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Post-diagnosis weight loss as a prognostic factor in non-small cell lung cancer

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Abstract

Background Cachexia and its most visible manifestation, weight loss, represent important poor prognostic factors for patients with non-small cell lung cancer. This work examines how severity of weight loss as an indicator of cachexia affects outcomes.

Methods In a retrospective observational study of electronic medical records, patients with non-small cell lung cancer were monitored for weight loss from an initial assessment (within 2 months of index diagnosis) to a landmark at 5 months (at least 3 months after initial assessment). Patients who survived to the landmark were then followed to determine the association of baseline body mass index (BMI) and weight loss during the assessment period with outcomes. Patients were clustered to determine how BMI and weight loss related to survival as approximated by time of last appearance in the database, a strong proxy for time of death.

Results Twelve thousand one hundred and one patients were divided into 5 cachexia risk groups based on a combination of weight loss and initial BMI. More severe groups demonstrated progressively worse outcomes, with the most severe group surviving for a median of 263 days (95% CI 254–274) from index and having a 1-year survival rate of 31%. The least severe group survived for a median of 825 days from index (95% CI 768–908) and had a 1-year survival rate of 78%. Cachexia risk group was a stronger predictor of survival than any baseline variable, including disease stage, performance status, or age.

Conclusions In this study, we showed that increasing weight loss and, to a lesser extent, decreasing BMI, led to substantially worse outcomes for non-small cell lung cancer patients independent of other variables. We suggest risk score groups that provide an improved approach for identifying poor prognosis patients with the greatest need.

Keywords NSCLC; Lung cancer; Weight loss; Cachexia

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Introduction

Cancer-associated muscle wasting is a common and debilitating symptom of late-stage cancer. It is commonly associated with cancer cachexia, a clinical syndrome that includes loss of appetite, unintended weight loss, and fatigue but is distinguished from a caloric deficit by the inability to reverse its consequences with nutritional support alone and the frequent presence of concomitant abnormalities in metabolism and inflammation.[1] Cancer-associated muscle wasting is seen in most late-stage cancer populations but is particularly common in lung and gastrointestinal cancers and may be the presenting symptom at diagnosis.[2] Patients with substantial cachexia have worse prognoses independent of other factors,[3] and patients with low body mass index (BMI) have worse outcomes independent of weight loss.[4]

Historically, involuntary weight loss was the most visible manifestation of cachexia and was typically used as a key qualitative factor to diagnose its presence. However, patients can have significantly different levels of weight loss, and varying standards have been proposed for defining a cachectic population based on weight loss and potentially additional factors such as food intake, inflammation, BMI, and muscle measures.[3,5] In 2011, an international panel of

experts established a consensus definition of cachexia to help standardize clinical trials and clinical management of cachexia, identifying patients with cancer cachexia as those meeting at least one of the following three definitions:

(i) weight loss >5% over the previous 6 months.
(ii) weight loss >2% and BMI <20.
(iii) weight loss >2% and sarcopenia as assessed by appendicular skeletal muscle index.[6]

While this consensus has helped establish a starting point for discussing cancer cachexia and its consequences, it does not distinguish among patients with differing severity of cachexia or identify those with particularly poor prognoses. Martin e*t al*. explored whether patients could be subdivided into groups based on BMI and reported weight loss at diagnosis to determine whether patients with greater weight loss had reduced survival; they identified five groups with differing expected survival that could be identified based on combinations of BMI and weight loss.[7]

In this study, we present a complementary approach to that used by Martin *et al*.[7] While they examined the consequences of cachexia in clinical datasets that included patients with heterogeneous tumours and self-reported weight loss, we identified a cohort of patients with non-small cell lung cancer (NSCLC) in an electronic medical records (EMR) database who had repeated measures of weight. For these patients, we could estimate the consequences of weight loss and BMI post-diagnosis on persistence in the database, which we have validated as a strong proxy for duration of survival (last interaction is within 60 days of death date at least 91% of the time; manuscript in preparation).

Materials and methods

Data source

Electronic medical records data were obtained from the IMS Health™ Oncology Database, which is an integrated database consisting of oncology EMR and additional data (medical/pharmacy claims and hospital charge data master records) for a subset of patients. The database contains de-identified biomedical data from more than 600 000 US cancer patients who received care from approximately 550 providers/facilities in 37 states. For this study, data were used from 2005 to December 2012.

