AWARD NUMBER: W81XWH-20-1-0785

TITLE: A Novel Risk Prediction Model for Checkpoint Inhibitor-Related Autoimmune Toxicities

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CONTRACTING ORGANIZATION: Veterans Research and Education Foundation, St. Louis, MO

REPORT DATE: August 2021

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
August 2021	ANNUAL	01Aug2020-31Jul2021

4. TITLE AND SUBTITLE

A Novel Risk Prediction Model for Checkpoint Inhibitor-Related Autoimmune Toxicities

5a. CONTRACT NUMBER
W81XWH-20-1-0785

5b. GRANT NUMBER
CA191184

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER
0011468903

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) AND ADDRESS(ES)

Veterans Research and Education Foundation of St Louis
501 N Grand Blvd
St. Louis, MO 63103

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Recent research has shown the effectiveness of immunotherapy treatments in managing patients with both incurable and curable cancers. These immune checkpoint inhibitor treatments turn the patient's immune system against cancer cells, resulting in impressive and long-lived responses to cancer treatment in many patients. While incredibly effective for some, these treatments do not work for all patients and they are unfortunately associated with toxicities arising from the immune system attacking the patient's own body. So-called autoimmune toxicities can range from mild and self-limited, to severe and life threatening. The research reviewed here examines predictive features of these autoimmune toxicities. The goal is the development of a risk prediction model for autoimmune toxicities from cancer immunotherapy, with secondary goals examining the impact on survival from these immunotherapy induced autoimmune events and predictors of overall survival among cancer patients receiving immunotherapy.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	25	19b. TELEPHONE NUMBER *(include area code)*

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1. Introduction:

Immune checkpoint inhibitors (ICI) have revolutionized cancer therapy over the past decade. With extensive Federal Drug Administration (FDA) approvals in numerous cancer diagnoses, the impact of these therapies has been substantial. While effective and safe for some patients, the majority of those treated will not respond to ICI therapy, and therapy can be associated with substantial and life-changing autoimmune toxicities. The risk of treatment related autoimmune toxicities is currently described by clinical trials that were underpowered to detect their true incidence, and limited knowledge is known about relative risks of these toxicities among patients starting immunotherapy treatments. Additional knowledge of the risks of these autoimmune complications is needed, and validated tools to predict risks for an individual patient are crucial to ongoing counseling and treatment of individual patients. This grant's goal is to develop a risk prediction model for autoimmune toxicities related to ICI among cancer patients. Additional goals aim to better understand the impact of autoimmune toxicities on survival in cancer patients receiving ICI as well as better describe real-world rates of toxicities.

Objective: The objective of the proposed research is the development of a validated risk prediction tool for checkpoint inhibitor related autoimmune toxicities.

Specific Aims:

Aim 1 – To describe rates of autoimmune toxicities within a real-world patient dataset across multiple tumor types. We will utilize a large patient dataset from the VHA and WUSTL to describe observed rates of irAEs amongst patients receiving checkpoint inhibitors.

Aim 2 – To develop a risk prediction model for grade 3-4 immune related adverse events in patients receiving immunotherapy. We plan to utilize a large patient database from the VHA and WUSTL to develop a prediction model for immunotherapy toxicities.

Aim 3 – To assess the association between grade 3-4 immune related adverse events and clinical outcomes in patients receiving immunotherapy. We will conduct analyses of immune checkpoint inhibitor toxicity and its impact on PFS and OS amongst cancer patients treated with immune checkpoint inhibitors.

Study Design: This is a retrospective cohort study that is utilizing a large patient dataset of ICI recipients through the Veteran Affairs Health Administration and a second data set from Washington University in St. Louis. Rates of ICI toxicities are being assessed utilizing both datasets, and legacy as well as machine learning techniques will be utilized to determine the optimal risk prediction model for the development of autoimmune toxicities.

Impact: The research proposed is innovative and important for several reasons. (1) It will provide vital information about rates of ICI toxicities in a racially and economically diverse population. (2) It will develop and validate a crucial risk prediction tool that will help inform patients and physicians as to the relative risks of ICI related autoimmune toxicities. (3) It will investigate the relationships between toxicities and outcomes amongst ICI recipients, an evolving area of research. These findings will directly inform and impact patient care in an immediate manner, improving the management and outcomes of many cancer patients

2. Keywords

Immunotherapy, Cancer, Autoimmune, Immune related adverse events, Checkpoint inhibitors, Oncology, Immunology, Outcomes Research, Machine Learning, Regression analysis.

3. Accomplishments

We achieved final Department of Defense Institutional Review Board approval on 11/23/2020 (a delay from anticipated approval). As such, work on the grant commenced only after this date. The accomplishments over the past 9 months for the grant are listed below, and are laid out using the approved Statement of Work as an outline.

MAJOR TASK 1: *Regulatory Approval and Credentialing*

Task Overview: All necessary regulatory approvals have been obtained. There were initial delays in obtaining Department of Defense IRB/HRPO approval, but these were obtained on 11/23/2020. Initial annual reviews have been completed at participating sites.

- ***Subtask 1: IRB Approvals at WUSTL and STLVAMC***
    - This has been completed prior, all approvals obtained/established by August 2020
- ***Subtask 2: VA WoC Appointments for WUSTL collaborators***
    - This has been completed for key investigators, and for a collaborating team of chart abstractors (Washington University Resident Physicians). However, some team members have not necessitated a without compensation appointment at the St. Louis VA Medical Center (Inez Oh, PhD and Randi Foraker, PhD).
- ***Subtask 3: Data sharing arrangements for WUSTL and STLVAMC***
    - This has been delayed at the present time after regulatory concerns were raised. The sharing of data at this time in the grant is not necessary and we have pushed forward with alternate aims of the grant. Potential workarounds for this component of the grant have been developed (model sharing instead of data sharing).
- ***Subtask 4: Coordinate with sites for annual IRB approval, continuing review annually***
    - Initial annual review is approved at the St. Louis VA Medical Center.
    - Washington University in St. Louis initial annual review is approved.
- ***Subtask 5: HRPO review/approval of IRB protocols***
    - HRPO approval reviews completed at all sites and DOD.

MAJOR TASK 2: *Analysis of VA and WUSTL data to obtain rates of autoimmune toxicities*.

Task Overview: The analysis of the dual datasets at the St. Louis Veterans Affairs Medical Center and Washington University is ongoing. Several key tasks have already been completed. The initial plan to utilize ICD Codes to identify toxicities has been employed with success, however a recent publication has raised potential complications to this approach. In an article entitled *Comparative assessment of manual chart review and ICD claims data in evaluating immunotherapy-related adverse events* by *Nashed, Zhang, et al*, a curated list of ICD codes was found to be ineffective at capturing autoimmune toxicity events among cancer patients receiving immunotherapy. As such, the abstraction of charts has become a significantly more important component of the study. This will add additional time, and has delayed some components of the tasks below. However, the current approach is to define the autoimmune events within a subset of patients by chart review and determine if pharmacy records can be utilized to quickly identify autoimmune events via evidence of

steroid prescriptions. If this can be shown, it will be a valuable and important contribution to the literature. Data obtained from ICD Code diagnosis and prednisone prescription methods will be reviewed below as the current status stands.

