

Autoimmune side-effect of immunotherapy in lung cancer treatment revealed from large-scale cohort

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Abstract

Although immune checkpoint inhibitors have illustrated strong benefits in patient survival and have been widely acknowledged in treating lung cancer, they may be subject to increased risk of immune-related adverse effects (irAEs). Although existing literature have studied the mechanisms of irAEs of immunotherapy, it is difficult to quantify such effect, especially at a large-scale real-world population level. In this paper, the autoimmune-related risk of multiple immune checkpoint inhibitors is compared with that of chemotherapy based on Medicaid and CHIP TAF (T-MSIS Analytic File) data of over 100,000 patient samples from 2012 to 2018. Results show that the irAEs of immunotherapy is significantly higher than chemotherapy in both unadjusted and adjusted samples from the dataset. Analysis on subpopulation and specific disease types further shows that certain immunotherapy treatments are associated with higher risk of irAEs, and the risk of certain autoimmune diseases may vary. We also illustrate the robustness of our conclusion through additional sensitivity analysis, confirming the necessity of keeping track of autoimmune side effects of immune checkpoint inhibitors for medicine researchers. Our methods are also available to evaluate effectiveness and side effects of novel therapies at a large-scale population level.

Keywords: lung cancer, immunology, causal inference, survival analysis, autoimmune, chemotherapy

1 Introduction

Immune checkpoint inhibitors have received phenomenal clinical success in treating multiple types of cancer, and have innovated the landscape of modern cancer therapy [1]. Since the approval of immune checkpoint inhibitor, Ipilimumab, by the U.S. Food and Drug Administration (FDA), many types of immunotherapy have been discovered for specific cancer types. The most common immunotherapies in recent years for cancer treatment are immune checkpoints T-lymphocyte-associated protein 4 (CTLA-4) inhibitors and programmed cell death protein 1 (PD-1) inhibitors [2]. There are also other types of immune checkpoint inhibitors, such as LAG-3 inhibitors.

Unlike conventional mechanism of chemotherapy, immunotherapy enables certain aspects of immune system to eliminate targeted tumor cells [3]. CTLA-4 inhibitor binds to CTLA-4 receptor, blocks the expression of CTLA-4 protein, thus preventing its attachment to B7 receptor in APCs and decreasing the activation threshold of T cells, increasing immune responses against tumor cells [4]. Programmed cell death protein 1 (PD-1) inhibitors, including Pembrolizumab (Keytruda[™]) and Nivolumab (Opdivo[™]), reactivate the host immune response against cancer through suppression of PD-1, which is a transmembrane protein mediating intracellular signaling events during T cell activation [5], and is crucial for the maintenance of peripheral tolerance and containing immune responses to avoid immunopathology [6]. The ligands of PD-1, PD-L1 and PD-L2, both found on the surface of antigen-presenting cells, also lead to the development of novel immunotherapy, such as Atezolizumab and Avelumab. Both PD-1 and PD-L1 inhibitors have been proven helpful in treating many different types of cancer [7]. In addition to the substantial treatment effects and survival gains of immune checkpoint inhibitors [8, 9], immunotherapy avoids common cytotoxic damage to non-tumor cells due to conventional radiotherapy and chemotherapy [10], and has gained increasing clinical popularity for various types of cancer, such as lung cancer, breast cancer [11] and melanoma [2]. Currently several common immunotherapies have been applied in lung cancer treatment: Nivolumab (Opdivo[™]), Pembrolizumab (Keytruda[™]), Ipilimumab (Yervoy[™]) and Atezolizumab (Tecentriq[™]). Novel immunotherapy drugs are also being invented in recent years, such as Dostarlimab, but are either not formally approved or less widely applied due to recency.

Although the functionality has been proven effective [6], immune checkpoint inhibitors may also lead to certain side effects [12]. Common adverse effects of immunotherapy include diarrhea, fatigue, nausea, decreased appetite [13] and neurologic complications [10]. Besides, by targeting a checkpoint protein, the inhibitors

may remove certain safeguards on the immune system. Correspondingly, immune system may attack other parts of the body, which can cause serious reactions, known as autoimmune-related adverse effects (irAEs) [14]. Common irAEs including hypothyroidism and thyroiditis have been reported in clinical application of immunotherapy clinical trials and small-size observational studies [15]. However, irAEs are still not well explored at a large-population level due to the recency of clinical application [16]. Moreover, although most patients under immunotherapy are reported with irAEs, some adverse effects may have much lower incidence rate, which makes large-scale observational studies necessary.

Recent advancement of electronic health data (EHR) has facilitated studies on evaluating adverse events of novel treatment strategies based on large-population scale real-world data (RWD) [17]. RWD is a source of information related to patient health conditions and healthcare delivery [18], often collected routinely by hospitals or healthcare agencies. Common sources of RWD include nationwide insurance datasets, hospital medical records and medicaid data. One advantage of RWD is accumulation of sufficient evidence of side effects with smaller probabilities to dissect issues pertaining to multiple sectors [19]. Moreover, observational data sources such as health claims [20] are usually population based, longitudinally collected and structurally constructed, which facilitates large-scale studies.

However, real world data may also face several challenges. One major drawback of using RWD is the difficulty in justifying causality. Different from experimental data, RWD is collected without specific research purpose, thus identification the treatment effects may be challenging. RWD may also incorporate incomplete or missing data, stimulated reporting and duplicate reporting. To address such issues, we employed matching method from the causal inference literature to reduce the biased relationship between immunotherapy and subsequent irAEs, therefore establishing a strengthened causal effect.

The scope of this paper focuses on evaluation of autoimmune risk of immune checkpoint therapy in lung cancer treatment. Lung cancer has been the primary cause of cancer-related mortality leading to over 1.5 million deaths per year worldwide [21], and is widely known to be challenging for immunotherapy treatments [22]. Despite the success of several immunotherapies in certain cancers, immunotherapy have historically failed in lung cancer [22]. However, recent studies have demonstrated significant survival benefit of immunotherapy in treating lung cancer [23]. This paper focuses on a comprehensive cohort study of the immune-related adverse effect of immunotherapy on

lung cancer patients, utilizing the real world dataset of United States Medicaid data, in comparison to irAEs of traditional chemotherapy.

The paper is organized as follows: in Sec 2.2 we present the workflow of data processing and visualize the number of patients (records) after each procedure, based on inclusion-exclusion criteria (see Sec 2.5). The matching methodology is introduced in Sec 3, and the main results are provided in Sec 4, where Kaplan Meier curves are provided and log-rank test for the hazard ratio is conducted along with weighted cumulative incidence ratio. Sec 4.3 shows the results of sensitivity analysis, where we investigate whether the risk increase for specific irAEs and immunotherapy (Nivolumab, Pembrolizumab, Ipilimumab and Atezolizumab). Additional analysis using different sub-population and matching criteria are provided in Sec 4.4. We wrap up the study with discussions in Sec 5.

2 Materials and methods

2.1 Overview of the CMS dataset

Our study utilizes the RWD of de-identified medicaid claim data from The Centers for Medicare and Medicaid services (CMS). Medicaid is a joint federal and state program that helps cover medical costs for patients with limited income and resources. The medicaid dataset contains the medicaid claims from patients prior to December 31, 2018, with a total of more than 500,000 unique patients with 30+ million records. **Written informed consent have been acquired from the patients before the enrollment of medical plan for research purposes, and the consent forms are required for each patient to receive chemo- or immunotherapy treatment.** The claims records provide diagnosis codes encoded by the International Statistical Classification of Diseases and Related Health Problems, in mixed ninth (ICD-9) and tenth edition (ICD-10). Treatment procedures are encoded according to Current Procedural Terminology and Healthcare Common Procedure Coding System (HCPCS). Details of the treatments such as date and dosage are also provided. In particular, the diagnosis date of lung cancer and earliest irAEs are listed, which enables investigation of the causal relationship between immune inhibitors and irAEs.

2.2 Study cohort

The summary of dataset after each data processing procedure is visualized in Fig.1 to show how much data is selected, merged and filtered in each step. 5725 qualified patients with immunotherapy and 102490 qualified patients with chemotherapy are

finally acquired as the targeted population of the study. Table 1 provides the detailed demographics after the data filtering procedure.

