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External validation of **C**ardiac disease, **H**ypertension, and **L**ogarithmic **L**eft anterior descending coronary artery radiation dose **(CHyLL)** for predicting major adverse cardiac events after lung cancer radiotherapy

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A B S T R A C T

Background and purpose: Major adverse cardiac events(MACE) are prevalent in patients with locally advanced-non-small cell lung cancer(LA-NSCLC) following radiotherapy(RT). The **CHyLL** model, incorporating coronary heart disease(**C**HD),**Hy**pertension(HTN),**L**ogarithmic **L**ADV15 was developed and internally-validated to predict MACE among LA-NSCLC patients. We sought to externally validate CHyLL to predict MACE in an independent LA-NSCLC cohort.
Patients and methods: Patients with LA-NSCLC treated with RT were included. CHyLL score was calculated:5.51CHD + 1.28HTN + 1.48ln(LADV15 + 1)-1.36CHD*ln (LADV15 + 1). CHyLL performance in predicting MACE was assessed and compared to mean heart dose(MHD) using Cox-proportional hazard(PH) analyses and Harrel's concordance(C)-indices. MACE and overall survival(OS) among low-vs high-risk groups(CHyLL < 5 vs ≥ 5) were compared.
Results: In the external validation cohort($N = 102$), the median age was 71 years and 55% were females. Most($n = 74$,73%), had clinical Stage III disease and 35(34%) underwent surgery. CHyLL demonstrated good MACE prediction with C-index of 0.73(95% Confidence Interval(CI):0.58–0.89), while MHD did not (C-index = 0.46 (95% CI:0.30–0.62)). Per CHyLL, 32(31%) and 70(69%) patients were considered low-and high-risk for MACE, respectively. CHyLL consistently identified lower MACE rates in the low-vs high-risk group(log-rank $p = 0.108$):0 vs 8%(12 months),5 vs 16%(24 months),5 vs 16%(36 months),and 5 vs 19%(48 months) post-RT. In the pooled internal and external validation cohort($N = 303$), MACE rates in low-vs high-risk groups were statistically significantly different(log-rank $p = 0.01$):1 vs 6%(12 months),3 vs 12%(24 months),6 vs 19%(36 months),and 6 vs 21%(48 months).
Conclusions: CHyLL was externally validated and superior to MHD in predicting MACE. CHyLL has the potential to identify high-risk patients who may benefit from cardio-oncology optimization and to estimate personalized LADV15 constraints based on cardiac risk factors and acceptable MACE thresholds.

Introduction

Patients with lung cancer are at high risk of major adverse cardiac events (MACE) which are associated with cardiac radiation dose and baseline cardiovascular risk [1–3]. Cardiac radiation dose has been identified to be predictive of survival in patients with locally advanced non-small cell lung cancer (LA-NSCLC) after thoracic radiotherapy (RT) [4]. Nonetheless, avoiding dose to the whole heart while maintaining target coverage is often challenging due to the extent and/or location of disease and proximity to other important organs at risk, such as the lungs or esophagus [5]. Therefore, establishment of dose constraints for crucial cardiac substructures such as the coronary vessels is important to reduce MACE while optimizing oncologic outcomes [6,7].

MACE (including myocardial infarction, unstable angina, heart failure hospitalization or urgent visit, coronary revascularization, and/or cardiac death) are prevalent among patients with NSCLC and are associated with morbidity and mortality [1]. Given the high baseline cardiovascular risk in this population, with more than 40% harboring baseline cardiovascular disease [8], there is a need for a validated MACE prediction tool in patients with lung cancer receiving RT that