- ***Subtask 1: Identify ICD9/10 codes for autoimmune toxicities of interest***
  - Based off a study through Ohio State University and our own analysis, we have identified a comprehensive list of candidate ICD codes for autoimmune toxicities of interest. Key autoimmune toxicities that would routinely result in alteration of therapy and administration of steroid therapy were chosen. Broadly these fall into three main groups, including Pulmonary, Hepatic and GI (colitis) events. These are all listed below via table form, in significant detail, within Table 1, 2 and 3:

Table 1: Pneumonitis/Pulmonary Autoimmune ICD Toxicity Codes

Pneumonitis Diagnosis	ICD10	ICD9	Pneumonitis Diagnosis	ICD10	ICD9	Pneumonitis Diagnosis	ICD10	ICD9
Drug induced pneumonitis	J70.4	508.8	Dyspnea	R06.2	786.07	Chronic respiratory failure, with hypercapnia	J96.12	518.8
Acute drug-induced interstitial lung disorders	J70.2	508.8	Chest pain on breathing	R07.1	786.52	Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia	J96.20	518.5
Pneumonitis due to inhalation of other solids and liquids	J69.8	507.8	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia	J96.00	518.51	Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia	J96.20	518.8
Cough	R05	786.2	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia	J96.00	518.81	Acute and chronic respiratory failure, with hypoxia	J96.21	518.5
Dyspnea, unspecified	R06.00	786.1	Acute respiratory failure, with hypoxia	J96.01	518.51	Acute and chronic respiratory failure, with hypoxia	J96.21	518.8
Orthopnea	R06.01	786	Acute respiratory failure, with hypoxia	J96.01	518.81	Acute and chronic respiratory failure, with hypercapnia	J96.22	518.5
Shortness of breath	R06.02	786.1	Acute respiratory failure, with hypercapnia	J96.02	518.51	Acute and chronic respiratory failure, with hypercapnia	J96.22	518.8
Acute respiratory distress	R06.03	518.8	Acute respiratory failure, with hypercapnia	J96.02	518.81	Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia	J96.90	518.8
Acute respiratory distress	R06.03	770.9	Chronic respiratory failure, unspecified whether with hypoxia or hypercapnia	J96.10	518.83	Respiratory failure, unspecified, with hypoxia	J96.91	518.8
Other forms of dyspnea	R06.09	786.1	Chronic respiratory failure, with hypoxia	J96.11	518.83	Respiratory failure, unspecified, with hypercapnia	J96.92	518.8

Table 2: Hepatic Autoimmune ICD Toxicity Codes

Hepatitis Realated Diagnosis	ICD10	ICD9	Hepatitis Related Diagnosis	ICD10	ICD9
Autoimmune hepatitis	K75.4	571.42	Hepatic sclerosis	K74.1	571.9
Nonspecific reactive hepatitis	K75.2	573.3	Hepatic fibrosis with hepatic sclerosis	K74.2	571.9
Other chronic hepatitis, not elsewhere classified	K73.8	571.49	Primary biliary cirrhosis	K74.3	571.6
Hepatic failure, unspecified with coma	K72.91	572.2	Secondary biliary cirrhosis	K74.4	571.6
Hepatic failure, unspecified with coma	K72.91	572.8	Biliary cirrhosis, unspecified	K74.5	571.6
Hepatic failure, unspecified without coma	K72.90	572.8	Unspecified cirrhosis of liver	K74.60	571.5
Acute and subacute hepatic failure without coma	K72.00	570	Other cirrhosis of liver	K74.69	571.5
Acute and subacute hepatic failure with coma	K72.01	570	Toxic liver disease with hepatic necrosis, without coma	K71.10	573.3
Acute and subacute hepatic failure with coma	K72.01	572.2	Toxic liver disease with hepatic necrosis, with coma	K71.11	572.2
Inflammatory liver disease, unspecified	K75.9	573.3	Toxic liver disease with hepatic necrosis, with coma	K71.11	573.3
Toxic liver disease with acute hepatitis	K71.2	573.3	Nonspecific elevation of levels of transaminase and lactic acid dehydrogenase	R74.0	790.4
Liver disorders in diseases classified elsewhere	K77	573.8	Obstruction of bile duct	K83.1	576.2
Hepatic fibrosis	K74.0	571.5	Disorder of bilirubin metabolism, unspecified	E80.7	277.4

Table 3: GI Autoimmune ICD Toxicity Codes

Colitis	ICD10	ICD9	Colitis	ICD10	ICD9
Toxic gastroenteritis and colitis	K52.1	558.2	Eosinophilic gastritis or gastroenteritis	K52.81	535.71
Other specified noninfective gastroenteritis and colitis	K52.89	558.9	Eosinophilic gastritis or gastroenteritis	K52.81	558.41
Other specified noninfective gastroenteritis and colitis	K52.89	787.91	Eosinophilic colitis	K52.82	558.42
Indeterminate colitis	K52.3	558.9	Collagenous colitis	K52.831	558.9
Gastroenteritis and colitis due to radiation	K52.0	558.1	Lymphocytic colitis	K52.832	558.9
Toxic gastroenteritis and colitis	K52.1	558.2	Other microscopic colitis	K52.838	558.9
Food protein-induced enterocolitis syndrome	K52.21	558.3	Microscopic colitis, unspecified	K52.839	558.9
Food protein-induced enteropathy	K52.22	558.3	Noninfective gastroenteritis and colitis, unspecified	K52.9	558.9
Other allergic and dietetic gastroenteritis and colitis	K52.29	558.3	Diarrhea	R19.7	787.91
Other allergic and dietetic gastroenteritis and colitis	K52.29	787.91	Unspecified abdominal pain	R10.9	789
Eosinophilic gastritis or gastroenteritis	K52.81	535.7	Melena, blood in stool	K92.1	578.1
Mucus in stool	R19.5	787.7			

Subtask 2: Evaluate pharmacy data to identify patients receiving steroids

- We have identified within both our Veterans Affairs Dataset and the Washington University in St. Louis dataset those patients receiving an outpatient prescription of Prednisone (steroid-therapy) following an initial dose of a checkpoint inhibitor up to 6 months after their final dose of a checkpoint inhibitor. These numbers and details are presented below:

Table 4: Checkpoint inhibitor administered and Number of patients receiving prednisone in Washington University Dataset

Medication Administered	Number of Patients	Patients Receiving Prednisone
Pembrolizumab	695	82
Nivolumab	1078	157
Ipilimumab	333	79
Totals:	2106	318

Table 5: Patient Diagnosis and Toxicity Identification by ICD Code and Prednisone Prescription from Washington University

Cancer Type	Number of Patients Receving Prednisone
Neuroendocrine	9
Lung	91
Esophageal	8
Stomach	5
Head and Neck	33
Kidney	21
Liver	11
Melanoma	72
Colorectal	19
Hodgkin Lymphoma	9
Breast	19
Bladder	6

Table 6: Patient Diagnosis, Toxicity Identification by ICD Code alone from VA

Diagnosis	Number of Patients	Colitis	Regional Enteritis	Hepatitis	Renal Toxicity	Pneumonitis
Esophageal Cancer	65	9	0	0	8	7
Trachea/Bronchus/Lung	1991	190	2	25	253	155
Stomach/Gastric	30	6	0	1	1	3
Head and Neck Cancer	364	37	0	2	48	38
Colon Cancer/Rectal CA	79	14	1	1	15	4
Liver Cancer	219	26	0	8	44	7
Bladder Cancer	364	42	1	6	101	22
Kidney Cancer	286	35	3	7	56	13
Melanoma	399	45	2	5	55	14
Breast Cancer	0	0	0	0	0	0
Neuroendocrine	46	6	0	0	8	1
Hodgkin Lymphoma	8	1	0	0	3	1
Total:	3851					

These results are outlined in Tables 4, 5, 6 and 7. Table 4 provides a brief overview of varieties of checkpoint inhibitor administered and the numbers of patients within each group receiving prednisone (potential autoimmune toxicities) within the Washington University dataset. Within Table 5, the diagnoses and toxicity rates (by Prednisone prescription) are outlined from Washington University. Table 6 outlines the toxicities identified via ICD toxicity codes, broken down into particular toxicities by organ system affected. Finally, within Table 7, the close correlation of ICD code toxicities with prednisone prescriptions are outlined and the variety of diagnoses contained within the VA database is reviewed.