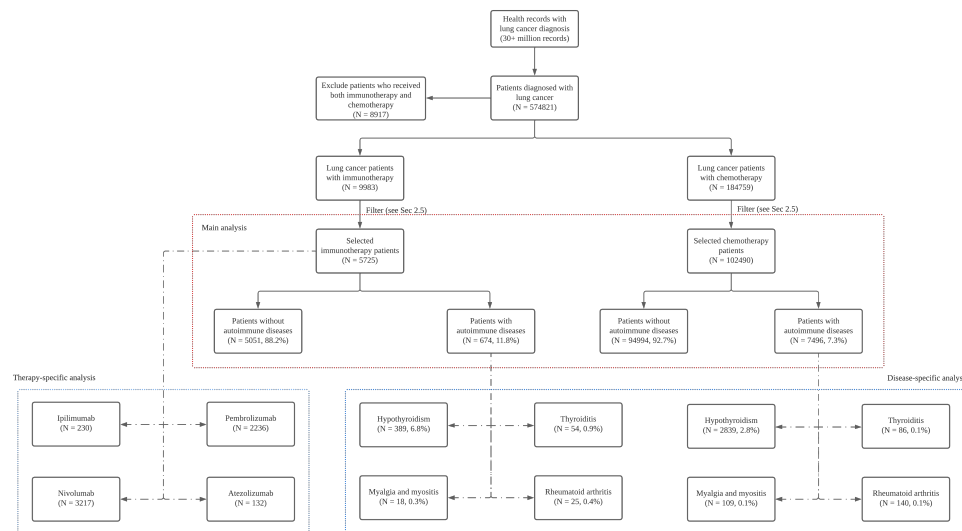


Fig. 1: Diagram of filtering the patient samples. A patient may receive combined immunotherapy and exhibit multiple syndromes after treatment.

2.3 Immunotherapy and chemotherapy identification

We extracted the lists of immunotherapy and chemotherapy HCPCS codes for lung cancer, while other types of treatment for cancer are omitted, such as radio therapy and targeted therapy. The complete list of common CPT/HCPCS codes for immunotherapy is shown in Table 3, and chemotherapy codes are provided in the Supplementary Material Table S1. The most common immunotherapy treatments in the dataset are Nivolumab and Pembrolizumab, while Atezolizumab and Ipilimumab are also common therapies for lung cancer. Other immunotherapy treatments have very limited sample size in the dataset due to recency, and are categorized as other therapies.

2.4 Inclusion criteria

In this study, patients with at least two lung-cancer diagnosis records with chemotherapy or immunotherapy records are included, and their entire treatment histories are extracted from the database. The lung cancer mainly includes small-cell, non-small cell cancer and carcinoid, all of which can be identified through PheWAS codes and

descriptions. Patients with any ICD records from Table S4 after lung cancer treatment are considered as having an irAE event, with the time-to-event length defined as the time difference from therapy initiation date to the date of first irAE diagnosis.

2.5 Exclusion criteria

To decrease the possibility of coding mistakes and rule out other factors which may induce biased conclusion, multiple exclusion rules were applied to filter out disqualified patients.

1. To rule out patients with potential treatment from other sources, patients whose first record is less than 30 days before the first lung cancer therapy shall be excluded from the study, following existing literature [24]. This filtering procedure is to eliminate patients with insufficient treatment history in the database, which may indicate prior cancer treatment or irAE events. In the main analysis, the quiescence time is set as 30 days, and in the sensitivity analysis different quiescence time will be discussed.
2. The first therapy for cancer the patients shall be prior to the first date of diagnosis with immune related adverse events, as there is little evidence that shows the causal relationship between therapy and autoimmune effects.
3. The patients that receive both immunotherapy and chemotherapy are excluded, because the cause of immune related adverse events cannot be properly identified.

2.6 Outcomes identification

The primary outcome of the study is the autoimmune-disease-free survival time after treatment of therapy, defined as the initiation date of immunotherapy or chemotherapy to the first record date of autoimmune-related diseases. Patients with no ICD records of irAEs are identified as having no events, and the at-risk (censoring) time is thereby defined as the treatment initiation time to the date of the last record of the lung cancer patient found in the database.

In the main analysis, the treatment initiation time is calculated regardless of the lines of the immunotherapy. A patient with irAEs is identified by consulting the corresponding ICD-9/ICD-10 codes of irAEs in the records. The types of autoimmune-related diseases are manually collected following expert suggestions and conventions of previous irAE studies, along with corresponding ICD-9 and ICD-10 codes from PheWAS, which are summarized in Supplementary Material Table S4. 56 categories of ICD codes relevant to irAEs are examined in this study, and the most common irAEs include Hypothyroidism, Rheumatoid arthritis, Myalgia (myositis) and thyroiditis. Due

to the scope of this study, the definition of irAEs slightly discriminates from other studies. Some less severe autoimmune syndromes unlisted in the code list, such as skin rash and fatigue [25], are excluded from the study. The observational data is right censored at 3 years. Diagnosis after 3 years of initial treatment will be considered irrelevant to the therapy treatment.

In the main analysis any autoimmune diseases in the code list are considered as irAE. Section 4.3.2 provides sensitivity analysis results for four particular types of diseases: hypothyroidism, thyroiditis, myalgia and myositis and rheumatoid arthritis. Other types of autoimmune diseases also exist in the records, but the sample size is not adequate for sensitivity analysis.

3 Methods

3.1 Cox proportional hazards model

Cox proportional hazards model is a popular technique used for survival-time (time-to-event) outcomes modeling on one or more predictors. Cox proportional hazards model does not require any assumptions about the distribution of event times, only assuming that:

1. Survival curves for different strata must have hazard functions that are proportional over the time t ,
2. The relationship between the log hazard and each covariate is linear, which can be verified with residual plots.

The response variable $\lambda(t)$ is defined as a hazard function which assesses the probability that the event of interest (in this study, this is defined as the time span from the first treatment to the first irAE diagnosis) occurred before t . The equation models this hazard as an exponential function of an arbitrary baseline hazard λ_0 when all covariates are null, and β is the regression coefficient of all covariates X :

$$\lambda(t) = \lambda_0(t) \exp(X \cdot \beta) \quad (1)$$

In the paper, standard log-rank test is also used to evaluate whether survival functions of the immunotherapy and chemotherapy groups are equal. The log-rank test is a statistical test used to compare the survival distributions of two or more groups. It is commonly employed in clinical trials and epidemiological studies to assess whether there are significant differences in the time to an event (such as death, disease progression, or failure) between groups.

3.2 Matching method

In this study, the treatment group is defined as patients who only receive immunotherapy, and the control group contains the patients who only receive chemotherapy. We apply matching method to assign higher weight to chemotherapy patients who have high similarity to each immunotherapy patients, following existing causal inference methods [26].

Matching methods efficiently alleviates the potential imbalance issue between the treatment and control group. In this study, each qualified patient that receives immunotherapy is matched to all 'similar' patients in the control group. A patient is considered 'similar' to another patient if all matching criteria are met:

1. The same sex, race and ethnicity, if the information is available without contradictory records. In the case of contradiction, i.e., when male and female coexist in the record of a patient, we mark the patient as 'ambiguous'. An ambiguous patient will only be matched to ambiguous patient in the control group, following [26].
2. Age stratification. The difference in age of two matched patients should be no more than 2 years.
3. The same level of hospital visit rate. Percentile stratification in hospital visit rate is widely used in literature as an indicator of healthcare resource utilization pattern [27]. Hospital visit rate is defined as the average frequency of hospital visit (according to the record) during one year before the first diagnosis of lung cancer, which reveals the healthcare utilization of a patient. The healthcare utilization is classified into three categories: low (less than 67% quantile), medium (33% quantile to 67% quantile) and high (more than 33% quantile). Only patients with the same level of healthcare utilization can be matched.
4. Similar disease severity. In this study qualitative evaluation of disease severity is utilized as the matching criteria for previous disease burden. Two indicators are considered for defining similarity of disease burden: number of unique ICD codes found in the record prior to the first diagnosis of cancer, which quantifies the overall health condition of patients, as well as expert annotation. The level of disease severity is stratified into three categories: low (less than 67% quantile), medium (33% quantile to 67% quantile) and high (more than 33% quantile). Only patients with the same level of disease burden will be matched.
5. Exposure of treatment. The number of treatment cycles and the amount of exposure to the drug can be an important risk factor of irAEs. Therefore, the exposure of chemo- and immunotherapy for matched patients should be comparable. Guidance for dosage (exposure) comparison can be found in [24, 27].

Each patient in the control group may be selected multiple times as matched samples for different patients with immunotherapy. After acquiring the matched samples, we reweight the matched samples by inverse probability weighting [26]. Every patient in the treatment group is assigned with 1. If a treatment group patient has n matched samples, each sample will be assigned with an equal weight of $\frac{1}{n}$.