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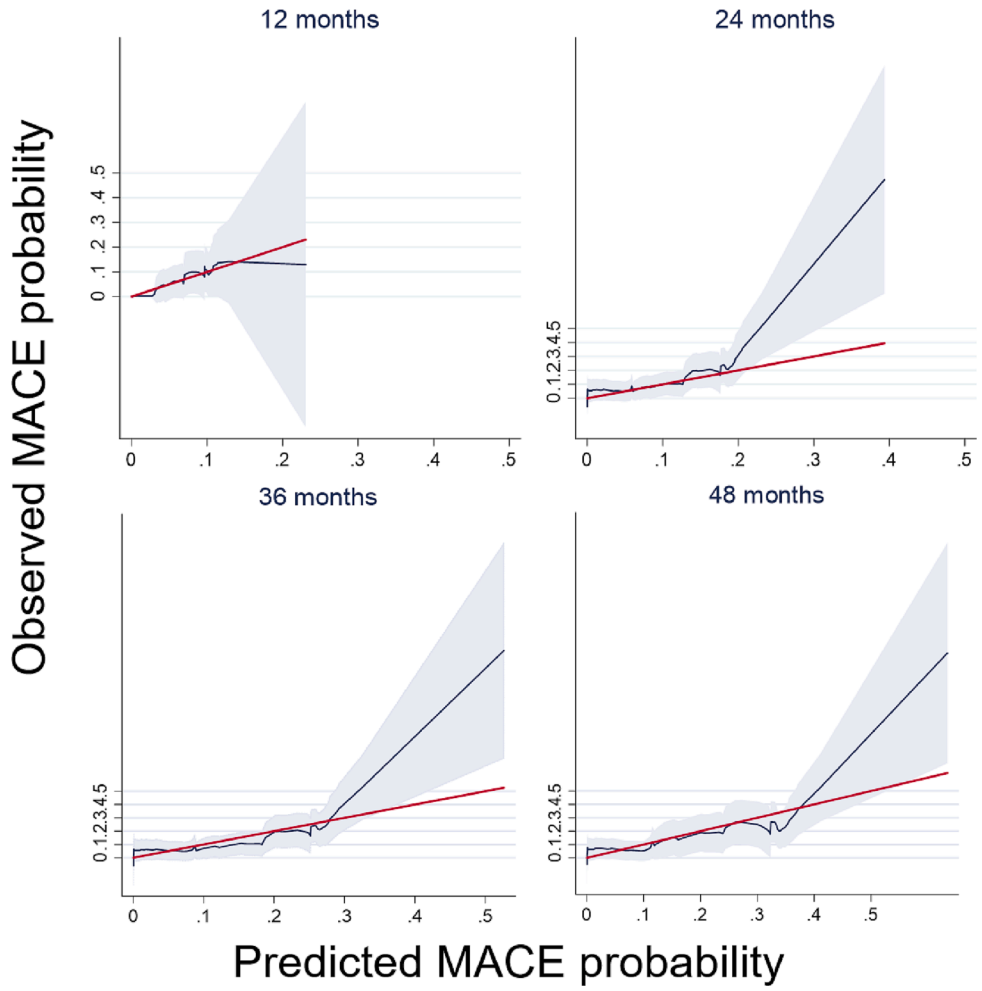

Fig. 1. Calibration plots of MACE prediction model performances among the external independent validation cohort in 12 months-intervals up to 48 months. Perfect prediction line: red straight line; model prediction line: dark blue with 95% confidence interval (light blue area).

incorporates the interaction between baseline cardiac risk factors and comorbidities with cardiac radiation dose exposure [1,9,10]. Importantly, prior cardiac substructure dose volume studies identified the left anterior descending (LAD) coronary artery percent volume receiving ≥ 15 Gy (V15Gy) to be the strongest independent MACE predictor even when compared to whole heart metrics such as mean heart dose (MHD), which are widely used in established guidelines such as Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) and the National Comprehensive Cancer Network (NCCN) [9,11]. Furthermore, prior work has identified MHD as an inadequate surrogate of LAD V15Gy, with significant discordance between whole heart and LAD dose exposure, underscoring the importance of specific LAD dose monitoring [12].