Patient selection and timelines

The initial study cohort comprised patients aged ≥18 years with a diagnosis of lung cancer [International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) 162.1-162.9] as their only primary cancer diagnosis in a derived tumour type field. Those receiving treatment with a drug most commonly used for small-cell lung cancer (etoposide, irinotecan, or topotecan) were excluded in order to get a cleaner population that was primarily NSCLC, as were those with hospital records indicating surgical treatment that might influence weight (Current Procedural Terminology (CPT) codes 32035-32036, 32100-32160, 32200-32201, 32220-32225, 32310-32320, 32440-32540, 32651-32699, or any ICD-9 Vol. 3 Code 32.xx) for patients with linkage to hospital data.

The initial diagnosis of lung cancer was a patient's index date. Index dates were no later than 18 months before the end of the database. To be able to measure weight changes independently of survival, patients were required to have an initial weight measure within 2 months of index and at least one additional measure in the subsequent 3 months to show potential weight change; all patients were required to survive for at least 5 months after index to avoid immortal time bias. Patients with a single health system contact in their last 3 months in the database were excluded from the primary analysis because the survival proxy was deemed less reliable for these patients.

Weight and height measures

Patients' baseline weight was their first weight measure after their index date. Patients' maximum change from baseline was the difference between baseline and the lowest subsequent measure within 5 months of index. Patients with extreme baseline weights (below 100 lbs or above 250 lbs) were excluded as likely to display atypical weight change patterns. Patients with likely erroneous data (such as successive gains and losses of 20% of weight over a short period) were eliminated if not resolvable based on the overall record (<0.5% of patients). Patients in the database had on average 11 measures of weight.

Records indicating height <48 inches or >84 inches were excluded from analysis. Patients' height was determined based on the average of heights within 2 inches of the modal height (median if no mode existed), as long as no more than 25% of measures were outside of that window.

Time of death

Time of last appearance in the database was used as a proxy for time of death. For patients with last appearances close to the end of available data, typical interaction frequency was calculated for the 3 months before last appearance, and patients with less than twice their typical interaction frequency before the end of available data were censored.

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Table 1 Cohort attrition

	Patients excluded	% Excluded	Patients remaining
Lung cancer as sole primary cancer during study period	—	—	44 482
No use of drugs primarily associated with small-cell lung cancer	7107	16.0	37 375
No major surgery codes	1635	4.4	35 740
Survived for at least 5 months post-index	13 831	38.7	21 909
Patients at least 18 years old	2	0.0	21 907
Patients with weight measures	4965	22.7	16 942
Patients without uninterpretable weights	73	0.4	16 869
Patients with valid baseline weight (100–250 lb)	1497	8.9	15 372
Patients without other data abnormalities	3	0.0	15 369
Patients with valid height	390	2.5	14 979
Patients with >1 database interactions in last 3 months	2878	19.2	12 101

Identification of cachexia risk groups

A combination of analytical methods and judgement were used to determine weight loss and BMI categories. Initially, the population was divided along each dimension into 13 categories that balanced spreading the overall population, traditional breakpoints, and apparent inflection points in each curve. The 13 categories were clustered into six provisional groups for each dimension. All possible cluster combinations were tested in a Cox model with survival as the dependent variable and categorized BMI, categorized weight loss, and their interactions as dependent variables. The top 1000 combinations based on score and Akaike information criterion were used to determine most common strong breakpoints. The provisional groups were tested for potential improvements, such as by holding one dimension fixed and testing finer gradations along the other dimension. Final group determination included judgement regarding materiality of differences between closely related models and preferences for convenient breakpoints.

After determining estimates for median overall survival and 1-year survival for each weight loss/BMI combination, the 36 combinations were ordered by survival, and seven groups were created at natural breakpoints. When assembled into a grid, two of these groups that had scattered members were merged into their neighbours to create contiguous groups. Ambiguous choices were resolved by comparing alternatives using a log-rank test to evaluate similarity within and between cachexia risk groups.

Statistical methods

Baseline characteristics were described by groups. Median survival time and 1-year survival rate with 95% confidence interval (CI) were estimated by the Kaplan–Meier method. Multivariate Cox models were built to evaluate the effect of cachexia risk groups, and generalized likelihood-based R^2s were reported.[8] Where data were missing, an 'Unknown' categorical variable was used. The impact of explanatory variables was assessed by comparing likelihoods of models with all or a subset of variables based on Type III results from SAS PROC PHREG. Results were considered significant at the $P < 0.05$ level. Analysis was done in SAS (version 9.2, SAS Institute Inc., Cary, NC, USA).