Table 7: Patient Diagnosis, Drug Therapy and Toxicity Identification by ICD Code and Prednisone Prescription from VA

Diagnosis	Number of Patients	Toxicity by ICD Code	Toxicity By Prednisone Prescription
Esophageal Cancer	65	17	14
Trachea/Bronchus/Lung	1991	499	510
Stomach/Gastric	30	13	4
Head and Neck Cancer	364	97	58
Colon Cancer/Rectal CA	79	26	15
Liver Cancer	219	70	41
Bladder Cancer	364	136	75
Kidney Cancer	286	87	80
Melanoma	399	106	99
Breast Cancer	0	0	0
Neuroendocrine	46	10	5
Hodgkin Lymphoma	8	4	4
Immunotherapy Drugs			
Pembrolizumab	2140	418	434
Ipilimumab	265	59	79
Atezolizumab	396	65	79
Nivolumab	1867	464	419
Durvalumab	335	49	91
Cemiplimab	18	2	3
Avelumab	3	0	0

Subtask 3: Comparison of patients identified in ST1 with ST2 4-7

- We have performed initial analyses within the Veterans Affairs population of the clinical/demographic characteristics of patients who have received prednisone versus those that have not. Initial analyses of patient characteristics, including rates of comorbidities, sex, age, and tumor type are described below in Table 8. Additional assessments including rates of toxicities by immunotherapy received are outlined in Tables 4 - 7 above.

Table 8: Patient Diagnosis, Toxicity Identification by ICD Code from VA

Demographic clinical characteristics	Total (N=2,841)		P-value
	Prednisone Yes n=361	Prednisone No n=2,480	
Age (mean years, range)	68.7 (71)	68.7 (68)	0.20†
Male (%)	95.6	96.9	0.19*
Charlson score index (mean)	4.6	4.5	0.68†
Cancer type (%)			0.02*
Bladder	6.4	8.1	
Colon/Rectal	0.8	1.1	
Esophageal	1.7	1.2	
Head and Neck	3.6	8.5	
Hodgkin Lymphoma	0.6	0.2	
Kidney	9.4	5.9	
Liver	5.5	5.4	
Melanoma	12.7	11.5	
Neuroendocrin	0.6	0.7	
Stomach	0.3	0.7	
Trachea/Bronchus/Lung	58.5	56.9	
* Chi-square test			
† T-test			

- ***Subtask 4: Abstraction of charts to confirm toxicities found in ST1&ST2***
  - Abstraction has taken some additional time. The onboarding of an abstractor team has been somewhat hampered by excess clinical responsibilities during the COVID-19 pandemic as residents had less free time than anticipated during the planning and design stages of the project. At this time, we have trained and on-boarded a team of four resident Washington University in St. Louis physicians. Training procedures and data dictionaries have been developed as well as standardized database forms and policies. Active abstraction is proceeding currently with Lung cancer and Melanoma as the priority diagnoses. Lung cancer is the dominant component of both Washington University and St. Louis Veterans Affairs databases and will constitute the bulk of abstraction.

- ***Subtask 5: Compilation of data and reporting of findings***
    - This is still ongoing and we are awaiting abstraction results prior to compilation/publication as this will make our findings and conclusions more definitive.
- ***Subtask 6: Manuscript preparation and publication***
    - As above, this is still ongoing due to progress on abstraction of charts and adjudication of immunotherapy toxicity events.

MAJOR TASK 3: *To develop a classic regression based risk prediction model*

Task Overview: We have proceeded with the development of a risk prediction model to predict both the development of autoimmune toxicities (model 1) and overall survival (model 2) for cancer patients receiving immunotherapy. We have utilized prednisone prescription to identify patients experiencing autoimmune toxicities (method still pending validation) and have reliable markers of survival based from VA death records. Results are detailed below. Final risk model development is still in progress at this time, but univariate and initial multivariate analyses have been completed.

- ***Subtask 1: Classification of patients with autoimmune toxicity as in Aim 1***
    - As detailed above patients who have developed a presumed autoimmune toxicity event have been identified within the dual datasets at the St. Louis VA and Washington University via two methods: ICD codes and Prednisone prescription. These determinations (outlined above) have been utilized to identify toxicity events.

- ***Subtask 2: Establishment of candidate predictors and covariates for model***

We have examined various candidate predictors for potential autoimmune events as well as overall survival for patients undergoing checkpoint inhibitor therapy for a cancer diagnosis. The key components of the current analyses are included in Table 9. Additional planned assessments include leukocyte subsets (absolute neutrophil count, absolute lymphocyte count and absolute eosinophil count), concurrent medications (statin therapy, hypoglycemic therapy), prior antibiotic history, impact of racial disparities, and geographic details. A particularly detailed sub-analysis of metabolic impacts of autoimmune toxicities and overall survival among those receiving immunotherapy will be pursued. The role of these factors have been established through extensive review of the literature as well as analyses of our own data sources. Many of these analyses have been completed, but some are actively ongoing and details of these will be presented below.

Table 9: Univariate Predictors Examined for Survival/Toxicity

Univariate Predictors Examined
Age
Cancer Diagnosis
Immunotherapy Drug Received
Charlson Comorbidity Index
History of Dementia
History of Stroke
History of Peptic Ulcer Disease
History of Connective Tissue Disease
History of Myocardial Infarction
History of Hemiplegia
History of Leukemia or Lymphoma
History of Diabetes Mellitus
History of Heart Failure
History of Peripheral Vascular Disease
History of Renal Disease
History of HIV Infection
History of Liver Disease
Albumin Levels
Creatinine
White Blood Cell Count
Hemoglobin
Body Mass Index

- ***Subtask 3: Univariate analysis of candidate predictors in VA dataset***

  - We have performed initial univariate analyses of candidate predictor variables for patients within the Veterans Affairs dataset. Outcomes assessed included associations with prednisone prescription and association with overall survival at 1 and 2 years. An extensive list of candidate predictors was considered as outlined in Table 9. Candidate predictors that were found to have a significant univariate association are presented in Tables 10, 11 and 12. Associations were examined between potential predictors and prednisone prescription (marker of autoimmune toxicity) as well as overall survival at 1 and 2 years.

Table 10: Univariate Association with Prednisone Prescription

Univariate Associarteion with Prednisone Prescription

Variable	OR	95% CI	P-value
Kidney	1.404	0.968, 2.039	0.07
Bladder	0.657	0.431, 1.001	0.051
Lung	1.296	1.056, 1.589	0.01
Pembrolizumab	0.821	0.669, 1.007	0.06
Atezolizumab	0.627	0.394, 0.999	0.049
Durvalumab	1.874	1.344, 2.613	0.0002
CPD	1.365	1.100, 1.695	0.005
albumin<3	0.451	0.342, 0.596	<0.0001
1<=creatinine <1.5	1.24	1.002, 1.536	0.045
10<=HgB<=13	0.77	0.618, 0.959	0.03
Hgb<10	0.366	0.267, 0.502	<0.0001
BMI <18.5	0.572	0.359, 0.911	0.0004
30<BMI<=35	1.699	1.268, 2.277	0.0003