After the re-weighting procedure the risks of irAEs among patients in two groups are compared. We conduct a survival analysis between two groups, along with the 95% confidence intervals. We first plot the Kaplan-Meier curve of two groups separately for original samples (before matching procedure) and matched samples, and test the difference of survival time distribution from irAEs. We further calculate the 95% confidence interval of hazard ratio. For pre-match samples, we apply Greenwood formula [28] for interval estimation. For matched samples, we apply Bootstrap method for interval estimation [29].

4 Results

4.1 Results overview

5725 lung cancer patients who received immune checkpoint inhibitors without prior autoimmune diseases are identified from cms database, with treatment initiation date ranging from 2011 to 2018. 2236 patients received Pembrolizumab, 132 received Atezolizumab, 3217 were on Novolumab and 230 were on Ipilimumab. For comparison group, 102490 patients were identified who only received chemotherapy without prior autoimmune diagnosis. The distribution of immunotherapy and chemotherapy patients do not differentiate significantly in age or gender. 98.5% of the patients with immune checkpoint inhibitors can be matched to at least one sample from chemotherapy patients.

The distribution of immunotherapy treatments is presented in table 1. Pembrolizumab and Nivolumab has been increasingly popular after 2013, which has been confirmed in existing literature [30]. Although novel checkpoint inhibitors evolve each year, their application is limited, constituting a small percentage in the data.

4.2 Risk comparison of irAE

The Kaplan-Meier survival plot for immunotherapy in comparison to chemotherapy is shown in Figure 2. In the pre-matching analysis, we utilize all the samples who are qualified for this study, with vanilla log-rank test and cumulative incidence rate calculation. In post-matching analysis, adjusted samples are acquired through matching

procedure and are assigned with corresponding weights (Section 3). Hazard ratio and accumulative incidence rate is shown in Table A11. According to both unadjusted (pre-matching) and adjusted (post-matching) samples, immunotherapy for lung cancer patients was associated with significantly higher risk of irAEs ($p < 0.005$).

4.3 Sensitivity analysis

We conducted several additional sensitivity analyses to illustrate the robustness of our conclusion.

To investigate the irAEs of different immunotherapy type, we conduct a drug-specific analysis on each type of immunotherapy, including Pembrolizumab, Nivolumab, Atezolizumab and Ipilimumab (see section 4.3.1). If a patient receives combination immunotherapy, they will be counted once in each subgroup of specific treatment they receive.

Immune checkpoint inhibitor may increase the risk of certain type of diseases [31]. To validate this we additionally investigated the increased risk of immune checkpoint inhibitors on four major types of irAEs: hypothyroidism, thyroiditis, rheumatoid arthritis and myalgia (see section 4.3.2).

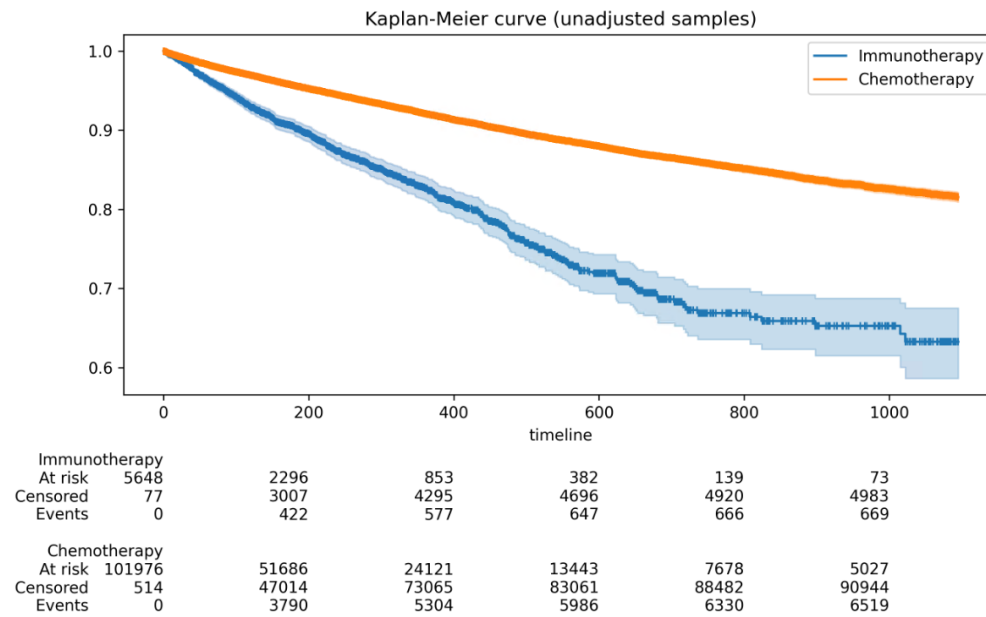
We also conducted stratified sensitivity analysis. In the main analysis, we set a 30-day quiescence, indicating the diagnosis of lung cancer must be at least 30 days after the first medical record date. We extensively investigate 60 days and 90 days as quiescence periods in the Supplementary Material Table S3.

4.3.1 Therapy-specific analysis

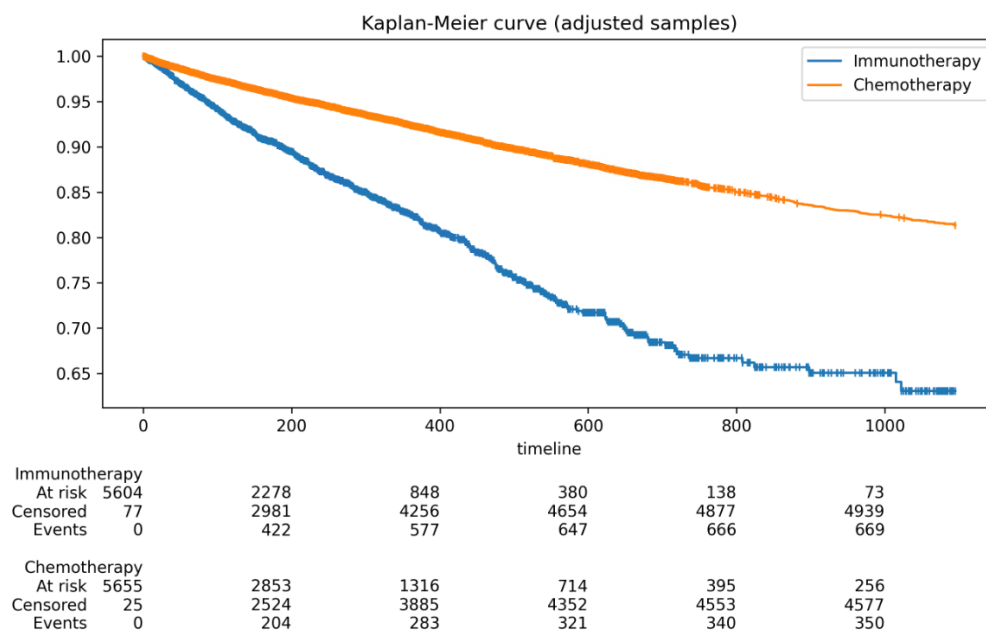
In this section, we quantitatively compare irAEs among different immunotherapies. Four main immunotherapy treatments are considered in this study: Ipilimumab Yervoy, Pembrolizumab Keytruda, Nivolumab Opdivo and Atezolizumab Tecentriq. While there are also other types of immunotherapy, the sample size is not enough for therapy-specific analysis. The Kaplan-Meier curves for unadjusted and adjusted samples are shown in Fig 3. Details of cumulative incidence ratio (CIR) are shown in Table 4.

4.3.2 Disease-specific analysis

Existing literature has revealed that immunotherapy may increase the risk of certain autoimmune-related diseases. In this section we explore the irAEs of immunotherapy on five main categories of irAEs from the observations: diabetes [32], hypothyroidism [33], Hashimoto's thyroiditis [34], rheumatoid arthritis [35] and myalgia and myositis [36]. While the adverse effect of diabetes is not statistically significant, the other four



(a) Kaplan-Meier curve for unadjusted samples with 95% confidence interval.



(b) Kaplan-Meier curve for adjusted samples. See Table 2 for post-match confidence interval.

Fig. 2: Kaplan-Meier curve for unadjusted and adjusted samples through time (in days).