Results

Cohort attributes

This study focused on patients in the IMS Health EMR with NSCLC who had a baseline weight measure in the first 2 months, additional weight measures in the subsequent 3 months, and survived for at least 5 months. While requiring 5 months of survival reduces generalizability, it permits multiple observations of weight while avoiding bias wherein longer survivors have more opportunity to lose weight. Table 1 shows cohort attrition for this study. 15 369 patients

Table 2 Cohort demographics

N	12 101
Age:	
Mean	66.9
>65	63%
% Male	52%
Race:	
Caucasian	48%
African American	6%
Other/unknown	46%
Cancer stage:	
Stage 1	5%
Stage 2	3%
Stage 3	12%
Stage 4	17%
Unknown	62%
Baseline BMI	26.3
Performance status:	
0	10%
1	14%
2+	4%
Unknown	71%

BMI, body mass index

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Table 3 Formation of cachexia risk groups

A

Median Survival (days)		Weight Loss (%)					
		<-14	-14 – -10	-10 – -7	-7 – -3	-3-0	>=0
BMI	<20	252	248	339	388	419.5	523
	20-23	242	322	366	400	534	599
	23-25	255	361	376.5	436	566	645
	25-27	260.5	314.5	333.5	488	610	746
	27-30	295	357	412	448	605	905
	>=30	279	390	425	502.5	548	835

B

% Surviving 1 Year		Weight Loss (%)					
		<-14	-14 – -10	-10 – -7	-7– -3	-3-0	>=0
BMI	<20	24.0%	28.4%	45.0%	54.0%	56.0%	64.1%
	20-23	28.7%	44.4%	50.2%	54.5%	69.1%	68.0%
	23-25	25.8%	48.0%	50.8%	58.6%	71.1%	71.7%
	25-27	31.8%	43.1%	46.4%	60.7%	72.4%	75.2%
	27-30	40.9%	48.4%	54.6%	61.6%	72.0%	79.5%
	>=30	31.4%	51.8%	57.2%	64.0%	69.8%	79.7%

C

	Cachexia Risk Group				
	Group 1	Group 2	Group 3	Group 4	Group 5
N	918	2209	4125	3711	1138
Median Survival (days)	263	356	457	583	825
95% CI	(254-274)	(342-372)	(440-473)	(559-611)	(768-908)
% Surviving 1 Year	31.4%	48.6%	59.4%	70.6%	78.3%
95% CI	(28.4-34.4%)	(46.5-50.7%)	(57.9-60.9%)	(69.1-72.0%)	(75.8-80.6%)
Within-Group Difference (p-value*)	0.1486	0.0876	0.0381	0.2061	0.3448

BMI, body mass index; CI, confidence interval
*Based on log-rank tests comparing Kaplan–Meier curves of the BMI/weight loss% cells comprising each cachexia risk group.

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met the primary requirements to be included in this study; 14 979 of these also had valid BMI measures. The cohort was further limited to the 12 101 patients who had more than one database contact in their final 3 months, which was important for accuracy of the death date proxy.

Table 2 shows patient characteristics for the study cohort. Most patients in this study with known stage had advanced or metastatic cancer at baseline.

Clustering patients

To understand what levels of weight loss led to meaningful differences in outcomes for patients, we clustered patients by baseline BMI and weight loss. Initially, we examined the two variables independently. When patients were divided into 20 successive groups of 606 patients for each variable, there was a nearly continuous increase in survival with each variable, with weight loss having a steeper slope. Median survivals ranged from a low of 387 days to a high of 559 days for BMI groups and from a low of 263 days to a high of 726 days for weight loss groups.

Patients were assigned to six continuous groups for each variable, with breakpoints chosen to provide the best joint fit for survival data. The 36 groups created by combining these two parameters were then merged into five groups that represented different levels of cachexia risk based on outcomes (see methods). Tables 3A and 3B show survival for the 36 individual groups, while Table 3C summarizes values for the five cachexia risk groups. Differences within groups were marginally significant or non-significant, while the difference among groups was highly significant ($P < 0.0001$). As was suggested by the cachexia consensus definition,[6] baseline BMI is most significant when it is low (<20). Weight loss impacts survival more broadly, and patients with any weight loss have worse prognosis than patients with none.

Table 4 shows patient characteristics for the five groups. Relative to the overall cohort, the higher risk cohorts showed a higher percentage of patients with late-stage disease. Surprisingly, they also tended to be a bit younger, perhaps indicating a tendency towards more aggressive disease in younger patients. While lower baseline BMI was associated with worse outcomes by itself, the stronger influence of weight loss on survival led to clustering of groups with diverse baseline BMI that obscured this effect.

