Memorial Sloan Kettering Cancer Center

Validating Cancer Modulated Allostatic Load as a Composite Biomarker for Mortality in Patients with Cancer

#6123

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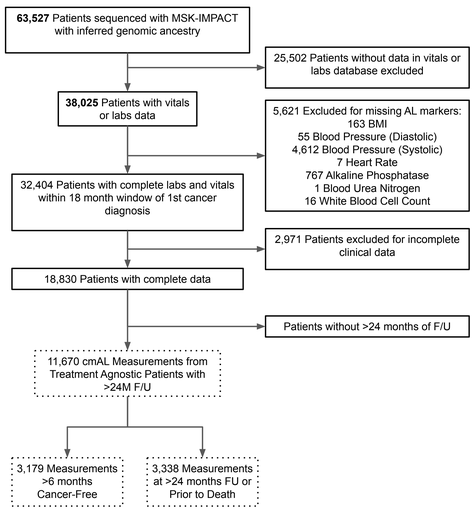
Research Summary

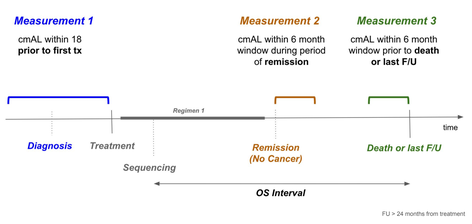
- Allostatic load (AL) is the cumulative burden of chronic stress and life events typically measured by lab and vital values routinely collected during standard care. AL has been associated with adverse socioenvironmental stressors and increased mortality rates including risk of cancer death.
- Despite modifications of AL as a result of progressing cancer and anti-cancer treatments, cancer-modulated allostatic load (cmAL) may serve as a valuable biomarker for cancer outcomes, and highlight similar disparities across sociodemographic groups agnostic of a history of cancer diagnosis.
- Recent investigations have shown associations of cmAL with overall mortality rates in patients with non-small cell lung cancer (NSCLC) and breast cancer, as well as various social determinants of health. The impact of cmAL on different malignancies, particularly in the context of genetic variations identified through genomic profiling, is yet to be thoroughly investigated.
- Previous studies have been confined largely to specific cancer types, predominantly breast cancer and NSCLC. These studies revealed that higher allostatic load is associated with elevated mortality rates and poor tumor characteristics, suggesting an intricate relationship between chronic stress, physiological dysregulation, and disease prognosis. However, these findings necessitate further expansion of cancer types, thus enabling a comprehensive understanding of the impact of AL across different malignancies.
- Our research focuses on investigating the influence of cmAL on cancer outcomes from patients sequenced with MSK-IMPACT genomic profiling. We hypothesize that markers measuring AL can collectively be used as biomarker for prognosis and tumor genetics, affecting across various cancer types, including but not limited to NSCLC, colorectal, breast, prostate, ovarian, and pancreatic cancers. Through statistical models that account for confounders like age, sex, and comorbidities, we offer a comprehensive view of the intricate relationship between cmAL and cancer outcomes.

Methods

Consort Diagram



Patient Timeline and Allostatic Load Measurements



We measure cmAL using 10 standard biomarkers reflecting the functioning of four physiological systems: cardiovascular, metabolic, renal, and immune.[2][4] The cmAL biomarkers below were obtained from patient records collected during various timepoints (Timeline), where measurement 1 is our reference measurement, collected prior to the first treatment.

For each biomarker, a score of 1 was assigned if the value fell beyond the defined threshold, indicating physiological dysregulation. A composite AL score was then calculated by summing these scores. The range for the composite AL score was 0 to 10, with higher scores suggesting a higher degree of physiological dysregulation.

After calculating AL, the composite AL scores were divided into quartiles and medium for further analysis. [2] Survival analysis was performed to examine the relationship between AL and patient demographics, genomic data, and comorbidities. This allowed for a detailed study of correlations between physiological stress and patient survival, providing important insights into disease pathophysiology and patient prognosis.

To gather clinical and genomic data, we developed a pipeline consisting of structure clinical data (e.g. Tumor markers, vitals demographics) and NLP derived variables such as prior outside treatments and presence of cancer.