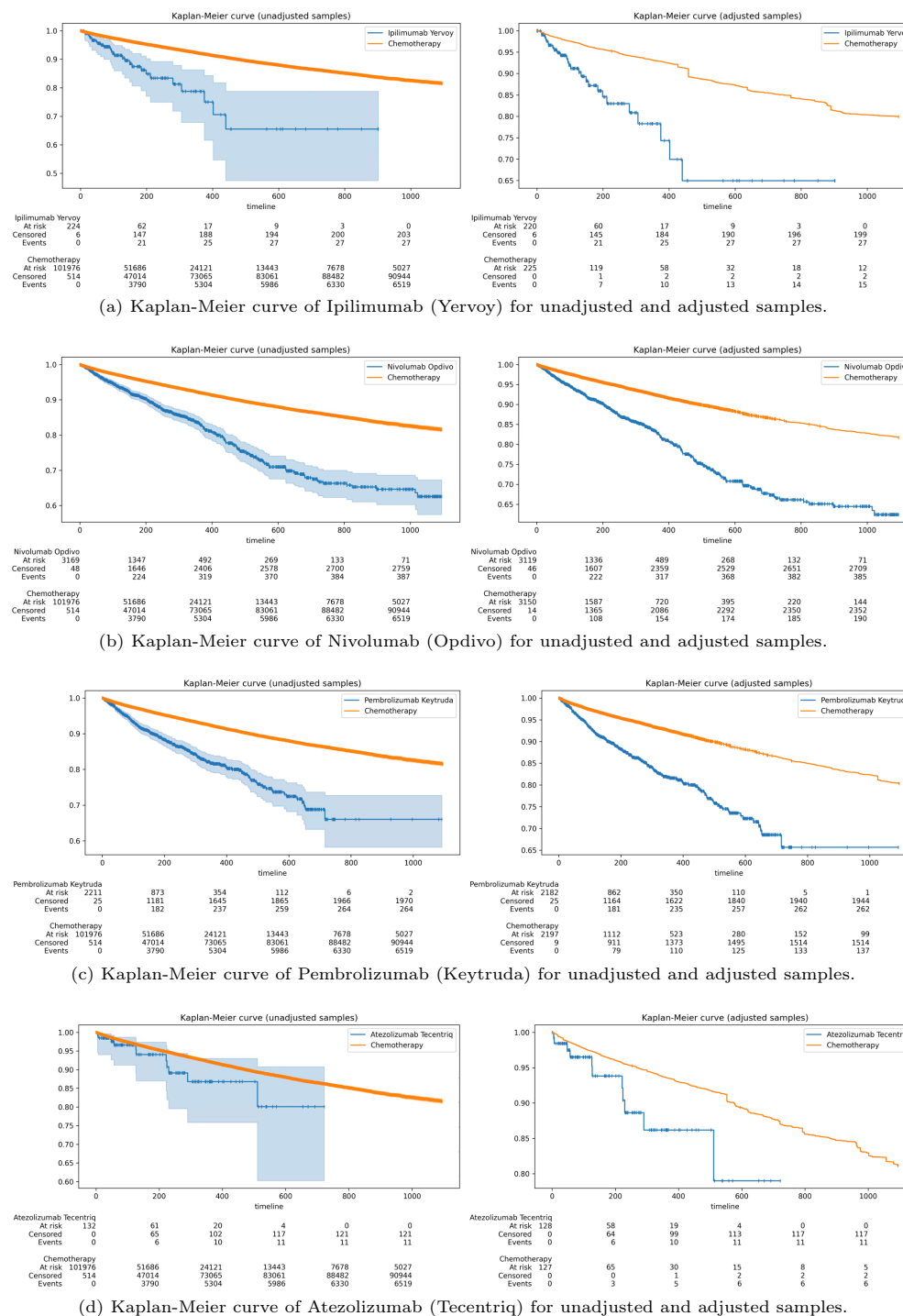


Fig. 3: Therapy-specific analysis for unadjusted (left) and adjusted (right) samples.

diseases are shown to be significantly related to immunotherapy. Table 5 shows the detailed results for unmatched and matched samples.

4.4 Additional analysis

4.4.1 Sub-population analysis

This study additionally analyzes irAEs among different subsets of study populations. We compared the risk of irAEs across different age groups. Comparison across different age groups in Supplementary Material Table S2 reveals that found that the irAE is statistically significant across all age groups, especially for patients of age 30 to 40.

4.4.2 Sensitivity on quiescence time

In the main analysis, the quiescence time is fixed to 30 days, which indicates that any patient with no prior medical history at least 30 days before the first diagnosis of lung cancer will be excluded from the study. By further setting the time to 60 days, 90 days and 120 days, we explore whether the conclusion is robust to the selection of the period length of quiescence, with results shown in Table S3. The results illustrates the robustness of the conclusion to selection criteria of patients.

4.4.3 Sensitivity on matching criteria

To balance the covariates of treatment group and control group, two variables are defined to quantify the overall health condition and the frequency of hospital visit: the total number of disease types of a patient one year prior the first diagnosis of lung cancer (sickness) and the number of hospital visits one year prior to the first diagnosis (hospital utilization). In the main study both variables are stratified into 3 levels by 33.3% and 66.6% quantile, and only patients with identical level of sickness and hospital utilization will be matched. Table S11 shows the results using different stratify strategies, which indicates that the results is insensitive to the matching criteria.

5 Discussion

In this study we conducted a large-scale cohort study to analyze the risk of autoimmune diseases associated with immuno checkpoint therapy on lung cancer patients. Results have shown that patients who received immunotherapy has patients with immunotherapy have a higher risk of developing irAEs, in comparison with lung cancer patients who receive chemotherapy. Specifically, certain immunotherapy treatments are associated with higher risk of autoimmune-related adverse effects, and risk of certain

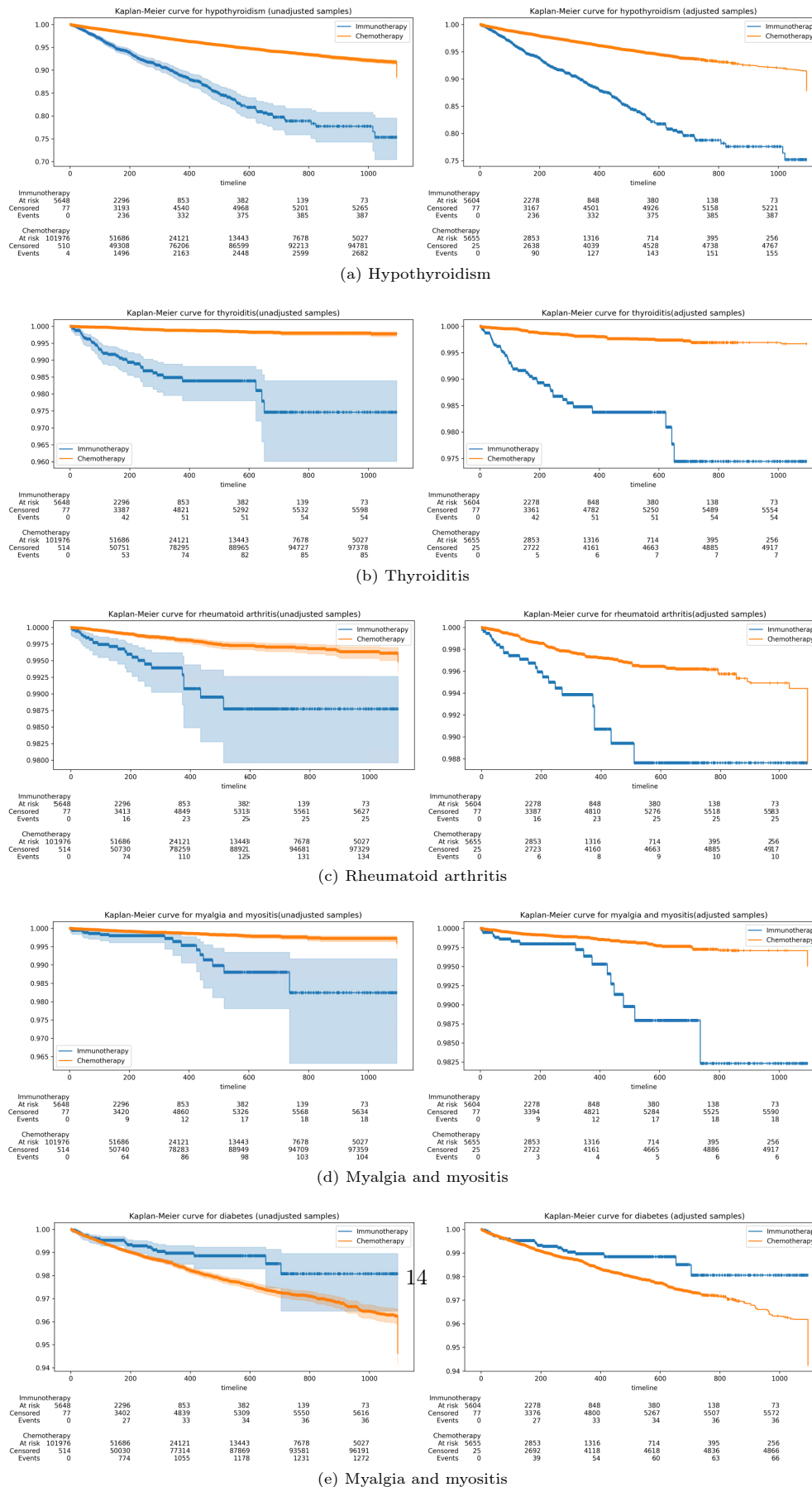


Fig. 4: Disease-specific analysis for unadjusted (left) and adjusted (right) samples.