Figure 1 shows Kaplan–Meier survival curves for the cachexia risk groups; the five groups show consistent well-

Table 4 Cohort demographics

	Overall $N = 12\ 101$	Group 1 $N = 918$	Group 2 $N = 2209$	Group 3 $N = 4125$	Group 4 $N = 3711$	Group 5 $N = 1138$	*P*-value
Stage							<.0001
1	5%	1.7%	3.2%	4.6%	6.2%	11.4%	
2	3%	2.7%	3.1%	3.4%	3.1%	3.3%	
3	12%	15.4%	14.6%	13.8%	10%	7%	
4	17%	27.3%	20.2%	18.2%	13.6%	11.0%	
Unknown	62%	52.8%	58.9%	59.9%	67.5%	67.4%	
Gender							0.026
Male	52%	56.5%	53.9%	51.9%	51.2%	51.9%	
Age							<.0001
Mean(SD)	66.86(10.0)	63.70(10.11)	66.35(10.02)	67.19(10.01)	67.41(10.01)	67.36(9.34)	
Age Groups							
≤50	7.4%	11.4%	8.2%	6.9%	7.2%	4.8%	<.0001
≥65	62.8%	49.2%	61.0%	64.0%	65.2%	64.5	<.0001
≥80	7.8%	3.8%	6.1%	8.4%	9.1%	7.7	<.0001
Age ranges							<.0001
≤50	6.1%	8.7%	6.7%	5.7%	6.3%	4.0%	
50–54	7.2%	12.1%	7.5%	7.0%	6.3%	6.1%	
55–59	10.1%	12.9%	9.9%	10.4%	8.9%	10.8%	
60–64	13.9%	17.1%	14.9%	13.0%	13.3%	14.6%	
65–69	18.3%	17.8%	18.3%	17.7%	18.7%	19.6%	
70–74	17.1%	14.7%	17.8%	17.3%	16.8%	18.0%	
75–79	19.6%	13.0%	18.8%	20.6%	20.6%	19.2%	
≥80	7.8%	3.8%	6.1%	8.4%	9.1%	7.7%	
BMI							<.0001
Mean(SD)	26.25(5.55)	25.85(5.05)	24.51(4.52)	26.57(5.22)	25.99(4.39)	29.66(4.0)	
Weight loss							<.0001
Mean(SD)	−4.8(4.91)	−17.2(3.56)	−9.6(2.56)	−4.7(2.66)	−0.7(2.05)	1.5(1.97)	
PS							<.0001
0	10.1%	10.8%	9.7%	10.4%	9.9%	10.1%	
1	14.4%	19.6%	17.3%	15.0%	12.0%	10.1%	
2+	4.3%	6.2%	4.9%	4.5%	3.2%	4.1%	
Unknown	71.2%	63.4%	68.2%	70.1%	75.0%	75.7%	

PS, performance status; BMI, body mass index; SD, standard deviation

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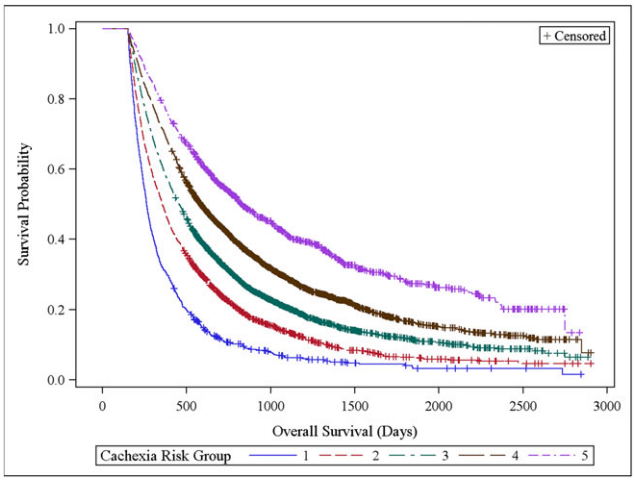
Figure 1 Kaplan–Meier survival curves for the cachexia risk groups.



separated risk profiles across time, indicating that the cachexia risk groups are important prognostic factors. We next built Cox models for survival using baseline variables and/or cachexia risk groups as explanatory variables. As shown in Table 5, a model including all variables shows that the cachexia risk groups are highly significant variables. The overall model R^2 is 12.88%, while reduced models with only the cachexia risk groups or baseline variables have R^2 of 7.51% and 6.82% respectively, showing that the cachexia groups appear to have comparable and relatively independent explanatory power to the combination of age, disease stage, gender, performance status, and index year in this dataset. By comparison, a similar model using baseline covariates and the weight loss criteria from Fearon et al. (5% weight loss or 2% for patients with a BMI less than 20) [6] would give an overall model R^2 of 10.34%, 4.65% for the cachexia definition alone.

