were men, and 6% had Rai stage III to IV at diagnosis. The median follow-up time was 7 years. As assessed by the CLL-IPI, 44% were low risk, 34% intermediate risk, 18% high risk, and 4% very high risk CLL at diagnosis (Table I). The median SCC-PRS was 1.47 (range, 0.24-3.03). There were 162 patients (13%) with a history of any skin cancer before the CLL diagnosis, and 61 patients (4.8%) had SCC before CLL diagnosis. A total of 124 patients had ≥1 SCCs after the CLL diagnosis (Fig 1, *A*; Table II), which correlates to an 8.7% incidence rate at 5 years for developing SCC after the CLL diagnosis, and 19 of these patients also had SCC before their CLL diagnosis. Among patients treated for CLL, 313 received T-cell immunosuppressive treatments before the SCC diagnosis or at the last follow-up.

In univariate analyses, significant associations of clinical and prognostic characteristics with risk of SCC among patients with CLL were observed for each 10-year increase in age (HR=1.62; 95% CI: 1.36-1.92), male sex (HR=1.67; 95% CI: 1.10-2.54) (Fig 1, *B*; Table III), prior history of any skin cancer (HR=4.80; 95% CI: 3.37-6.83) (Fig 1, *C*; Table III), and increased CLL-IPI per category (HR=1.42; 95% CI: 1.13-1.80) (Fig 1, *D*; Table III).

We plotted the Kaplan-Meier survival curve according to 3 CLL-IPI risk groups (low, intermediate, and high to very high risk) among those with and without history of any skin cancer before the CLL diagnosis (Fig 1, *E*) and observed significant differences ($P = 5.7 \times 10^{-13}$). Those with a prior history of skin cancer (regardless of CLL-IPI category) had a higher risk of developing SCC than those without a prior history of skin cancer. Specifically, the 3-year incidence of SCC among those with high to very-high CLL-IPI and no prior history of skin cancer was 6%. This 3-year rate increased to 13% among the low CLL-IPI with prior skin cancer, to 20% among those with intermediate CLL-IPI with prior skin cancer, and to 17% among those with high to very high CLL-IPI with prior skin cancer (Fig 1, *E*).

When we included CLL-IPI, sex, and prior history of any skin cancer in a multivariable model (age not included because it is part of the CLL-IPI), these factors were still statistically significant and independent, with an observed C statistic = 0.69 (95% CI: 0.62-0.76) (Table III).

In a univariate analysis, SCC-PRS was also associated with risk of SCC among patients with CLL (PRS per SD HR=2.58; 95% CI: 1.50-4.43) (Table III; Fig 1, *F*). When we included SCC-PRS, sex, prior history of any skin cancer, and CLL-IPI in a multivariable model among 378 patients with CLL who had all 4 components, these factors were still statistically significant and independent with a C statistic = 0.75 (95% CI: 0.68-0.81) (Table III).

Types of first-line CLL treatments are described in Supplemental Table II. In a univariate model, we observed an association between T-cell immunosuppressive treatments with the risk of SCC after the CLL diagnosis (HR=2.04; 95% CI: 1.31-3.18). This association was slightly stronger in a multivariable analysis after adjusting for age, sex, and prior history of SCC (HR=2.29; 95% CI: 1.47-3.55), with a C statistic = 0.69 (95% CI: 0.63-0.74) (Table IV). In sensitivity analyses, when censoring cases at date of treatment, we found that age, male sex, CLL-IPI, prior history of any skin cancer, and PRS were still associated with risk of SCC, both in univariate and multivariable models, and the results remained consistent (results not shown).

DISCUSSION

It is well established that patients with CLL have a higher risk of developing skin cancer, yet, few studies have investigated whether CLL factors are associated with this risk. In our large cohort of patients with newly diagnosed CLL, we found the 5-year incidence rate of SCC was 8.7%, and with these events, having a prior history of any skin

SCC by history of any skin cancer before the CLL diagnosis: yes (*red*), no (*green*). (**D**) Incidence of SCC by CLL international prognostic index (*CLL-IPI*): low risk (*green*), intermediate risk (*blue*), high to very-high risk (*red*). (**E**) Incidence of SCC by history of any skin cancer before the CLL diagnosis and CLL-IPI stratified by 6 categories: low-risk CLL-IPI (*solid green line*), intermediate-risk CLL-IPI (*solid blue line*), high- to very high-risk CLL-IPI (*solid red line*), low-risk CLL-IPI with prior history of any skin cancer (*dashed green line*), intermediate-risk CLL-IPI with prior history of any skin cancer (*dashed blue line*), high- to very high-risk CLL-IPI with prior history of any skin cancer (*dashed red line*). (**F**) Incidence of SCC by polygenic risk score tertiles: Tertile 1 (*green*), Tetile 2 (*blue*), Tertile 3 (*red*).