Markers for Composite Allostatic Load Score

cmAL Marker	Physiological System	Marker Description
Heart rate	Cardiovascular System	Elevated heart rate may indicate cardiovascular strain due to anxiety or heart disease.
Systolic blood pressure	Cardiovascular System	High systolic blood pressure signals hypertension and increases risk of stroke, heart disease, and kidney function.
Diastolic blood pressure	Cardiovascular System	High diastolic blood pressure indicates sustained pressure in arteries during heart rest, potentially hindering oxygen delivery to the heart muscles.
Body Mass Index	Metabolic System	BMI measures metabolic regulation. A high BMI often indicates obesity, linked to health issues like heart disease, diabetes, and certain cancers.
Alkaline phosphatase	Metabolic System	ALP enzyme catalyzes essential bodily processes. Elevated levels may indicate liver disease or bone disorders.
Blood glucose	Metabolic System	High blood sugar may signal insufficient insulin production by the pancreas, crucial for regulating healthy blood sugar levels.
Albumin	Metabolic System	Albumin, a plasma protein synthesized by the liver, serves as a marker for nutritional status. Reduced levels may indicate kidney or liver disease, or inflammation.
Creatinine	Renal System	Creatinine, a byproduct of creatine, which fuels muscle energy, is entirely eliminated by the kidneys.
Blood Urea Nitrogen	Renal System	Healthy kidneys filter urea and eliminate waste from the blood.
White blood cell count	Immune System	Low WBC can signal autoimmune disorders or severe stress, while high WBC may result from smoking or inflammatory diseases like RA. Additionally, cancer and its treatments can alter WBC levels.

Results

Stage, Comorbidities, Ancestry, and Socioeconomic Factors are associated with cmAL

Patient Characteristics

Demographic Characteristics	Overall, N = 11,664[1]	Low Allostatic Load, N = 7,487[1]	High Allostatic Load, N = 4,177[1]	p-value[2]
Cancer Type				<0.001
Non-Small Cell Lung Cancer	1,633 (100%)	1,019 (62%)	614 (38%)	
Breast Cancer	1,182 (100%)	991 (84%)	191 (16%)	
Colorectal Cancer	1,451 (100%)	936 (65%)	515 (35%)	
Ovarian Cancer	884 (100%)	512 (58%)	372 (42%)	
Prostate Cancer	641 (100%)	461 (72%)	180 (28%)	
Pancreatic Cancer	621 (100%)	249 (40%)	372 (60%)	
Gender				<0.001
Female	6,481 (100%)	4,427 (68%)	2,054 (32%)	
Male	5,183 (100%)	3,060 (59%)	2,123 (41%)	
Ancestry				<0.001
EUR	8,802 (100%)	5,594 (64%)	3,208 (36%)	
AFR	563 (100%)	329 (58%)	234 (42%)	
EAS	682 (100%)	516 (76%)	166 (24%)	
SAS	238 (100%)	161 (68%)	77 (32%)	
ADM	1,332 (100%)	855 (64%)	477 (36%)	
Stage at Diagnosis				<0.001
1	1,956 (100%)	1,393 (71%)	563 (29%)	
2	2,197 (100%)	1,426 (65%)	771 (35%)	
3	3,324 (100%)	2,206 (66%)	1,118 (34%)	
4	4,187 (100%)	2,462 (59%)	1,725 (41%)	
Deceased	3,862 (100%)	2,173 (56%)	1,689 (44%)	<0.001
TMB High	1,540 (100%)	941 (61%)	599 (39%)	0.007
Received Immunotherapy	2,979 (100%)	1,830 (61%)	1,149 (39%)	<0.001
Received Targeted Therapy	3,111 (100%)	1,925 (62%)	1,186 (38%)	0.002
Age at Treatment	62 (52, 70)	60 (50, 69)	65 (56, 71)	<0.001
Smoking History				<0.001
Former/Current Smoker	5,085 (100%)	3,107 (61%)	1,978 (39%)	
Never	6,268 (100%)	4,198 (67%)	2,070 (33%)	
Insurance				0.8
Not Medicaid	10,826 (100%)	6,955 (64%)	3,871 (36%)	
Medicaid	796 (100%)	507 (64%)	289 (36%)	
Yost Index				0.001
Q1	2,865 (100%)	1,913 (67%)	952 (33%)	
Q2	2,942 (100%)	1,895 (64%)	1,047 (36%)	
Q3	2,772 (100%)	1,776 (64%)	996 (36%)	
Q4	2,858 (100%)	1,763 (62%)	1,095 (38%)	

Comorbidities

Comorbidities Characteristics	Overall, N = 11,664[1]	Low Allostatic Load, N = 7,487[1]	High Allostatic Load, N = 4,177[1]	p-value[2]
Multiple Comorbidities	1,670 (100%)	740 (44%)	930 (56%)	<0.001
Diabetes	1,726 (100%)	734 (43%)	992 (57%)	<0.001
Heart Failure	247 (100%)	110 (45%)	137 (55%)	<0.001
Myocardial Infraction	383 (100%)	201 (52%)	182 (48%)	<0.001
Renal Disease	488 (100%)	132 (27%)	356 (73%)	<0.001
Liver Disease	1,464 (100%)	835 (57%)	629 (43%)	<0.001
Peripheral Vascular Disease	478 (100%)	239 (50%)	239 (50%)	<0.001
Chronic Pulmonary Disease	1,854 (100%)	1,091 (59%)	763 (41%)	<0.001
Cerebrovascular Disease	247 (100%)	131 (53%)	116 (47%)	<0.001
Peptic Ulcer Disease	224 (100%)	133 (59%)	91 (41%)	0.13
Hemiplegia or Paraplegia	58 (100%)	24 (41%)	34 (59%)	<0.001
HIV or AIDS	23 (100%)	14 (61%)	9 (39%)	0.7
Dementia	28 (100%)	14 (50%)	14 (50%)	0.12