Table 11: Univariate Association with Overall Survival at 1 Year

Univariate Analysis for Overall Survival at 1 Year

Variables	HR	95% CI	P-Value
Age	1.01	1.002, 1.020	0.02
Atezolizumab	1.38	1.15, 1.67	0.001
Durvalumab	0.28	0.21, 0.40	<0.0001
Charlson Score index	1.02	1.01, 1.04	0.004
HF	1.27	1.13, 1.43	<0.0001
CVD	1.15	1.02, 1.29	0.03
Hepatic Disease	1.39	1.09, 1.77	0.01
Liver disease	1.2	1.07, 1.34	0.002
BMI (2841)			<0.0001
BMI <18.5	1.83	1.56, 2.14	
18.5<=BMI<25 (ref)			
25<=BMI<30	0.63	0.56, 0.72	
BMI>=30	0.51	0.43, 0.59	

Table 12: Univariate Association with Overall Survival at 2
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Univariate Association with Overall Survival at 2 Years			
Variables	**HR**	**95% CI**	**P-Value**
Esophageal	2.24	1.57, 3.20	<0.0001
Bladder	1.29	1.10, 1.52	0.002
Liver	1.36	1.12, 1.65	0.002
Melanoma	0.54	0.46, 0.65	<0.0001
Durvalumab	0.33	0.25, 0.43	<0.0001
Charlson Score index	1.02	1.01, 1.04	0.003
HF	1.27	1.14, 1.42	<0.0001
PVD	1.11	1.01, 1.23	0.03
CVD	1.13	1.02, 1.26	0.03
Hepa	1.31	1.05, 1.65	0.02
Liver disease	1.15	1.04, 1.28	0.01
3<=albumin<=3.5	2.28	2.02, 2.58	
albumin<3	6.48	5.75, 7.30	
Creatinine (2838)			<0.0001
creatinine <1 (ref)			
1<=creatinine <1.5	0.61	0.55, 0.67	
1.5<=creatinine <2	0.62	0.52, 0.76	
creatinine >=2	1.23	1.01, 1.49	
WBC (2839)			<0.0001
WBC<12 (ref)			
WBC>=12	3.37	3.00, 3.79	
HgB (2776)			<0.0001
HgB>13 (ref)			
10<=HgB<=13	1.84	1.62, 2.08	
Hgb<10	4.28	3.75,4.89	
BMI (2841)			<0.0001
BMI <18.5	1.75	1.50, 2.04	
18.5<=BMI<25 (ref)			
25<=BMI<30	0.65	0.58, 0.73	
BMI>=30	0.55	0.48, 0.63	

We have undertaken significant assessments of the role of body mass index (BMI) on outcomes for immunotherapy recipients. This has been driven by research supporting the role of BMI as potentially predictive of toxicity events and survival from cancer immunotherapy. Significant findings to date have shown an association with a BMI > 30 (classified asobese) and improved overall survival. These findings are presented below in Figure 1 (Kaplan Meier assessment) and in Table 13 (representing a multivariate model with comorbidities and age as covariates.

Table 13: Multivariate Association of BMI with Overall Survival at 1 year
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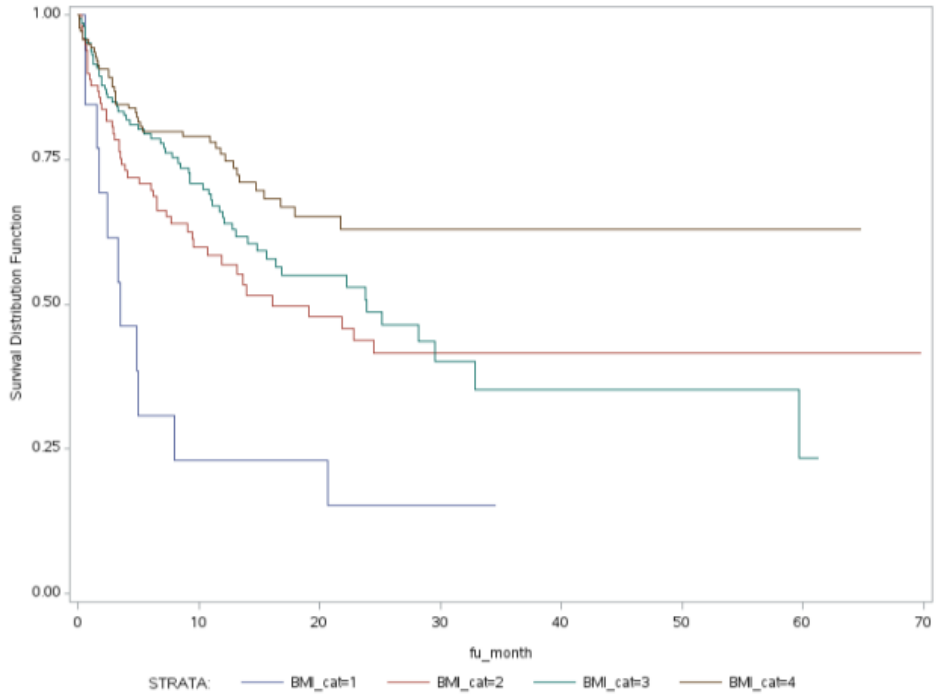
Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limit
Obesity (BMI > 30)	0.402	0.200 - 0.809
Romano Comorbidity Score	1.085	0.993 - 1.186
Age	0.991	0.955 - 1.016

Figure 1: Overall Survival among immunotherapy Recipients stratified by BMI



- ***Subtask 4: Exclusion of covariate pairs with strong correlation in VA dataset***
  - Work on this Subtask is ongoing currently.
- ***Subtask 5: Multivariate analysis and finalization of the model in VA dataset***

Table 14: Multivariate association with Prednisone Prescription (Presumed autoimmune toxicity) in VA data

Effect	Odds Ratio Estimate	95% Confidence Interval
BMI (BMI < 18.5 vs BMI 18.5 - 25)	0.633	0.394 - 1.019
BMI (BMI 25 - 30 vs 18.5 - 25)	1.092	0.848-1.406
BMI (BMI 30 - 35 vs 18.5 - 25)	1.557	1.141-2.123
BMI (BMI > 35 vs BMI 18.5 - 25)	1.291	0.853-1.955
Hemoglobin (10-13 vs >13)	0.872	0.692-1.101
Hemoglobin (<10 vs >13)	0.506	0.355 - 0.722
Albumin (3-3.5 vs >3.5)	0.941	0.737 - 1.202
Albumin (< 3 vs > 3.5)	0.681	0.497 - 0.932
Diabetes Mellitus	0.736	0.588 - 0.920
Renal Disease	1.607	1.056 - 2.446
Lung Disease	1.315	1.034 - 1.673
Nivolumab Use	0.729	0.529 - 1.003
Pembrolizumab Use	0.659	0.477 - 0.910
Atezolizumab Use	0.506	0.295-0.865

Within Table 14, we review an initial multivariate model for risk factors associated with prednisone prescription from the VA dataset. These will likely serve as potential predictors within our evolving risk prediction model (classic logistic regression model). Additional work and refinement of this model is ongoing.

- ***Subtask 6: Validation of the model utilizing WUSTL dataset***
    - Work on this Subtask is ongoing currently.

MAJOR TASK 4: *To develop a machine learning based risk prediction model*

Task Overview: The bulk of this task is still sometime in the future, and work continues on the process of setting up the model, denoting and cleaning the data, as well as appropriately identifying autoimmune toxicity events so that the model is accurate and effective. We have developed the basic framework for the model at this time and have run a preliminary attempt at model derivation. Initially, we had planned to use the *Autoprognosis* python model to develop the machine learning model, but we have abandoned this approach to utilize more traditional protocols in model development. This is mainly due to increased machine learning expertise among our research staff (Dr. Inez Oh).