Table II. Clinical characteristics of skin cancers before and after the chronic lymphocytic leukemia (*CLL*) diagnosis

Characteristics	Overall	Only before CLL diagnosis	Only after CLL diagnosis	Both before and after CLL	Unknown timing
Any skin cancer, No.*	340	104	164	58	14
SCC, No.	166	42	105	19	0
Basal cell carcinoma, No.	171	59	86	21	5
Merkel cell carcinoma, No.	2	0	2	0	0
Other nonmelanoma, No.	16	2	14	0	0
Melanoma, No.	65	32	29	2	2
Unknown type, No.	36	14	15	0	7
No. of SCCs per individual*					
1 skin cancer, No.	97	38	59	0	0
2 skin cancers, No.	29	3	19	7	0
>2 skin cancers, No.	40	1	27	12	0
Median (range), No.	1 (1-26)	1 (1-5)	1 (1-25)	5 (2-26)	…

No., Number; *SCC*, squamous cell carcinoma.
*Patients with CLL can have multiple types of skin cancers.

Table III. Factors associated with squamous cell carcinoma risk after the chronic lymphocytic leukemia (*CLL*) diagnosis

			Univariate model			Multivariable model 1 (n = 907, events = 90)			Multivariable model 2 (n = 378, events = 53)		
Characteristics	No.	Event	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age at CLL diagnosis per 10-y increase	1267	122	1.62	1.36-1.92	<.001						
Male sex	1267	122	1.67	1.10-2.54	.02	1.62	0.99-2.64	.05	2.21	1.13-4.34	.02
Prior any skin cancer	1259	121	4.80	3.37-6.83	<.001	5.16	3.43-7.77	<.001	4.22	2.46-7.25	<.001
CLL-IPI* (continuous per category)	911	91	1.42	1.13-1.80	.003	1.31	1.05-1.64	.02	1.43	1.02-1.98	.04
Intermediate vs low risk	307	31	1.22	0.75-1.20	.43						
High vs low risk	164	23	2.22	1.31-3.79	.003						
Very-high vs low risk	39	4	2.33	0.82-6.61	.11						
Polygenic risk score† (per SD)	544	73	2.58	1.50-4.43	<.001	…	…	…	2.72	1.49-4.94	.001
Tertile 2 vs 1	176	24	1.63	0.86-3.06	.13						
Tertile 3 vs 1	186	33	2.11	1.16-3.83	.014						
C statistic (95% CI)						0.69	0.62-0.76		0.75	0.68-0.81	

CI, Confidence interval; *HR*, hazard ratio; *IPI*, International Prognostic Index; *No.*, number.
*CLL-IPI includes age; therefore we do not adjust for age in multivariable models with CLL-IPI.
†Polygenic risk score based on 9 single nucleotide polymorphisms associated with squamous cell carcinoma risk.

cancer was the strongest risk factor for developing subsequent SCC with a ~5-fold increased risk. The prevalence of prior skin cancers of any type was 13% in our cohort, and in particular, the prevalence of SCC was 4.8%. Our results support findings from a meta-analysis of 17 studies among individuals without CLL that a prior history of SCC increases the risk of developing a secondary SCC.[34] Moreover, we were able to report that CLL-IPI was independently associated with the risk of SCC. Those with an aggressive disease at the time of CLL diagnosis had a higher risk for SCC. These results support prior studies demonstrating that in univariate analyses, Rai stage,[9,35] *IGVH* mutation status,[35] and lymphocyte doubling time[35] are associated with increased risk of skin cancer.

Of particular interest, when combining the prior history of any skin cancer and CLL-IPI levels with the risk of SCC, a person in the high to very-high risk CLL-IPI, yet no prior history of any skin cancer, had a better outcome (ie, reduced risk of SCC) compared with individuals with a prior history of any skin cancer regardless of their CLL-IPI level, indicating the importance of having a prior history of skin cancer in determining future SCC risk.