To address this need, our group recently developed a MACE risk prediction tool modeled from 500 LA-NSCLC patients treated with RT [10]: **CHyLL** score, incorporating baseline **C**oronary heart disease (CHD), **Hy**pertension, and **L**ogarithmic **L**AD artery V15 Gy (LADV15) [10]. The model incorporates both prior history of CHD, cardiac risk factors (hypertension), and radiation dose exposure to a critical cardiac sub-structure that is pathophysiologically related to specific cardiac endpoints, and the interaction between radiation dose and prior CHD [1,9,10]. While CHyLL was internally validated using 201 additional patients treated in the same institution as the development patients, the tool has not been externally validated. Therefore, this study investigated the performance of CHyLL in predicting MACE using a LA-NSCLC cohort from an independent institution.

Patients and methods

This was a multi-institutional retrospective study of consecutive lung cancer patients treated with thoracic RT: The external validation cohort consisted of 102 patients treated between August 2005 to August 2021 at Cedars-Sinai Medical Center in Los Angeles, California. The CHyLL score was developed and internally validated in a set of 701 patients treated between December 2003 and January 2014 at Brigham and Women's Hospital and Dana-Farber Cancer Institute in Boston, Massachusetts, as described [10].

In the external validation cohort, RT was planned (Varian Eclipse, Varian Medical Systems Inc) using 3D-conformal RT (3D-CRT) or intensity-modulated RT (IMRT) techniques in 1.8–2.0 Gy fractions. The heart and LAD were manually delineated per published atlas guidelines [13] and dose-volume histogram data extracted. Baseline medical history, cardiovascular risk factors, cardiac events, and cause of death were assessed by in-depth manual medical record review as previously described [9,14]—specifically including review of clinical notes, reports (e.g., diagnostic imaging, procedure, electrocardiogram), and laboratory data. Pre-RT coronary artery disease, congestive heart failure, or a CHD risk-equivalent (peripheral vascular disease, stroke, or extensive coronary artery calcifications) were considered to be pre-existing coronary heart disease (CHD) [1]. MACE was assessed post-RT for non-surgical patients, and 30 days or more postoperatively for patients who underwent surgery, until death or last follow-up. MACE included unstable angina, heart failure hospitalization or urgent visit, myocardial infarction, coronary revascularization, and/or cardiac death [1,10]

Table 1
Baseline, disease, and treatment characteristics of lung cancer patients in development and external validation cohorts.