- ***Subtask 1: Cleaning/Denoting dataset for ML protocols***
    - Work on this Subtask is ongoing currently.
- ***Subtask 2: Utilization of Autoprognosis python module to develop ML model***
    - Work on this Subtask is ongoing, and given changes in approach, Autoprognosis may not be utilized.
- ***Subtask 3: Utilization of manual ML protocols to develop routine ML model***

Table 15: Machine Learning Model Approaches

Table 12: Univariate Association with Overall Survival at 2

ML Models Utilized
Parameter Grid-Search
5-fold cross-validation
Logistic Regression
Decision Tree
Random Forest
Extra Trees
Gradient Boosting Classifier
K-nearest Neighbors

Table 16: Features Utilized in Candidate ML Modeling

Features Utilized in Model
Sex
BMI
Race
Cancer Diagnosis
Checkpoint Inhibitor
Creatinine
Hemoglobin
Albumin
MI
Hepatitis
HF
PVD
Renal Disease
HIV
Liver Disease
Diabetes
COPD

Table 17: Machine learning models for prediction of prednisone prescription from Washington University data

Model	Recall (Sensitivity)	Specificity	AUROC	Precision (PPV)	F1	Acc	NPV
GridSearch LR_Toxicity_PRED	0.69	1	0.73	0.19	0.9	0.9	0.9
GridSearch dtree_Toxicity_PRED	0.23	0.93	0.53	0.18	0.81	0.81	0.86
GridSearch RF_Toxicity_PRED	0.53	1	0.58	0.17	0.86	0.86	0.86
GridSearch xtree_Toxicity_PRED	0.55	1	0.57	0.18	0.86	0.86	0.86
GridSearch GB_Toxicity_PRED	0.57	0.98	0.58	0.17	0.85	0.85	0.86
GridSearch KNN_Toxicity_PRED	0.53	0.99	0.56	0.14	0.89	0.89	0.9

Model + SMOTE	Recall (Sensitivity)	Specificity	AUROC	Precision (PPV)	F1	Acc	NPV
GridSearch LR_Toxicity_PRED	0.59	0.61	0.63	0.21	0.6	0.6	0.9
GridSearch dtree_Toxicity_PRED	0.26	0.9	0.57	0.23	0.79	0.79	0.86
GridSearch RF_Toxicity_PRED	0.51	0.96	0.53	0.16	0.84	0.84	0.87
GridSearch xtree_Toxicity_PRED	0.49	0.96	0.53	0.16	0.84	0.84	0.86
GridSearch GB_Toxicity_PRED	0.53	0.96	0.57	0.16	0.83	0.83	0.86
GridSearch KNN_Toxicity_PRED	0.36	0.67	0.47	0.13	0.62	0.62	0.85

Table 18: Machine learning models + SMOTE for prediction of prednisone prescription from Washington University data

An initial run at a Machine Learning prediction model for prednisone prescription is outlined above in Tables 17 and 18. A variety of model approaches are presented (outlined in Table 15). Features considered are presented in Table 16. Within Table 18, synthetic minority oversampling technique (SMOTE) is employed to assist with perceived class imbalances within the dataset secondary to employed features. Initial accuracy and effectiveness of the modely will need refinement, but the process to develop the model has been created and employed.

- ***Subtask 4: Comparison of ML models (Autoprognosis vs Routine)***
  - This task is ongoing, and may not be completed given that we are no longer planning on utilizing Autoprognosis as an approach to machine learning model development.
- ***Subtask 5: Validation of optimal ML model with WUSTL data***
  - This task is ongoing and pending completion of other associated and dependent tasks.
- ***Subtask 6: Comparison of optimal ML model with Regression based model***

- This task is ongoing and pending completion of other associated and dependent tasks.

- ***Subtask 7: Preparation of manuscript and publication of results***
    - This will be pending additional work as above.

MAJOR TASK 5: *To correlate development of autoimmune toxicities with PFS and OS as compared to those not developing toxicity*

Task Overview: Initial analyses have been performed on this goal for a subset of tasks. We have utilized several techniques of identifying potential autoimmune toxicities, including ICD codes and prednisone prescriptions. Results of the initial assessments are presented below:

- ***Subtask 1: Calculate OS utilizing disease specific survival data***
    - Work on this subtask is ongoing currently.

- ***Subtask 2: Calculate OS and PFS data for patients with grade 3/4 toxicities***
    - We have completed several analyses comparing survival for patients who experienced grade 3/4 toxicities from ICI therapy.

Figure 2: Overall Survival for all cancer diagnoses from VA data among those receiving Prednisone vs those Not