We also found that the SCC-PRS was independently associated with risk of incident SCC among our cohort of patients with CLL. The PRS is a weighted average of the number of risk alleles across the representative SCC SNPs that have been validated in previous studies,[19] with the weights being the log of the odds ratio reported for each SNP. The weights

Table IV. Chronic lymphocytic leukemia (*CLL*) treatments associated with squamous cell carcinoma risk after CLL diagnosis

			Univariate model			Multivariable model* (n = 1259, events = 104)		
Characteristics	**No.**	**Events**	**HR**	**95% CI**	***P***	**HR†**	**95% CI**	***P***
Any T-cell immunosuppressive treatments‡	1261	104	2.04	1.31-3.18	.002	2.29	1.47-3.55	<.001
Any other CLL therapy			0.83	0.48-1.43	.49	0.71	0.41-1.23	.23
C statistic (95% CI)						0.69	0.63-0.74	

CI, Confidence intervals; *HR*, hazard ratio.
*We do not adjust for the chronic lymphocytic leukemia (CLL) International Prognostic Index (CLL-IPI) because treatment and CLL-IPI are highly correlated with each other.
†Adjusted for age, sex, and prior history of squamous cell carcinoma.
‡There were 313 patients treated with any T-cell immunosuppressive before the first squamous cell carcinoma diagnosis that occurred after the CLL diagnosis.

allow one to account for the effect size of each SNP on SCC risk.

The PRS is a widely used tool in recent years to calculate risk of different phenotypes.[36] Because a single variant is not informative for assessing disease risk, calculating the PRS allows us to estimate a summary score where the effect size is more informative, with sufficient information to identify those at "high risk." It is important to note that the frequencies of inherited genetic SNPs have significant racial differences, and studies have shown that predictive performance of European ancestry-derived PRS is lower in non-European ancestry samples.[37] The PRS calculated in our study was a weighted average of 9 known SCC susceptibility variants found in White individuals, and these findings complement a recent study that also calculated a SCC-PRS and found this score to be associated with risk of SCC,[38] regardless of CLL status.

In addition, another recent study calculated a SCC-PRS in renal transplant recipients and found that this SCC-PRS also predicted risk of developing SCC.[39] Together these studies highlight the important role of SCC germline genetics in SCC risk, regardless of the sample population, and suggest that these genetic sites may be important clues to the origins of such malignancies.

We found that T-cell immunosuppressive treatments (purine analogue-, alemtuzumab-, or bendamustine-based, or a combination of these) for CLL were also associated with the risk of SCC. These findings are supportive of the findings of a previous study that prior lymphoma treatment was associated with development of SCC in patients with CLL[10]; however, the exact treatments in that study were not reported. A recent study also reported a significant association between skin cancer, including SCC, BCC, melanomas, and Merkel cell carcinomas, and prior chemotherapy for CLL; however, the exact treatments were also not reported.[35]

Chemotherapeutic regimens can be mutagenic, and therefore, increase the risk of secondary malignancies. In addition, many of the chemotherapeutic agents used in CLL treatment are immunosuppressive and might increase the risk of development of skin cancer in patients with CLL.[40] However, there are conflicting data regarding the association between chemotherapy for treatment of lymphoma and the risk of secondary malignancies.[41-44] Treatment effect is also difficult to assess due to the change in treatments over time.

Finally, age and male sex were also associated with increased risk for SCC in our study, which is consistent with prior studies.[10,35,38]

The strength of this study is the large CLL cohort combining clinical CLL characteristics, SCC genetic data, and prior history of skin cancer data. These CLL factors enabled us to calculate the CLL-IPI for most of our patients. The fact that prior history of skin cancer was a strong risk factor to predict SCC in patients with CLL will enable clinicians to better counsel an individual patient and his or her risk in developing SCC.

A limitation of this study includes the small sample size when combining all risk factors in a single model. Only 380 patients had complete data for sex, prior history of any skin cancer, CLL-IPI, and PRS. However, our analysis was able to discern that these factors were significantly and independently associated with SCC.

Another limitation is that our cohort included White patients only. Prior studies have found that African Americans are more likely to have adverse prognostic factors, shorter time to initiation of therapy, and reduced overall survival compared with White patients.[45-47] Therefore, our results may not be generalizable and will need further validation

in other ethnicities, in particular, the PRS finding which was also based on variants discovered in White individuals, and as mentioned previously, these variants do not perform well in prediction across other races/ethnicities.[37]

CONCLUSION

Screening for SCC is important in newly diagnosed patients with CLL, because patients with CLL and SCC are more likely to have more frequent and more aggressive SCC and are at higher risk of death caused by metastatic SCC.[48] Our data suggest that more attention to patients with CLL is particularly relevant among patients who have a prior history of skin cancer, which is the most important risk factor with the largest effect size, those with aggressive CLL according to CLL-IPI score, and those receiving T-cell immunosuppressive treatments. In addition, the SCC-PRS is also an important factor in assessing risk of SCC for patients with CLL. Future studies should develop prediction models that include both CLL-specific and SCC-specific factors. This may lead to improved screening and counseling guidelines for newly diagnosed patients with CLL.

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