Patient baseline characteristics and comorbidities					
	Development	Internal Validation	p-value	External Validation	p-value
	N = 500	N = 201		N = 102	
Age at diagnosis	65.0 (57.0–72.5)	66.0 (59.0–74.0)	0.02	70.5 (64.0–77.0)	<0.01
Female gender	253 (50.6%)	103 (51.2%)	0.88	56 (54.9%)	0.43
Smoking status			0.24		<0.01
Non-smoker	45 (9.0%)	11 (5.5%)		24 (23.5%)	
Current	193 (38.6%)	86 (42.8%)		11 (10.8%)	
Former	262 (52.4%)	104 (51.7%)		67 (65.7%)	
Diabetes	69 (13.8%)	28 (13.9%)	0.96	30 (29.4%)	<0.01
Hypertension	254 (50.8%)	108 (53.7%)	0.48	66 (64.7%)	0.01
Dyslipidemia	239 (47.8%)	102 (50.7%)	0.48	56 (54.9%)	0.19
Congestive heart failure	38 (7.6%)	20 (10.0%)	0.31	8 (7.8%)	0.93
Coronary heart disease	181 (36.2%)	71 (35.3%)	0.83	32 (31.4%)	0.35
Stroke	6 (2.1%)	7 (5.1%)	0.09	7 (6.9%)	0.02
Lung cancer disease and treatment characteristics					
Clinical Stage (AJCC 7th)			0.14		<0.01
I	0 (0.0%)	0 (0.0%)		9 (8.8%)	
II	62 (12.4%)	17 (8.5%)		10 (9.8%)	
III	438 (87.6%)	184 (91.5%)		74 (72.5%)	
IV	0 (0.0%)	0 (0.0%)		8 (7.8%)	
Unknown	0 (0.0%)	0 (0.0%)		1 (1.0%)	
Nodal Stage			0.40		0.42
N0	62 (12.4%)	19 (9.5%)		17 (16.7%)	
N1	72 (14.4%)	27 (13.4%)		10 (9.8%)	
N2	254 (50.8%)	104 (51.7%)		53 (52.0%)	
N3	112 (22.4%)	50 (24.9%)		20 (19.6%)	
NX	0 (0.0%)	1 (0.5%)		2 (2.0%)	
RT total dose (Gy)	63.0 (54.0–66.0)	60.0 (54.0–66.0)	0.03	60.0 (55.8–60.0)	<0.01
RT total fractions	33.0 (27.0–33.0)	30.0 (27.0–33.0)	0.01	30.0 (30.0–33.0)	0.34
IMRT/VMAT	81 (16.2%)	81 (40.3%)	<0.01	82 (80.4%)	<0.01
Surgery	203 (40.6%)	74 (36.8%)	0.35	35 (34.3%)	0.24
Chemotherapy					
Induction	105 (21.0%)	28 (13.9%)	0.03	26 (25.5%)	0.32
Concurrent	413 (82.6%)	181 (90.0%)	0.01	75 (73.5%)	0.03
Adjuvant	160 (32.0%)	78 (38.8%)	0.09	3 (2.9%)	<0.01
Organs at risk RT dose					
Mean heart dose (Gy)	11.6 (5.4–18.8)	13.4 (8.1–20.1)	0.01	12.1 (7.2–19.1)	0.23
LADV15 (%)	9.6 (0.0–42.3)	22.8 (0.4–41.8)	0.01	30.6 (0.0–52.1)	<0.01
Mean lung dose (Gy)	14.5 (10.9–17.0)	16.0 (12.7–18.0)	<0.01	15.4 (11.6–17.9)	0.11
Lung V5Gy (%)	41.4 (31.3–50.3)	47.1 (36.1–54.8)	<0.01	60.8 (44.9–73.5)	<0.01
Lung V20Gy (%)	24.7 (18.4–29.2)	26.5 (22.7–30.0)	0.01	27.5 (19.5–33.0)	<0.01

Categorical variables are reported as frequencies and percentages, while continuous variables as median and interquartile ranges (IQR). IMRT: intensity modulated radiation therapy. VMAT: volumetric-modulated arc therapy. LADV15: Left anterior descending artery V15 Gy (%). P-values were from comparisons of development vs internal or external validation cohorts.

Cardiac-specific death referred to fatalities from sudden cardiac events, acute myocardial infarction, heart failure, cardiovascular procedures, cardiovascular hemorrhages, or other cardiac causes [14].

Statistical Analysis

All analyses were done in STATA version 15.1. Medians and interquartile ranges (IQR) were reported for continuous variables, and frequencies and percentages were reported for categorical and ordinal variables.

External validation of CHyLL in MACE prediction

CHyLL model and MACE survival functions were generated using the development cohort (N = 500) with methods as described by Tjong et al [10]. The CHyLL score was calculated for the external validation cohort (N = 102) using the following formula [10]:

$$CHyLL = 5.51CHD + 1.28HTN + 1.48\ln(LADV15 + 1) - 1.36CHD \times \ln(LADV15 + 1)$$

CHyLL performance in predicting MACE was assessed using Cox-proportional hazard (PH) methods as in the original publication [10,15]. The discriminative ability of CHyLL to predict MACE was evaluated with bootstrapped Harrel's concordance index (C-index), using predicted risk values established from the development Cox-PH model. External validation cohort patients were randomly selected with replacement from the same pool to create 1000 cohorts of same sample size, generating the C-index estimates with 95% confidence intervals (CI). Results were compared to the ability of using MHD alone to predict MACE, which was also assessed using bootstrapped C-index. The C-index ranges from 0.5 (no discriminative ability) to 1.0 (perfect discrimination), with C-index of 0.7 considered to be good discrimination [16].