diseases is significantly higher than chemotherapy. Our result confirm the results of existing literature [37] and reveal the association of current immunotherapy drugs and the autoimmune-related adverse effects. Our result also suggests the slight difference in the presence of autoimmune syndromes among different immune checkpoint inhibitors, possibly due to difference of action mechanisms at PD-1 and PD-L1.

Thanks to the population size of lung cancer patients in the CMS source data, we conduct a significantly larger scale cohort study and explore autoimmune-related adverse effects from real world data compared to randomized controlled trials, which enables the discovery of certain diseases with very low incidence rate. Through a matching procedures, we investigate the causal relation between immunotherapy and the risk of autoimmune disorder with greater statistical power. Besides, our cohort study is broadly representative of real-world patients compared to the extrapolation from randomized controlled trial results, thus indicating more external validity [37]. An additional sensitivity analysis further shows that the risk of irAEs brought by immunotherapy is significant among different gender and age groups, which illustrates the robustness of our conclusion.

Our method complements the existing approaches of investigating irAEs of cancer therapies, and can be seen as a general methodology that can be extended to other treatment and disease phenotype researches. With specific drug (procedure) codes and corresponding ICD codes, our approach can evaluate any treatment type of interest for specific disease types, and has great potential for post-market adverse effect monitoring of FDA approved drugs. The sensitivity analyses conducted in the paper are also crucial for assuring the credibility of revealed adverse effects among different populations, i.e., age groups and genders.

There are also limitations in this study. First, to conduct the analysis, the diagnosis codes of irAEs must be pre-specified, while in the medical records, some less severe symptoms, such as fatigue and nausea, are not encoded to ICD codes properly, resulting in an potential inductive bias. Second, this study can only identify the date of diagnosis of certain disease, instead of the exact time of disease development. Therefore, some patients who have developed low-level autoimmune syndromes but were not clinically diagnosed, either due to inadequate syndromes or inaccessibility to hospital visits. Therefore, these patients cannot be accurately captured in the study. Besides, the ICD codes do not contain sufficient details that differentiate sub-categories of diseases or therapies, for example, histological sub-types and stage information of lung cancer or PD-L1 status. Another concern is the time difference of immunotherapy approval by FDA, and the approval of application on different cancer subtypes. For instance,

Table 1: Patient characteristics

		Ipilimumab		Nivolumab		Pembrolizumab		Atezolizumab		Immunotherapy		Chemotherapy	
		N ¹	p ²	N	p	N	p	N	p	N	p	N	p
Total		230	4.0%	3217	56.2%	2236	39.1%	132	2.3%	5725 ³	-	102490	-
Gender	Female	100	43.5%	1501	46.7%	1102	49.3%	55	41.7%	2706	47.3%	48495	47.3%
	Male	125	54.3%	1653	51.4%	1111	49.7%	76	57.6%	2926	51.1%	50731	49.5%
	Unknown	5	2.1%	63	2.0%	23	1.0%	1	0.8%	93	1.6%	3264	3.2%
Race and ethnicity	White	132	57.4%	1539	47.8%	1098	49.1%	62	47.0%	2781	48.6%	54160	52.9%
	Black	15	6.5%	473	14.7%	366	16.4%	24	18.2%	876	15.3%	18581	18.1%
	American Indian	5	2.2%	98	3.0%	124	5.5%	10	7.6%	231	4.0%	1293	1.3%
	Asian	2	0.9%	28	8.7%	14	0.6%	0	0	44	0.8%	1794	1.8%
	Hispanic	1	0.4%	9	0.3%	18	0.8%	0	0	30	0.5%	3065	3.0%
	Native Hawaiian	1	0.4%	4	0.1%	3	0.1%	0	0	8	0.1%	438	0.4%
	Two or more races	17	7.4%	221	6.9%	150	6.7%	9	6.8%	383	6.7%	2923	2.9%
	Unknown	57	24.8%	845	26.3%	463	20.7%	27	20.5%	1372	24.0%	20236	19.7%
Age	[0, 30)	10	4.3%	15	0.5%	8	0.4%	1	0.8%	31	0.5%	928	0.9%
	[30, 40)	12	5.2%	39	1.2%	17	0.8%	3	2.3%	65	1.1%	2291	2.2%
	[40, 50)	47	20.4%	273	8.5%	125	5.6%	9	6.8%	434	7.6%	15200	14.8%
	[50, 60)	87	37.8%	1130	35.1%	666	29.8%	41	31.1%	1884	32.9%	42147	41.1%
	[60, 70)	55	23.9%	1018	31.6%	717	32.1%	39	29.5%	1813	31.7%	28498	27.8%
	[70, 80)	14	6.1%	508	15.8%	444	19.9%	20	15.2%	980	17.1%	9909	9.7%
	[80, 100)	4	1.7%	196	6.1%	256	11.4%	19	14.4%	476	8.3%	2196	2.1%
	Unknown	1	0.4%	38	1.2%	3	0.1%	0	0	42	0.7%	1321	1.3%
Post-matching size		226	97.4%	3165	98.4%	2207	98.7%	128	97.0%	5681	98.5%		

Nivolumab was approved by FDA for metastatic squamous non-small cell lung cancer in March 2015, and was later extended to metastatic non-squamous non-small cell lung cancer in October, 2015. In contrast, Atezolizumab was approved in October, 2016. Such time span may lead to evolution of chemotherapy treatments and time shifts of patient characteristics. However, such shifts are discarded in this study leading to potential inference bias. Lastly, the dataset cannot incorporate all lung cancer patients in the U.S. and the medicaid dataset mainly contains patients with relatively lower income, which may not accurately reflect the characteristics of the entire population. Further studies are still needed to verify our findings in other populations.

In conclusion, this study analyzes the risk of irAEs in lung cancer patients who receive immunotherapy, and suggests the necessity of clinically monitoring the autoimmune adverse effects in the patients with immune checkpoint inhibitors. Our results confirms the increased risk of autoimmune-related adverse effects due to immunotherapy compared to chemotherapy, and inspires further studies on the mechanism of such risk and monitoring of other adverse effects of immunotherapy for lung cancer patients.

¹The number of patients in the category.

²The proportion (in percentage) of patients in relation to the sub-population.

³Some patients may receive combination therapy, which may be counted more than once in the subgroups.

⁴Cumulative incidence rate

Table 2: Cumulative incidence rate and hazard ratio

	<i>T</i> (months)	CIR ⁴ (immunotherapy)	CIR (chemotherapy)	Hazard ratio
Unadjusted	1	0.014 [0.012, 0.018]	0.0085 [0.0080, 0.0091]	1.76 [1.40, 2.20]
	2	0.031 [0.027, 0.036]	0.016 [0.015, 0.017]	2.08 [1.78, 2.43]
	3	0.044 [0.038, 0.049]	0.022 [0.021, 0.023]	2.16 [1.89, 2.46]
	6	0.069 [0.063, 0.076]	0.035 [0.033, 0.036]	2.24 [2.02, 2.48]
	12	0.097 [0.089, 0.101]	0.049 [0.048, 0.051]	2.29 [2.09, 2.49]
	24	0.116 [0.108, 0.124]	0.0606 [0.059, 0.062]	2.38 [2.20, 2.59]
	36	0.117 [0.109, 0.126]	0.064 [0.0626, 0.0655]	2.36 [2.18, 2.56]
log-rank test		$p < 0.01$		
Adjusted	1	0.015 [0.012, 0.018]	0.0085 [0.0082, 0.0087]	1.75 [1.23, 2.51]
	2	0.032 [0.027, 0.036]	0.016 [0.015, 0.016]	2.19 [1.69, 2.84]
	3	0.045 [0.039, 0.050]	0.021 [0.021, 0.023]	2.30 [1.85, 2.88]
	6	0.070 [0.063, 0.076]	0.034 [0.034, 0.035]	2.32 [1.94, 2.76]
	12	0.098 [0.090, 0.106]	0.048 [0.047, 0.048]	2.40 [2.08, 2.79]
	24	0.118 [0.109, 0.126]	0.057 [0.056, 0.058]	2.49 [2.18, 2.84]
	36	0.119 [0.110, 0.127]	0.059 [0.059, 0.060]	2.44 [2.14, 2.79]
log-rank test		$p < 0.01$		

Table 3: ICD code list of immunotherapies incorporated in the study.