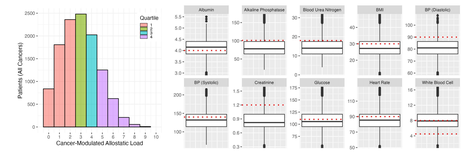
Thresholds: Heart rate ≥ 90 beats/min ; Blood pressure (systolic) ≥ 140 mmHg ; Blood pressure (diastolic) ≥ 90 mmHg ; Body mass index ≥ 30 kg/m ; Alkaline phosphatase: >101 ; Blood glucose: ≥ 110 ; Albumin: < 4 ; Creatinine: > 1.2 ; Blood Urea Nitrogen:≥ 18 ; White blood cell count: <4.5 and >8

[1] n (%)

[2] Pearson's Chi-squared test

Dynamic Changes in cmAL Over Cancer Trajectory

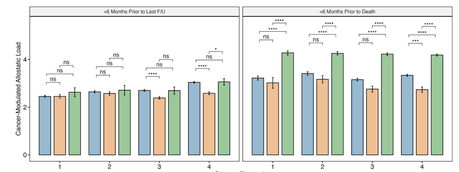
Pre-treatment cmAL Measurements



Histogram of patient distribution across cmAL scores and quartiles

Boxplots for biomarkers with reference line for corresponding cutoffs

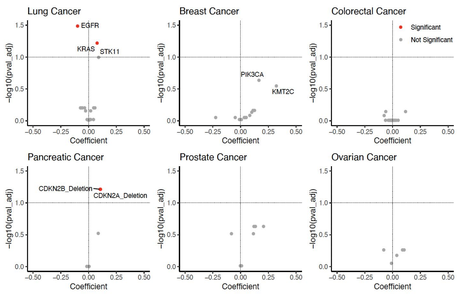
Measurements Over Patient Timeline



1. Pretreatment measurements for patients with >24 months FU: 11,603
2. Measurements during >6 months Cancer-Free: 3,163
3. Measurements at >24 months FU: 3,336

Bar graphs showing cmAL at different stages: Prior to treatment, during remission, and prior to last follow up or death

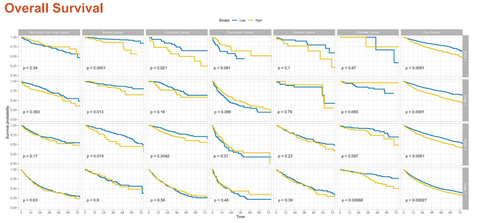
cmAL are associated with driver alterations



Volcano plots for genetic mutations in six different cancer types, with gene names displayed for those with a p-value less than 0.05. Points in red indicate genes with an FDR less than 0.1.

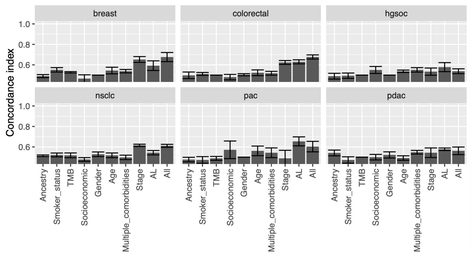
cmAL a Biomarker for Mortality in Patients with Cancer

Overall Survival



Kaplan-Meier survival curves comparing high and low allostatic load across four stages of breast, colorectal, non-small cell lung, and pancreatic cancer, with p-values indicating the statistical significance of the differences between the two groups.

Random Survival Forest



Barplots showing concordance index from multiple random survival forest models with 5-fold cross validation across cancer types. Models include individual variables (ie only stage, only gender, only cmAL, etc.) and all variables combined.

Biomarkers in cmAL drive the association with survival

Heatmap depicting the feature importance of individual cmAL component across different types of cancer.

Conclusion

- Elevated cmAL, linked to adverse outcomes, has been observed especially in males, advanced cancer stages patients, and those from a lower socioeconomic status.
- A range of comorbidities, whether multiple or singular, are strongly associated with higher cmAL.
- Measurements of cmAL changes over the course of cancer progression and remission, where patients in remission have lower cmAL relative to baseline, significant elevations when measured within 6 months prior to death.
- cmAL is found to correlate with an increased incidence of alterations in certain genomic biomarkers, such as EGFR and KRAS in NSCLC.
- Higher cmAL is associated with a poorer prognosis across diverse cancer types, a finding consistent across all stages of cancer.
- cmAL shows prognostic value when compared to other markers in different cancer types
- Individual biomarkers display variable contributions to the composite allostatic load score depending on the cancer type, with alkaline phosphatase and albumin emerging as consistently significant across various malignancies, suggesting their robustness as stress response indicators.
- Future work involves refining the cmAL data pipeline with cohort growth, extending the use of AL as a prognosis tool across cancer types, and investigating the intricate relationships between AL, genomic alterations, and cancer prognosis.

References

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