CHyLL calibration

Calibration of CHyLL score-predicted MACE rates in the external validation cohort was assessed using methods described by Royston et al. [17] To obtain individual predictions, the baseline survival hazard was extracted from development model and applied within the external validation cohort. The predicted and observed MACE probabilities at 12, 24, 36, and 48 months were then compared, and the predicted event probability graphed against observed event probability alongside the 95% CI areas using the stcoxcal command (Fig. 1) [17]. As we consider patients with approximately 20% actuarial MACE at 48 months to be high-risk patients, we consider calibration within 0–30% MACE risk interval in 48 months as most relevant [10].

CHyLL groups performance

Patients were then grouped according to CHyLL as low-risk (CHyLL < 5) or high-risk (CHyLL ≥ 5) for MACE [10]. Actuarial MACE events between CHyLL groups in external validation cohort were graphed and analyzed using Kaplan-Meier (KM) methods. OS between CHyLL groups were also compared using KM methods. Log-rank analyses were performed to compare MACE and OS between groups. Lastly, we explored the MACE rates according to CHyLL groups in the pooled external and internal test cohorts and reported the estimated MACE risk at 12, 24, 36, and 48 months.

Results

Patient characteristics from the external validation cohort and internal development and test cohorts are described in Table 1. The median follow-up in the external validation cohort was 23.5 (interquartile

Table 2
CHyLL Score and MHD Performances in Predicting MACE in the Internal (N = 201) and External validation Cohort (N = 102).

Model	Validation Cohort	Hazard Ratio (95% CI)	P-value	Harrel's C-Index (95% CI)
CHyLL Score	Internal (N = 201)	1.80(1.12—2.88)	0.015	0.76 (0.64–0.87)
	External (N = 102)	1.93 (0.92–4.05)	0.083	0.73 (0.58–0.89)
MHD	Internal (N = 201)	1.03 (0.98—1.07)	0.257	0.55 (0.43–0.68)
	External (N = 102)	1.00 (0.94–1.07)	0.896	0.46 (0.30–0.62)

CHyLL: Cardiac disease, **Hy**pertension, and **L**ogarithmic **L**eft anterior descending artery V15Gy; MHD: mean heart dose in Gy; MACE: major adverse cardiac events; CI: confidence interval; C-Index: concordance-index.

Table 3
MACE Rates Based on CHyLL Groups in Internal (N = 201) and External (N = 102) Test Cohorts.

	Internal Validation (N = 201)		External Validation (N = 102)	
CHyLL Group	Low-risk (n = 65 [32%])	High-risk (n = 136 [68%])	Low-risk (n = 32 [31%])	High-risk (n = 70 [69%])
Crude MACE (%)	2 (3%)	17 (13%)	1 (3%)	10 (14%)
MACE at 12 months (%)	2%	6%	0%	8%
MACE at 24 months (%)	2%	10%	5%	16%
MACE at 36 months (%)	7%	24%	5%	19%
MACE at 48 months (%)	7%	24%	5%	19%

MACE: major adverse cardiac events; **CHyLL: C**ardiac disease, **Hy**pertension, and **L**ogarithmic **L**eft anterior descending artery V15Gy; Low-risk: CHyLL < 5; High-risk: CHyLL ≥ 5.

range IQR: 15.3–53.2) months. Compared to the internal development cohort, the external validation cohort had older median age (70.5 vs 65.0 years; p < 0.01), more non-smokers (23.5 vs 9.0%; p < 0.01), more patients with diabetes mellitus (29.4 vs 13.8%; p < 0.01) and hypertension (64.7 vs 50.8%; p < 0.01), but similar baseline CHD (31.4 vs 36.2%; p = 0.35). While all patients were Stage II-III in the development cohort, there were patients with clinical Stage I (8.8%) and oligometastatic Stage IV (7.8%) disease (p < 0.01) in the external validation set. IMRT/VMAT use was higher in the external cohort (80.4 vs 16.2%; p < 0.01), with lower median prescribed RT dose (60.0 vs 63.0 Gy; p < 0.01), but higher LADV15, lung V5Gy, and lung V20Gy (p-values < 0.01).