Immunotherapy	Treatment mechanism	HCPSC Code
Ipilimumab	CTLA-4 Inhibitor	J9228
Nivolumab	PD-1 Inhibitor	J9299
Pembrolizumab	PD-1 Inhibitor	J9271
Atezolizumab	PD-L1 Inhibitor	J9022
Durvalumab	PD-L1 Inhibitor	J9173
Avelumab	PD-L1 Inhibitor	J9023

Declarations

- Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

- Author Contributions

Yan Sun and Shihao Yang conceived and planned the protocol of the study. Yan Sun and Yunfan Guan carried out the analysis and contributed to the interpretation of the results. Yan Sun took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

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Table 4: Cumulative incidence rate and hazard ratio

Therapy		Unadjusted			Adjusted		
	T (months)	immunotherapy	chemotherapy	Hazard ratio	immunotherapy	chemotherapy	Hazard ratio
Ipilimumab	1	0.022 [0.0029, 0.0406]	0.0085 [0.0080, 0.0091]	2.62 [1.09, 6.31]	0.022 [0.0029, 0.0406]	0.0080 [0.0068, 0.0093]	3.52 [0.44, 27.96]
	2	0.039 [0.014, 0.064]	0.016 [0.015, 0.017]	2.68 [1.39, 5.16]	0.039 [0.014, 0.064]	0.017 [0.015, 0.018]	3.05 [0.72, 12.88]
	3	0.048 [0.020, 0.075]	0.022 [0.021, 0.023]	2.46 [1.36, 4.46]	0.048 [0.020, 0.075]	0.023 [0.021, 0.025]	2.78 [0.80, 9.60]
	6	0.083 [0.047, 0.118]	0.035 [0.033, 0.036]	2.97 [1.89, 4.66]	0.083 [0.047, 0.118]	0.037 [0.034, 0.039]	3.47 [1.30, 9.24]
	12	0.104 [0.065, 0.144]	0.049 [0.048, 0.051]	2.99 [2.01, 4.47]	0.104 [0.065, 0.144]	0.051 [0.048, 0.054]	3.39 [1.48, 7.74]
	24	0.117 [0.076, 0.159]	0.0606 [0.059, 0.062]	3.09 [2.11, 4.50]	0.117 [0.076, 0.159]	0.0600 [0.056, 0.063]	3.56 [1.66, 7.67]
Pembrolizumab	1	0.016 [0.011, 0.022]	0.0085 [0.0080, 0.0091]	1.99 [1.43, 2.77]	0.016 [0.011, 0.022]	0.0092 [0.0088, 0.0097]	1.93 [1.06, 3.54]
	2	0.034 [0.027, 0.042]	0.016 [0.015, 0.017]	2.62 [1.09, 6.31]	0.034 [0.027, 0.042]	0.017 [0.016, 0.017]	2.37 [1.52, 3.71]
	3	0.048 [0.039, 0.057]	0.022 [0.021, 0.023]	2.43 [2.00, 2.94]	0.048 [0.039, 0.057]	0.023 [0.022, 0.024]	2.49 [1.70, 3.64]
	6	0.076 [0.065, 0.087]	0.035 [0.033, 0.036]	2.52 [2.16, 2.93]	0.076 [0.065, 0.087]	0.037 [0.036, 0.038]	2.40 [1.79, 3.22]
	12	0.104 [0.091, 0.116]	0.049 [0.048, 0.051]	2.49 [2.18, 2.84]	0.104 [0.091, 0.116]	0.051 [0.050, 0.052]	2.39 [1.86, 3.06]
	24	0.118 [0.105, 0.131]	0.0606 [0.059, 0.062]	2.49 [2.20, 2.82]	0.118 [0.105, 0.131]	0.061 [0.060, 0.062]	2.36 [1.88, 2.96]
Nivolumab	1	0.014 [0.010, 0.018]	0.0085 [0.0080, 0.0091]	1.67 [1.24, 2.25]	0.014 [0.010, 0.018]	0.0088 [0.0084, 0.0091]	1.67 [0.98, 2.83]
	2	0.030 [0.024, 0.036]	0.016 [0.015, 0.017]	2.00 [1.63, 2.45]	0.030 [0.024, 0.036]	0.016 [0.016, 0.017]	2.01 [1.37, 2.95]
	3	0.042 [0.035, 0.049]	0.022 [0.021, 0.023]	2.05 [1.72, 2.44]	0.042 [0.035, 0.049]	0.022 [0.022, 0.023]	2.03 [1.47, 2.80]
	6	0.066 [0.057, 0.074]	0.035 [0.033, 0.036]	2.08 [1.81, 2.39]	0.066 [0.057, 0.074]	0.035 [0.035, 0.036]	2.04 [1.58, 2.63]
	12	0.094 [0.084, 0.104]	0.049 [0.048, 0.051]	2.16 [1.93, 2.43]	0.094 [0.084, 0.104]	0.049 [0.048, 0.050]	2.13 [1.72, 2.64]
	24	0.119 [0.108, 0.130]	0.0606 [0.059, 0.062]	2.35 [2.12, 2.61]	0.119 [0.108, 0.130]	0.058 [0.057, 0.059]	2.31 [1.90, 2.80]
Atezolizumab	1	0.015 [0.010, 0.022]	0.0085 [0.0080, 0.0091]	1.79 [1.45, 2.18]	0.015 [0.010, 0.022]	0.0097 [0.0097, 0.0117]	2.28 [1.43, 3.79]
	2	0.030 [0.024, 0.036]	0.016 [0.015, 0.017]	1.99 [1.74, 2.29]	0.030 [0.024, 0.036]	0.018 [0.015, 0.020]	1.29 [0.26, 6.59]
	3	0.042 [0.035, 0.049]	0.022 [0.021, 0.023]	1.47 [0.55, 3.93]	0.042 [0.035, 0.049]	0.024 [0.021, 0.026]	1.08 [0.23, 4.97]
	6	0.045 [0.010, 0.081]	0.035 [0.033, 0.036]	1.43 [0.64, 3.20]	0.045 [0.010, 0.081]	0.038 [0.034, 0.042]	1.17 [0.33, 4.15]
	12	0.076 [0.031, 0.121]	0.049 [0.048, 0.051]	1.71 [0.92, 3.18]	0.076 [0.031, 0.121]	0.051 [0.047, 0.056]	1.57 [0.53, 4.64]
	24	0.083 [0.036, 0.130]	0.0606 [0.059, 0.062]	1.68 [0.93, 3.04]	0.083 [0.036, 0.130]	0.062 [0.057, 0.067]	1.53 [0.56, 4.19]
	36	0.083 [0.036, 0.130]	0.064 [0.0626, 0.0655]	1.68 [0.94, 3.04]	0.083 [0.036, 0.130]	0.064 [0.060, 0.069]	1.53 [0.56, 4.17]

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• Data Availability Statement

The introduction of datasets analyzed for this study can be found at: <https://www.ccwdata.org/web/guest/data-dictionaries>.