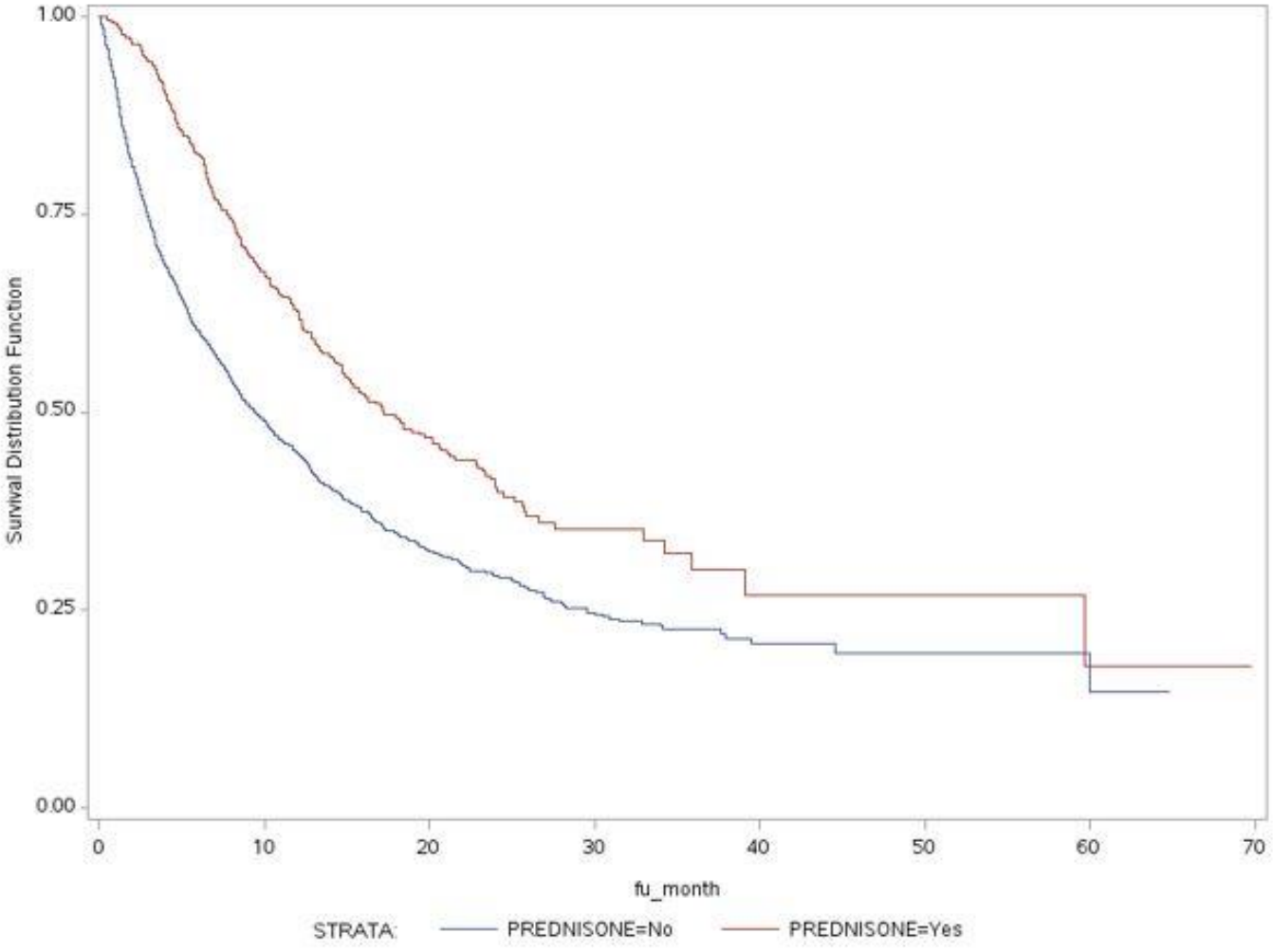
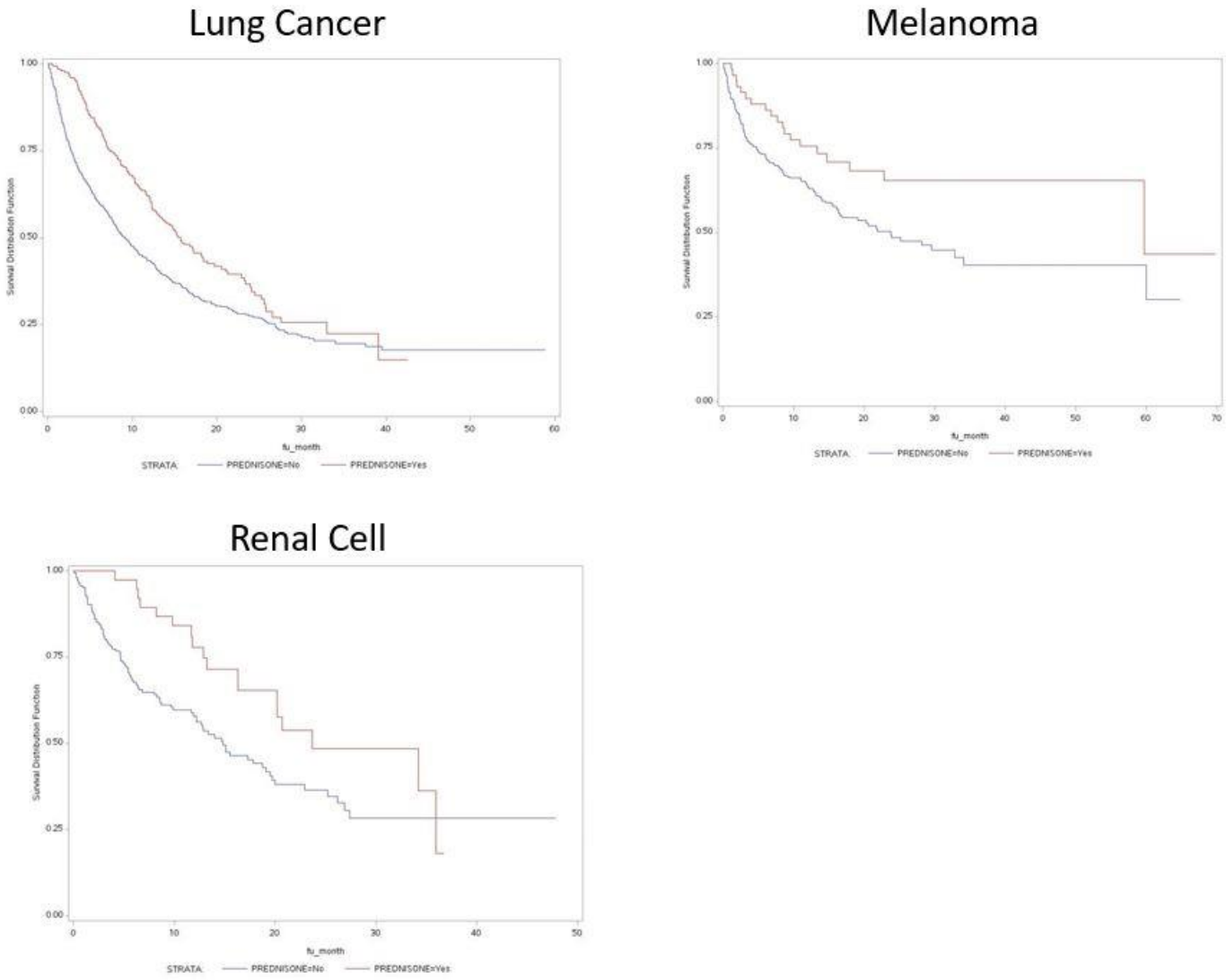


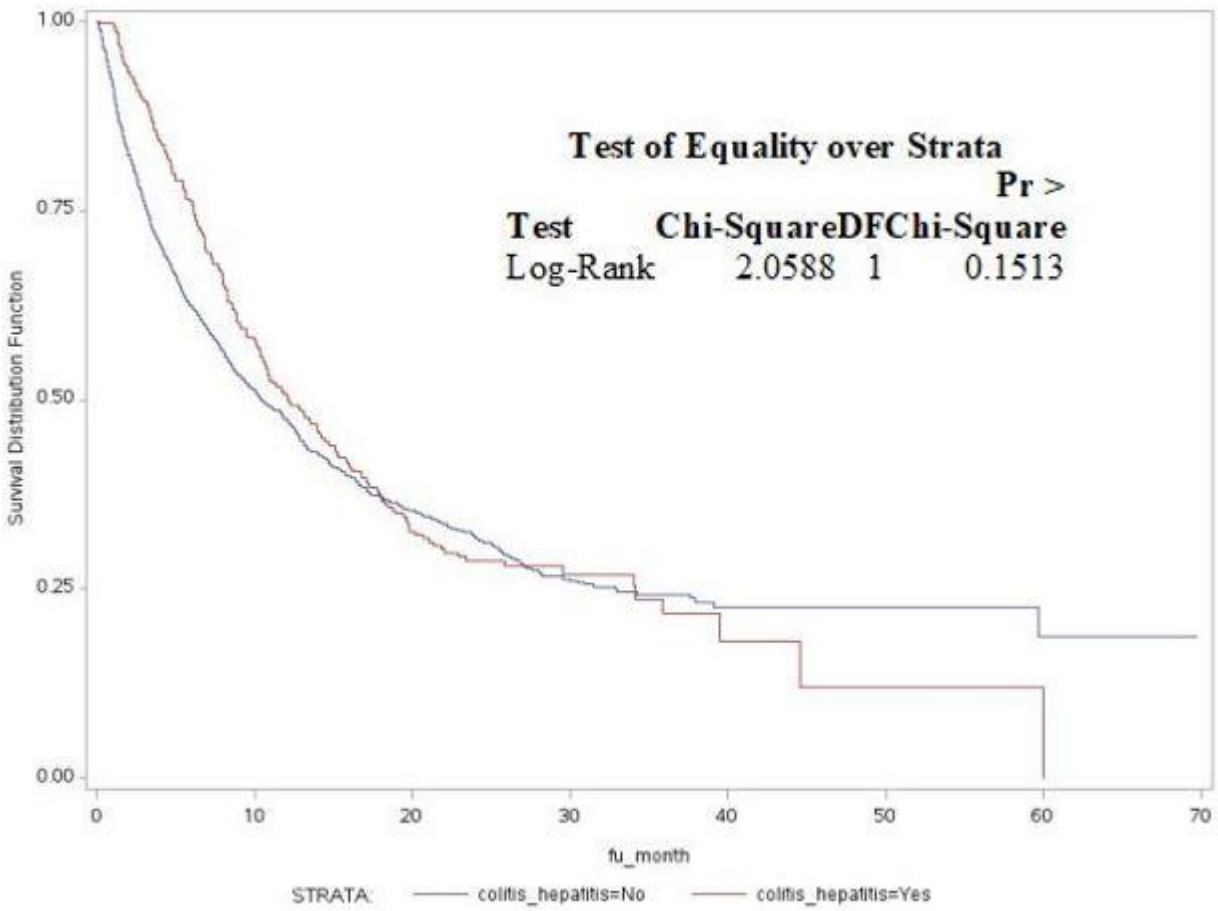
Figure 2 above shows a Kaplan-Meier survival analysis for patients from all cancer diagnoses who received ICI therapy, comparing those patients who received a prescription of prednisone during or within 6 months of completion of ICI treatments versus those who did not. Improved OS was observed and was statistically significant for patients receiving a prednisone prescription between the initial dose of ICI therapy and 6 months post ICI therapy concluded.