The median calculated CHyLL score in the external cohort was 6.3 (range: 0–8.1). Table 2 shows CHyLL score and MHD performance in predicting MACE among internal and external validation cohorts. CHyLL score was positively, but non-significantly associated with MACE (Hazard Ratio [HR] for a one-unit increase in CHyLL: 1.93 (95% CI: 0.92–4.05); p = 0.083). The model had good discrimination with C-index of 0.73 (95% CI: 0.58–0.89) (Table 2). MHD was not associated with MACE, and this model had poor concordance (HR: 1.00 (95% CI: 0.94–1.07)); p = 0.896; C-index = 0.46 (95% CI: 0.30–0.62)) (Table 2). The predicted vs observed MACE probability curve were highly concordant with perfect prediction curve with narrow 95% CI up to

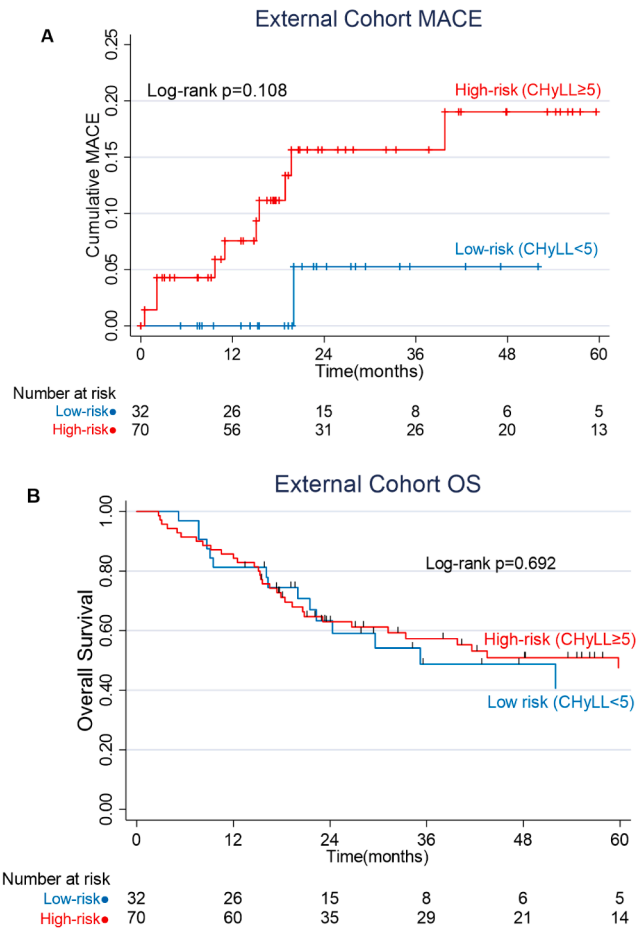

Fig. 2. A. Cumulative MACE observed incidence curves among external validation cohort (N=102) stratified according to low (CHyLL<5.00, blue) and high (CHyLL≥5.00, red) risk groups (Log-rank p= 0.108). Solid black line depicted CHyLL-predicted cumulative MACE curves **B.** Overall survival stratified according to low (CHyLL<5.00, blue) and high (CHyLL≥5.00, red) risk groups (Log-rank p=0.692).

around 10–20% at 12 and 24 months, and up to 30% at 36 and 48 months indicating good CHyLL calibration in this cohort (Fig. 1).