Discussion

In this retrospective analysis of 12 101 NSCLC patients from an EMR database, patients with greater weight loss during the 5 months post-baseline were found to have worse outcomes based on a strong proxy, time of last appearance of patient in the database. Lower BMI at baseline was found to influence survival, but to a lesser extent than weight loss. While the current definition of cachexia focuses on patients with at least 5% weight loss (or 2% with low BMI),[6] patients with any weight loss were found to have decreased survival in this study, and patients with low BMI had worse outcomes than patients with higher BMI even without weight loss. Weight loss before index visit may have occurred for some of these patients.

This study demonstrates that patient risk from cachexia-associated issues is a continuum and that progressively

Table 5 Impact of cachexia *risk* and baseline covariates on survival

Parameter	Parameter estimate	Standard error	χ^2	Pr > χ^2	Hazard ratio
Cachexia risk group					
Group 2	−0.40219	0.04136	94.5564	<.0001	0.669
Group 3	−0.68086	0.03881	307.7984	<.0001	0.506
Group 4	−0.91881	0.04009	525.2395	<.0001	0.399
Group 5	−1.22537	0.05186	558.3554	<.0001	0.294
Age (years)					
50–54	0.08704	0.05623	2.3960	0.1216	1.091
55–59	0.15019	0.05268	8.1287	0.0044	1.162
60–64	0.10005	0.04995	4.0115	0.0452	1.105
65–69	0.01674	0.04828	0.1202	0.7288	1.017
70–74	0.13756	0.04857	8.0219	0.0046	1.147
75–79	0.18529	0.04768	15.0985	0.0001	1.204
80+	0.27174	0.05766	22.2132	<.0001	1.312
Cancer stage					
Stage 2	0.21886	0.07878	7.7175	0.0055	1.245
Stage 3	0.46406	0.05964	60.5351	<.0001	1.591
Stage 4	0.87405	0.05727	232.8877	<.0001	2.397
Stage unknown	0.52818	0.05409	95.3547	<.0001	1.696
ECOG performance Status					
1	0.09681	0.04172	5.3852	0.0203	1.102
2+	0.44530	0.05741	60.1626	<.0001	1.561
Unknown	0.03171	0.03614	0.7697	0.3803	1.032
Gender					
Female	−0.27534	0.02077	175.6681	<.0001	0.759
Index year					
2005–2008	0.19198	0.02235	73.8012	<.0001	1.212

Reference groups were Cachexia Risk Group 1, age < 50, Stage 1, PS 0, male, and index year 2009 + . ECOG, Eastern Cooperative Oncology Group.

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higher levels of weight loss are associated with worsening prognosis. These results were statistically significant and substantial in magnitude, with median survival for patient cohorts ranging from 263 days to 825 days from index, with all patients required to survive 150 days to be included in this study.

These results were generally consistent with those reported by Martin *et al*.[7] but suggested a much stronger impact of weight loss than baseline BMI. This may be a consequence of using actual weight measures instead of self-reported historical weight loss, reducing variability in weight-loss measures. In addition, historical weight loss is correlated with post-weight-loss BMI, obscuring the relative impact of these two variables.

This study has limitations. First, data were derived from an EMR database and were often incomplete. Second, the patient cohort may have been biased by the selection criteria, including proxy measures that may not have completely removed small-cell lung cancer patients, may have selectively removed some types of patients (high weight and radiation treatment with etoposide) and the requirement that all patients survive for at least 5 months from index. Third, the requirement for patients to have more than one visit in the last 3 months in the database may limit generalizability. Fourth, patient weight loss before index was unknown, as were any efforts to provide supplemental nutrition to mitigate weight loss. Finally, time of death was estimated based on a proxy, time of last appearance in the database.

Conclusions

Patients with NSCLC were divided into five groups based on initial BMI and early weight loss, with boundaries based on clustering groups of patients with similar outcomes. Increasing weight loss and, to a lesser extent decreasing BMI, is significantly associated with worse outcomes independent of other variables. These factors provide an improved approach for characterizing cachexia risk over the initial presence/absence of cachexia described by Fearon *et al*.[6]

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The authors certify that they comply with the ethical guidelines for authorship and publishing of the *Journal of Cachexia, Sarcopenia and Muscle*.[9]

Conflict of interest

Karin Benoit, Li Li, and Daniel Mytelka are employees and minor shareholders of Eli Lilly and Company.

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