Figure 3: Overall Survival for Lung, Melanoma and Renal Cell Cancer from VA among those receiving Prednisone vs those Not



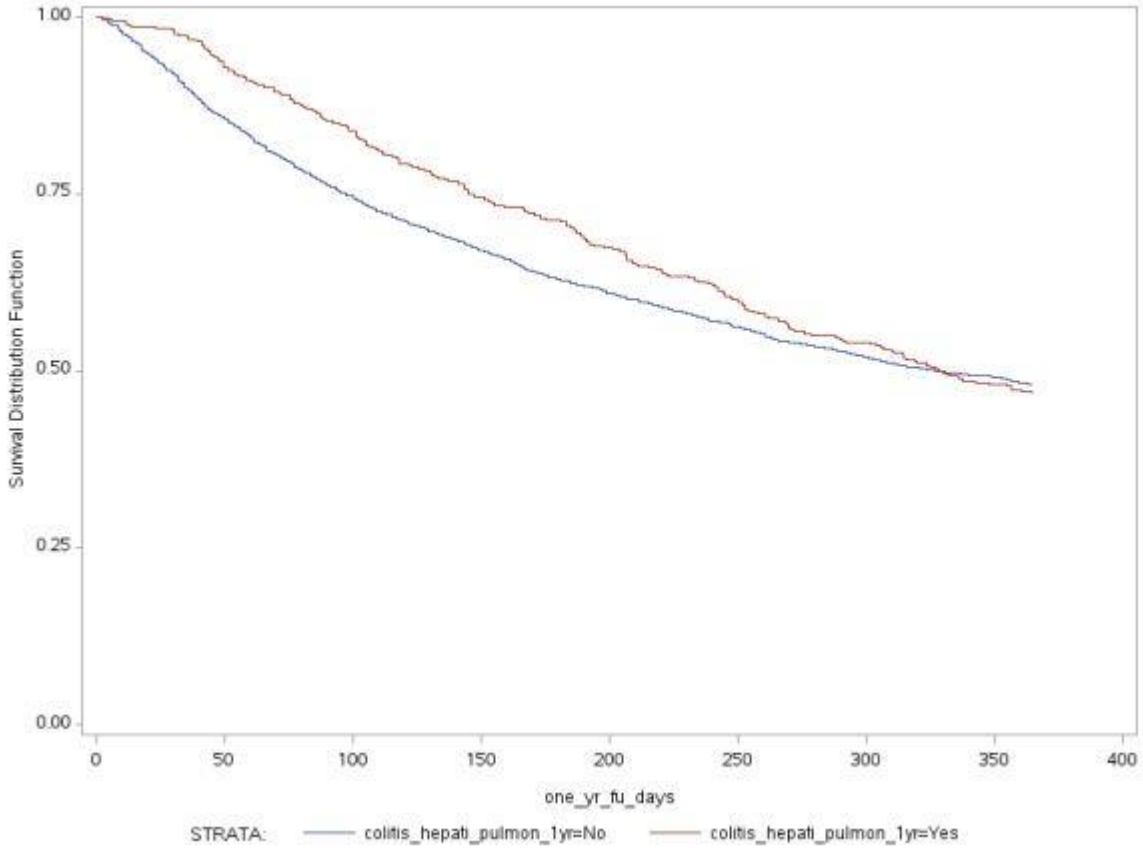
Above in Figure 3, the findings outlined in Figure 2 are examined for key cancer diagnoses of melanoma, lung cancer and renal cell carcinoma. Findings here all support an improvement in overall survival for patients receiving steroid therapy during ICI treatment. This supports the association of immune related adverse events with improved survival among these cancer patients.

Figure 4: Overall survival for all diagnoses with toxicity event via ICD Codes, VA Data



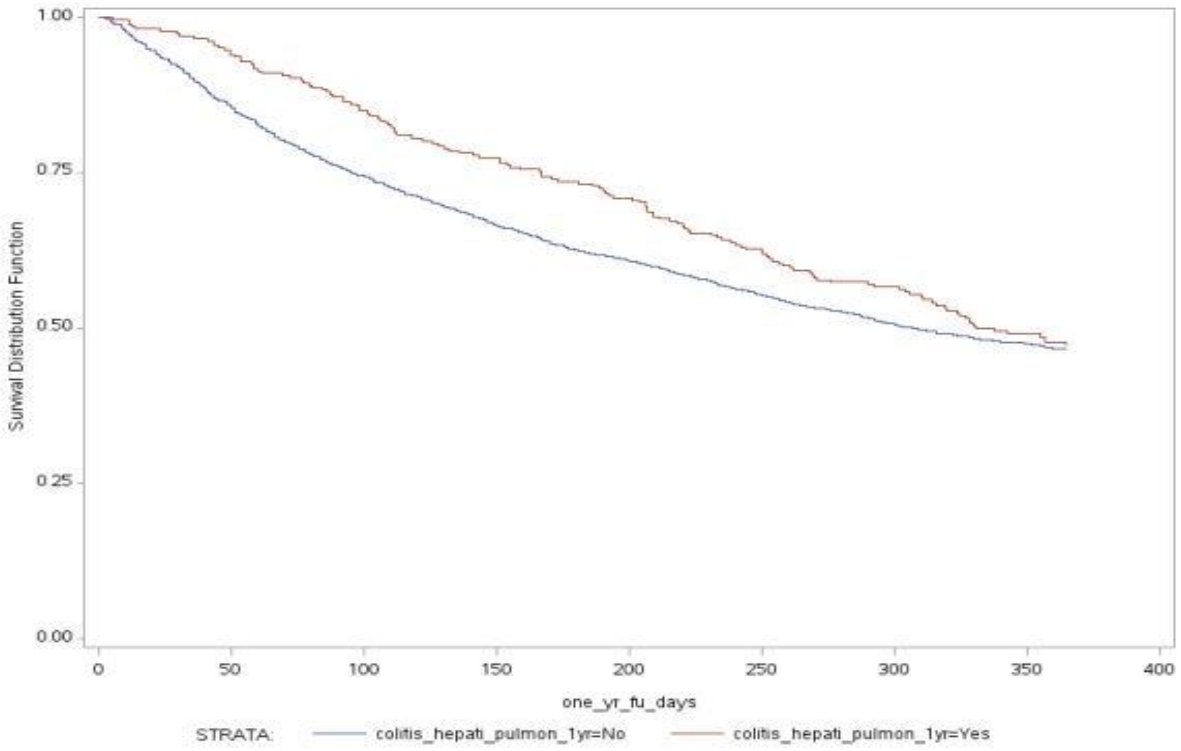
Above in Figure 4, the effectiveness of ICD codes to identify toxicity events is assessed via a survival analysis among all cancer diagnoses, who had a recorded ICD code for a toxicity event during ICI therapy and up to 6 months post ICI therapy. As noted here, the survival is not different among these cohorts, suggesting potentially that ICD codes are not identifying toxicity events as well as prednisone therapy. Additional analyses to assess this finding are ongoing.