From 102 external validation patients, 32 patients were classified as low-risk (CHyLL < 5) and 70 as high-risk (CHyLL ≥ 5). There were 11 patients (10.8%) with MACE post-RT in the external validation cohort, 1 (3%) in low-risk, and 10 (14%) in high-risk patients (Table 3). Comparing low vs high-risk groups, MACE rates at 12 months were: 0 vs 8%, at 24 months were: 5 vs 16%, at 36 months were: 5 vs 16%, and at 48 months were: 5 vs 19% (Log-rank p = 0.108; Fig. 2**A;** Table 3). In the same order, OS rates at 12 months were: 81 vs 84%, at 24 months were: 63 vs 63%, at 36 months were: 49 vs 57%, and at 48 months were: 49 vs 51% (Log-rank p = 0.692; Fig. 2**B**). From 54 deaths reported, 4 (9%) were directly MACE-related. In the pooled internal and external validation cohort patients (N = 303), MACE rates in low vs high-risk groups were statistically significantly different (log-rank p = 0.010): 1 vs 6% (12 months), 3 vs 12% (24 months), 6 vs 19% (36 months), and 6 vs 21% (48 months) (Fig. 3).

Discussion

CHyLL score, incorporating pre-existing cardiac risk factors (**C**HD and **Hy**pertension) and cardiac radiation dose (**L**ogarithmic **L**eft anterior descending [LAD] artery V15 Gy [LADV15]) performed well in predicting MACE after thoracic RT in patients with NSCLC treated in an

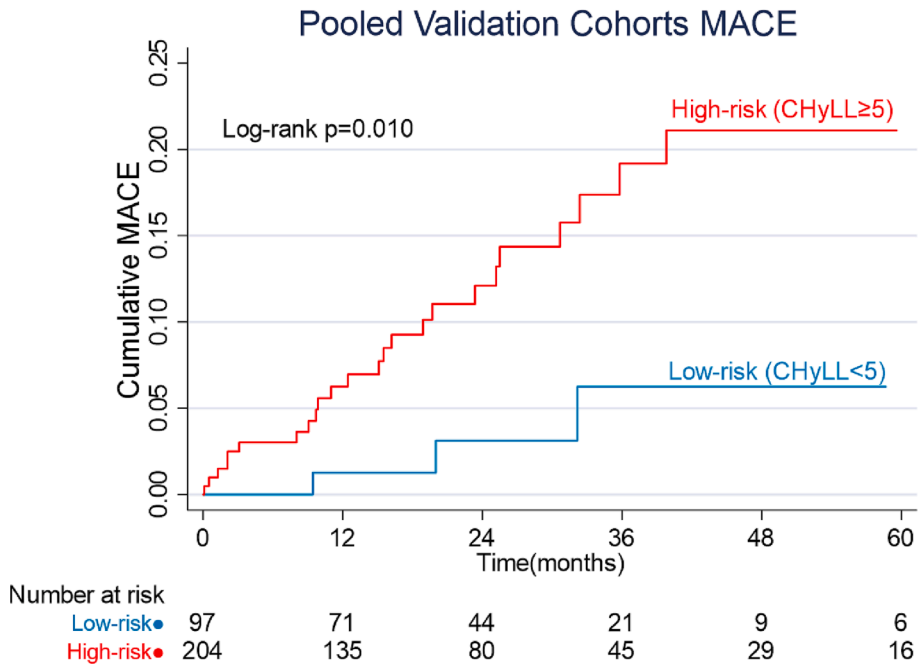

Fig. 3. Pooled internal and external validation cohort (N=303) MACE incidence curves stratified according to low (CHyLL<5.00, blue) and high (CHyLL≥5.00, red) risk groups (Log-rank p= 0.010).

independent, external validation cohort with a high c-index of 0.73. The high model concordance persisted despite differences between the external validation cohort compared to development cohort, indicating a robust model (Table 1). Conversely, the commonly employed and current guidelines-based MHD was a poor predictor of MACE with a c-index of 0.46. These results are consistent with the previously published internal validation cohort with CHyLL score and MHD c-indices of 0.76 and 0.55 respectively (Table 2) [10]. In sum, our studies demonstrate that whole heart radiation dosimetric factors such as MHD are not adequate for identifying patients at high risk for MACE [12], and a model like CHyLL that incorporates dosimetry to a critical cardiac substructure such as the LAD with a pathophysiologically relevant cardiac endpoint of MACE is promising.