Appendix A Supplementary Tables and Figures

Table 5: Cumulative incidence rate and hazard ratio

Therapy		Unadjusted			Adjusted		
<i>T</i> (months)		immunotherapy	chemotherapy	Hazard ratio	immunotherapy	chemotherapy	Hazard ratio
Hypothyroidism	1	0.0079 [0.0056, 0.010]	0.0033 [0.0030, 0.0036]	2.46 [1.80, 3.36]	0.0079 [0.0056, 0.010]	0.0036 [0.0035, 0.0037]	2.25 [1.33, 3.79]
	2	0.016 [0.012, 0.019]	0.0062 [0.0057, 0.0066]	2.64 [2.12, 3.30]	0.016 [0.012, 0.019]	0.0067 [0.0066, 0.0068]	2.48 [1.69, 3.63]
	3	0.023 [0.019, 0.027]	0.0084 [0.0078, 0.0089]	2.94 [2.45, 3.54]	0.023 [0.019, 0.027]	0.0090 [0.0088, 0.0091]	2.63 [1.92, 3.61]
	6	0.039 [0.034, 0.044]	0.014 [0.013, 0.014]	3.20 [2.78, 3.69]	0.039 [0.034, 0.044]	0.014 [0.014, 0.014]	3.02 [2.35, 3.88]
	12	0.056 [0.050, 0.062]	0.020 [0.019, 0.021]	3.26 [2.90, 3.67]	0.056 [0.050, 0.062]	0.020 [0.020, 0.021]	3.11 [2.53, 3.84]
	24	0.067 [0.061, 0.074]	0.025 [0.024, 0.026]	3.39 [3.05, 3.78]	0.068 [0.061, 0.074]	0.025 [0.025, 0.025]	3.26 [2.69, 3.94]
Thyroiditis	1	0.016 [0.011, 0.022]	0.0085 [0.0080, 0.0091]	1.99 [1.43, 2.77]	0.012 [3.2e-4, 0.0021]	1.0e-4 [9.1e-5, 1.2e-4]	1.93 [1.06, 3.54]
	2	0.0033 [0.0018, 0.0048]	1.6e-4 [1.5e-4, 1.7e-4]	9.77 [2.29, 38.72]	0.0033 [0.0018, 0.0048]	1.7e-4 [1.5e-4, 1.8e-4]	9.84 [2.31, 40.91]
	3	0.0046 [0.0028, 0.0063]	1.7e-4 [1.7e-4, 1.9e-4]	10.56 [2.84, 38.60]	0.0046 [0.0028, 0.0063]	1.8e-4 [1.7e-4, 2.0e-4]	11.05 [3.03, 40.27]
	6	0.0070 [0.0049, 0.0092]	3.5e-4 [3.3e-4, 3.6e-4]	9.61 [3.69, 25.74]	0.0070 [0.0049, 0.0092]	3.5e-4 [3.3e-4, 3.7e-4]	9.49 [3.64, 24.68]
	12	0.0088 [0.0064, 0.010]	5.7e-4 [5.5e-4, 6.0e-4]	8.18 [3.21, 20.36]	0.0088 [0.0064, 0.011]	5.8e-4 [5.5e-4, 6.1e-4]	8.82 [3.90, 19.95]
	24	0.0095 [0.0068, 0.011]	7.0e-4 [6.6e-4, 7.2e-4]	9.18 [4.64, 19.89]	0.0095 [0.0070, 0.012]	7.1e-4 [6.8e-4, 7.4e-4]	8.60 [4.02, 18.43]
RA	1	0.0094 [0.0069, 0.011]	7.1e-4 [6.9e-4, 7.4e-4]	8.27 [3.82, 20.10]	0.0095 [0.0070, 0.012]	7.2e-4 [6.9e-4, 7.5e-4]	8.55 [4.00, 18.27]
	2	0.0014 [4.3e-4, 0.0024]	2.0e-4 [1.2e-4, 2.9e-4]	7.14 [3.16, 16.13]	0.0014 [4.3e-4, 0.0024]	2.6e-4 [2.4e-4, 2.8e-4]	5.53 [0.97, 31.52]
	3	0.0019 [7.9e-4, 0.0031]	3.7e-4 [2.5e-4, 4.9e-4]	5.60 [2.86, 10.96]	0.0019 [7.9e-4, 0.0031]	4.3e-4 [4.1e-4, 4.6e-4]	4.17 [1.13, 15.45]
	6	0.0024 [0.012, 0.0037]	6.9e-4 [5.3e-4, 8.5e-4]	4.00 [2.26, 7.10]	0.0025 [0.0012, 0.0038]	7.4e-4 [7.1e-4, 7.8e-4]	2.69 [1.02, 7.11]
	12	0.0035 [0.0020, 0.0050]	0.0011 [8.6e-4, 0.0013]	3.94 [2.45, 6.35]	0.0035 [0.0020, 0.0051]	0.0011 [0.0010, 0.0011]	2.66 [1.20, 5.91]
	24	0.0044 [0.0027, 0.0061]	0.0013 [0.0010, 0.0015]	4.34 [2.83, 6.67]	0.0044 [0.0027, 0.0061]	0.0013 [0.0012, 0.0013]	3.13 [1.49, 6.55]
Myalgia (myositis)	1	5.2e-4 [0.0011]	1.9e-4 [1.0e-4, 2.7e-4]	2.88 [0.85, 9.72]	5.3e-4 [0.0011]	2.4e-4 [2.2e-4, 2.6e-4]	3.00 [0.32, 28.79]
	2	0.0010 [2.1e-4, 0.0019]	0.016 [0.015, 0.017]	1.99 [0.74, 5.29]	0.0011 [2.1e-4, 0.0019]	3.3e-4 [3.1e-4, 3.5e-4]	3.74 [0.67, 20.72]
	3	0.0012 [3.2e-4, 0.0021]	3.5e-4 [2.4e-4, 4.7e-4]	3.69 [1.64, 8.28]	0.0012 [3.2e-4, 0.0021]	4.1e-4 [3.8e-4, 4.3e-4]	3.23 [0.73, 14.39]
	6	0.0016 [5.5e-4, 0.0026]	6.0e-4 [4.5e-4, 7.6e-4]	2.89 [1.44, 5.82]	0.0016 [5.5e-4, 0.0026]	7.4e-4 [7.0e-4, 7.7e-4]	2.63 [0.79, 8.78]
	12	0.0019 [7.9e-4, 0.0031]	7.9e-4 [6.2e-4, 9.6e-4]	2.80 [1.49, 5.26]	0.0019 [7.9e-4, 0.0031]	9.5e-4 [9.2e-4, 9.9e-4]	2.73 [0.92, 8.13]
	24	0.0083 [0.036, 0.130]	0.0606 [0.059, 0.062]	1.68 [0.93, 3.04]	0.0030 [0.0016, 0.0044]	0.0012 [0.0011, 0.0012]	3.65 [1.43, 9.30]
Diabetes	1	0.012 [3.2e-4, 0.0021]	0.0018 [0.0015, 0.0021]	0.70 [0.33, 1.48]	0.0012 [3.2e-4, 0.0021]	0.0018 [0.0018, 0.0019]	0.73 [0.28, 1.92]
	2	0.0028 [0.0014, 0.0042]	0.0031 [0.0028, 0.0035]	0.93 [0.56, 1.54]	0.0028 [0.0014, 0.0042]	0.0031 [0.0030, 0.0031]	1.02 [0.51, 2.03]
	3	0.0035 [0.0020, 0.0050]	0.0044 [0.0040, 0.0048]	0.84 [0.54, 1.32]	0.0035 [0.0020, 0.0051]	0.0044 [0.0044, 0.0045]	0.94 [0.52, 1.72]
	6	0.0040 [0.0024, 0.0057]	0.0071 [0.0066, 0.0076]	0.63 [0.42, 0.96]	0.0040 [0.0024, 0.0057]	0.0069 [0.0068, 0.0070]	0.69 [0.41, 1.17]
	12	0.0058 [0.0038, 0.0077]	0.0098 [0.0092, 0.010]	0.68 [0.48, 0.97]	0.0058 [0.0038, 0.0078]	0.0091 [0.0090, 0.0092]	0.74 [0.48, 1.14]
	24	0.0063 [0.0042, 0.0083]	0.012 [0.011, 0.013]	0.65 [0.47, 0.91]	0.0063 [0.0043, 0.0084]	0.011 [0.011, 0.011]	0.70 [0.46, 1.06]
	36	0.0063 [0.0042, 0.0083]	0.012 [0.012, 0.013]	0.64 [0.46, 0.89]	0.0063 [0.0043, 0.0084]	0.011 [0.011, 0.011]	0.68 [0.45, 1.02]

Table A1: HCPCS codes for immunotherapy.