Figure 5: All Diagnoses, 1 year survival for toxicity by ICD code, VA data



Above, in Figure 5, 1-year survival among all cancer diagnoses for patients with an ICD code defined toxicity event are presented. There is notable initial separation of survival curves early on in the survival analysis, suggesting potentially a short-lived effect on survival from an autoimmune toxicity.

Figure 6: Overall survival among lung cancer patients among ICD code defined toxicity, VA



Above, in Figure 6, lung cancer patients were examined showing survival among patients with ICD code defined toxicity versus those without ICD code defined toxicity events.

- ***Subtask 3: Calculate and compare PFS data for patients with and without grade 3/4 toxicities, utilizing Kaplan-Meier methods***
    - This subtask is ongoing at this time.
- ***Subtask 4: Preparation and Publication of Manuscript***
    - This subtask is ongoing at this time.

4. Impact

***Current Impact*:** Currently, the impact is limited by the initial/early stage of the research project. We have already found significant and potential novel findings regarding BMI, and an association with improved overall survival among those receiving steroids while on ICI therapy. The finding of an association between steroid use during ICI therapy and improved survival suggests that adverse events are associated with significant improvement in clinical response and benefits. Furthermore, these findings suggest that the immunosuppression required to treat these adverse events do not eliminate the benefits from immunotherapy.

Potential Clinical Impact: The final product of the research will have significant impact on the understanding of clinical outcomes surrounding cancer immunotherapy, autoimmune related adverse events, and prognostic markers in the modern era of ICI therapy.

5. Changes/Problems

***Problems/Challenges Encountered*:** There have been several challenges encountered during the initial year of the grant. We will review these in depth here as well as the planned approach to overcome these complications.

***Uncertain Utility of ICD Codes to Identify Autoimmune Toxicities*:** The publication in February of a study from Ohio State bv *Nashed, Zhang, et al*, showing the inaccuracy of ICD codes for the detection of autoimmune related adverse events highlighted the potential complications of utilizing ICD codes to identify immune related adverse events. The inability to distinguish autoimmune events without extensive abstraction is a limiting factor to the current project and other similar retrospective/administrative data projects. *Planned Solution*: The current plan is for an approach utilizing steroid prescriptions to identify autoimmune toxicity events. Anecdotally, our clinical experience informs us that ICD codes for complications of therapy are infrequently entered by treating clinicians, and utilizing a prescription as a marker of an event should be a much more reliable approach. In this manner we hope to find a more sensitive and specific tool for identifying immune related adverse events. We are currently working to prove this approach using the melanoma subset of our Veterans Affairs dataset. If this is effective, we can expand these efforts to the additional cancer diagnoses. This will allow a more effective and appropriate means of identification and will be applicable across additional efforts at examining these immune related adverse events utilizing retrospective data.

***Chart Abstraction*:** Complicating the efforts above, chart abstraction has been a more complicated and time-consuming effort than initially expected. The initial plan to utilize resident physicians to complete chart reviews was complicated by training and regulatory requirements (predominately at the Veterans Affairs hospital), as well as increased clinical demands from the COVID-19 pandemic. *Planned Solution*: Currently we have succeeded in training a group of 4 resident physicians that are working actively to review clinical charts and abstract outcomes for the current study. The current team is well-trained and making substantial progress towards completion of the abstraction process.

***IRB Delays*:** Initial issues with delays in approval through the Department of Defense IRB did contribute early challenges to the initiation of the study. Furthermore, there is little doubt that the initial processing of the grant was complicated by the onset of the COVID-19 pandemic in March 2020, one month after notification of the award. Once the approvals were in place by November 2020, we were able to proceed with the study and have made substantial progress over the past 9 months. Limitations on gathering as a research group and clinical demands have certainly reduced/limited progress on the research in numerous ways.

***COVID-19 Related Challenges*:** As noted above, COVID-19 has clearly impacted the study in numerous ways. Increased workloads among the research team has limited time spent on chart abstraction as well as statistical analysis and oversight. The limitations on group meetings has changed the nature of collaboration. For the most part, we have been able to catch up from initial delays in the research and are now well-positioned to move forward.

***Limitations of Washington University in St. Louis Dataset*:** The dataset at Washington University in St. Louis is a very robust dataset, but runs currently only from 2016 through mid-

2018. This leaves out 3 years of potential additional patients treated with ICI therapy. We have arranged via additional outside funding to extract an additional 3 years of data from the Washington University in St. Louis administrative databases, and we expect this will increase out patient dataset from Washington University to roughly 7000 patients. This will improve our ability to extract meaningful findings and increase the validity of our conclusions.

6. Products

Final Product: The goal of this research and grant is to produce a risk prediction model for severe autoimmune toxicities from checkpoint inhibitor therapy among patients undergoing immunotherapy treatment for cancer. The utility of this tool will be significant, as it will allow clinicians to better counsel, select therapy and provide appropriate prognostic information for cancer patients. Additional goals of the research are to better explore predictors of toxicity, and predictors of overall survival among cancer patients.

Progress Towards Final Product: As is outlined above under the Accomplishments section, significant progress has been made towards the goals of the grant. We have identified potential predictors of autoimmune toxicities and overall survival among cancer patients receiving immunotherapy. We have also made significant progress in the processing of our active datasets, as well as the training of our personnel to assist with ongoing research efforts.

***Publications*:** Current publications are in production regarding the impact of immunotherapy following definitive chemoradiation for lung cancer, as well as our findings on the role of BMI in predicting benefit from cancer immunotherapy. The target conference for presentation of findings and data is the annual American Society of Clinical Oncology meeting, which is held in June on an annual basis. Given the approval of the Department of Defense IRB in November 2020, we had very limited time to submit data to this conference (due date for submissions was February 2021). As such, we have limited conference abstracts and publications to review from the initial year of this grant. We plan for progress on publication to occur within the coming year.

7. Participants & Other Collaborating Organizations

St .Louis Veterans Affairs Medical Center: The St. Louis VA Medical Center remains an ongoing and active research site for this grant. A brief review of resources is outlined below:

Clinical Facilities: The John Cochran VA Medical Center is a full-service, level I health care facility. It provides both inpatient and ambulatory care with over 65 subspecialties including hematology/oncology. We are the largest hematology/oncology section in Missouri for Veterans to receive care. The majority of the patients served come from east central Missouri and southwestern Illinois.

Research Divsion: The staff for the research division involved in this proposal includes a full time statistician. Mrs. Luo has a Master degree in Public Health. She has over 15 years of experience as a statistician. She has expertise in analyses using SAS and is capable of using R and STATA as well. Given the space is shared with additional VA research teams, this offers an environment for collaboration and trouble shooting with other statisticians when needed in close proximity.

***Washington University in St. Louis*:** Washington University in St. Louis continues as an active participating site in the ongoing research. A brief updated overview of resources is outlined below:

Clinical Facilities:
Barnes Jewish Hospital: Barnes Jewish Hospital is the largest hospital in Missouri. The medical staff consists of over 1,800 attending physicians. The hospital contains 1,315 licensed beds providing care to over 50,000 admissions annually.

Siteman Cancer Center: Siteman cancer center is the only National Cancer Institute designated Comprehensive Cancer Center in Missouri and within a 240-mile radius of St. Louis. Over 300 clinicians and researchers staff it. It is a member of the National Comprehensive Cancer Network. Given the distance to neighboring comprehensive centers, Siteman has a large referral basis with patients coming from all over the state to receive care.

Research Facilities: Washington University in St. Louis is a world-class, robust research environment with extensive academic and research resources and ideal opportunities for collaboration.