While there was a non-significant positive association between CHyLL score and CHyLL-stratified risk groups with MACE (Fig. 2**A**), the pooled external and internal validation analyses showed high MACE rates at all time points post RT (Fig. 3) and the CHyLL model categorized the majority of patients in both cohorts as high-risk (Table 2). Notably, the inability to find a statistically significant relationship (defined as $p < 0.05$) in the external validation cohort alone is likely due to the limited sample size with only 102 patients. Nonetheless, CHyLL performances were highly consistent between external and internal test cohorts (Table 2 and 3), with similar hazard ratios for CHyLL score, as well as similar crude and actuarial MACE rates at 12, 24, 36, and 48 months between low (CHyLL $<$ 5) vs high-risk (CHyLL $\geq$ 5) groups. Furthermore, the observed MACE rates between CHyLL groups were highly concordant with the CHyLL-predicted rates, indicating good model calibration in this external validation cohort (Fig. 1). Together, these findings support the validity and clinical utility of CHyLL predicting MACE in this population. Furthermore, the relationship between baseline cardiac risk, LAD dose exposure, and MACE highlights a major survivorship issue that has likely been under-appreciated in this population and underscores the clinical need for involvement of cardio-oncology and implementation of guideline-directed cardiac risk optimization such as statin use and hypertension control [18–22].

Practically, the CHyLL score is simple to calculate for clinicians from clinical records, by abstracting the patient's baseline CHD and HTN status, contouring the LAD, and calculating the LADV15 [10,13,23]. The CHyLL score can identify high-risk patients who may benefit from cardio-oncology assessment and early intervention for risk reduction optimization. Furthermore, CHyLL has the potential to aid lung RT planning, by personalizing LADV15 constraints based on a patient's clinical history to remain low risk (CHyLL $<$ 5). For instance, the calculated LADV15 constraint was 28.3% for patients with no CHD or hypertension, and 11.3% for patients with hypertension (but no CHD) [10]. The ease of calculation from readily available clinical information supports the ability to implement this model in the clinic.

Notably, in this external validation cohort, CHyLL score was not shown to predict OS (Fig. 2**B**). While MACE was prevalent soon after RT (Fig. 3), the majority of reported deaths (91%) were not primary cardiac events. This finding emphasizes the importance of optimizing cardiac RT predictive models to cardiac specific outcomes such as MACE instead of OS, which may be primarily driven by cancer progression in lung cancer [24,25]. Inclusion of hard cardiac endpoints such as MACE will be important for future lung RT trials.

Lastly, there are several limitations of our study to note. The primary limitation is the small size of the external validation cohort, although the model still demonstrated high concordance despite notable baseline characteristic differences, indicating a robust model. Additional limitations included the retrospective study design at a single tertiary care referral center, which may result in under-capturing cardiac events, particularly those that occur at local hospitals, and thus the MACE rate may be under-estimated. The study also focused on LADV15 and CHyLL model, and we recognize that other substructures are likely clinically relevant—particularly for non-MACE cardiac endpoints such as arrythmias, pericardial events, or valvulopathies [3,26,27]. Nonetheless, this multi-institutional study demonstrated robust findings across two independent institutions, supporting the generalizability of the results. Having access to the original CHyLL development data [10], this study was able to directly demonstrate CHyLL calibration in our external validation cohort bolstering the model applicability. CHyLL score application has the potential to widen the therapeutic ratio of RT for lung cancer patients.

Data sharing statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Declaration of Competing Interest

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