Chemotherapy name	Code	Code type	Description
CARBOPLATIN	J9045	HCPC	Carboplatin, 50 mg
CISPLATIN	J9062	HCPC	Cisplatin, 50 mg
CISPLATIN	C9418	HCPC	CISPLATIN, POWDER OR SOLUTION, BRAND NAME, PER 10 MG
CISPLATIN	J9060	HCPC	Cisplatin, powder or solution, per 10 mg
CISPLATIN	209622	HCPC	REIMB CISPLATIN 10 MG VIAL (PLATINOL).
DOCETAXEL	J9170	HCPC	Docetaxel, 20 mg
DOCETAXEL	J9171	HCPC	Injection, docetaxel, 1 mg
ETOPOSIDE	J9181	HCPC	Etoposide, 10 mg
ETOPOSIDE	J9182	HCPC	Etoposide, 100 mg
ETOPOSIDE	C9425	HCPC	ETOPOSIDE, BRAND NAME, 10 MG
ETOPOSIDE	C9414	HCPC	ETOPOSIDE, ORAL, BRAND NAME, 50 MG
ETOPOSIDE	J8560	HCPC	Etoposide; oral, 50 mg
GEMCITABINE	J9201	HCPC	Gemcitabine HCl, 200 mg
IRINOTECAN	81350	CPT4	IRINOTECAN TOXICITY, UGT1A1*28, GENOTYPING
IRINOTECAN	J9206	HCPC	Irinotecan, 20 mg
MECHLORETHAMINE	J9230	HCPC	Mechlorethamine HCl, (nitrogen mustard), 10 mg
METHOTREXATE	83520	CPT4	METHOTREXATE LEVEL
METHOTREXATE	J9250	HCPC	Methotrexate sodium, 5 mg
METHOTREXATE	J9260	HCPC	Methotrexate sodium, 50 mg
METHOTREXATE	J8610	HCPC	Methotrexate: oral, 2.5 mg
PACLITAXEL	J9264	HCPC	Injection, paclitaxel protein-bound particles, 1 mg
PACLITAXEL	J9267	HCPC	INJECTION, PACLITAXEL, 1 MG
PACLITAXEL	J9265	HCPC	Paclitaxel, 30 mg
PACLITAXEL	C9431	HCPC	PACLITAXEL, BRAND NAME, 30 MG
PEMETREXED	J9305	HCPC	Injection, pemetrexed, 10 mg
PEMETREXED	C9213	HCPC	INJECTION, PEMETREXED, PER 10 MG
VINBLASTINE	J9360	HCPC	Vinblastine sulfate, 1 mg
VINORELBINE	C9440	HCPC	VINORELBINE TARTRATE, BRAND NAME, PER 10 MG
VINORELBINE	J9390	HCPC	Vinorelbine tartrate, per 10 mg

Table A2: 3-year cumulative incidence rate and hazard ratio for stratified age groups.

Unmatched samples			
	CIR (immunotherapy)	CIR (chemotherapy)	Hazard ratio
≤ 30	0.041 [0,0.087]	0.044 [0.036,0.052]	1.88 [0.59,5.97]
(30, 40]	0.14 [0.054,0.22]	0.059 [0.049,0.069]	3.42 [1.74,6.73]
(40, 50]	0.13 [0.10,0.17]	0.067 [0.063,0.071]	2.82 [2.16,3.68]
(50, 60]	0.12 [0.10,0.13]	0.067 [0.065,0.070]	2.21 [1.93,2.54]
> 60	0.12 [0.10,0.13]	0.061 [0.059,0.063]	2.36 [2.12,2.63]
Matched samples			
	CIR (immunotherapy)	CIR (chemotherapy)	Hazard ratio
≤ 30	0.039 [0,0.083]	0.042 [0.034,0.050]	1.83 [0.55,6.01]
(30, 40]	0.13 [0.052,0.23]	0.061 [0.049,0.069]	3.40 [1.71,6.72]
(40, 50]	0.13 [0.10,0.17]	0.066 [0.062,0.073]	2.84 [2.15,3.69]
(50, 60]	0.12 [0.10,0.13]	0.068 [0.066,0.072]	2.20 [1.90,2.57]
> 60	0.13 [0.10,0.13]	0.064 [0.058,0.065]	2.34 [2.10,2.65]

Table A3: 3-year cumulative incidence rate and hazard ratio for different quiescence time threshold.

Unmatched samples				
Quiescence time	CIR (immunotherapy)	CIR (chemotherapy)	Hazard ratio	
30	0.117 [0.109, 0.126]	0.064 [0.063, 0.066]	2.36 [2.18, 2.56]	
60	0.112 [0.102, 0.133]	0.063 [0.062, 0.066]	2.34 [2.12, 2.55]	
90	0.114 [0.107, 0.128]	0.063 [0.063, 0.067]	2.41 [2.31, 2.62]	
120	0.110 [0.099, 0.131]	0.061 [0.059, 0.065]	2.29 [2.12, 2.75]	
Matched samples				
Quiescence time	CIR (immunotherapy)	CIR (chemotherapy)	Hazard ratio	
30	0.119 [0.110, 0.127]	0.059 [0.059, 0.060]	2.44 [2.14, 2.79]	
60	0.113 [0.101, 0.131]	0.057 [0.057, 0.058]	2.46 [2.12, 2.82]	
90	0.115 [0.105, 0.127]	0.056 [0.055, 0.057]	2.38 [2.10, 2.84]	
120	0.110 [0.098, 0.132]	0.054 [0.052, 0.063]	2.42 [2.13, 2.86]	

Table A4-1: ICD-9 code for autoimmune diseases and syndromes included in the database (part 1).

icd	Super PheWAS Code	PheWASString
135	697	Sarcoidosis
245	Thyroiditis	Thyroiditis
245	Thyroiditis	Thyroiditis, acute and subacute
245.1	Thyroiditis	Thyroiditis, acute and subacute
245.2	Thyroiditis	Chronic lymphocytic thyroiditis
245.3	Thyroiditis	Thyroiditis
245.8	Thyroiditis	Thyroiditis
245.9	Thyroiditis	Thyroiditis
250.01	DM	Type 1 diabetes
250.03	DM	Type 1 diabetic ketoacidosis
250.1	DM	Diabetes mellitus
250.11	DM	Type 1 diabetic ketoacidosis
250.13	DM	Type 1 diabetic ketoacidosis
250.21	DM	Type 1 diabetes
250.23	DM	Type 1 diabetes
250.31	DM	Type 1 diabetes
250.33	DM	Type 1 diabetes
250.41	DM	Type 1 diabetes nephropathy
250.43	DM	Type 1 diabetes nephropathy
250.51	DM	Type 1 diabetic retinopathy
250.53	DM	Type 1 diabetic retinopathy
250.61	DM	Type 1 diabetic neuropathy
250.63	DM	Type 1 diabetic neuropathy
250.71	DM	Type 1 diabetic peripheral circulatory disorders
250.73	DM	Type 1 diabetic peripheral circulatory disorders
250.81	DM	Type 1 diabetes
250.83	DM	Type 1 diabetes
250.91	DM	Type 1 diabetes
250.93	DM	Type 1 diabetes
279.49	279.2	Autoimmune disease NEC
283	283.1	Autoimmune hemolytic anemias
337.1	337.1	Peripheral autonomic neuropathy
443	443.1	Raynaud's syndrome
555	IBD	Crohn's disease
555.1	IBD	Crohn's disease
555.2	IBD	Crohn's disease
555.9	IBD	Crohn's disease
556	IBD	Ulcerative colitis
556	IBD	Ulcerative colitis
556.1	IBD	Ulcerative colitis
556.2	IBD	Ulcerative colitis
556.3	IBD	Ulcerative colitis
556.4	IBD	Ulcerative colitis
556.5	IBD	Ulcerative colitis
556.6	IBD	Ulcerative colitis
556.8	IBD	Ulcerative colitis
556.9	IBD	Ulcerative colitis
571.42	70.4	Chronic hepatitis
571.6	571.6	Biliary cirrhosis
579	557.11	Celiac disease
696	696.42	Psoriatic arthropathy
696.1	696.41	Psoriasis vulgaris
710	695.42	Systemic lupus erythematosus

Table A4-2: ICD-9 code for autoimmune diseases and syndromes included in the database (part 2).

icd	Super PheWAS Code	PheWASString
710.1	709.3	Systemic sclerosis
710.2	709.2	Sicca syndrome
710.9	709	Diffuse diseases of connective tissue
714	RA	Rheumatoid arthritis
714.3	RA	Juvenile rheumatoid arthritis
720	715.2	Ankylosing spondylitis
725	717	Polymyalgia Rheumatica
795.79	279.7	Other immunological findings
D59.0	283.1	Autoimmune hemolytic anemias
D59.1	283.1	Autoimmune hemolytic anemias
D86.9	697	Sarcoidosis
D89.89	Other immune disorders	Other disorders of the immune mechanism
E06.1	Thyroiditis	Thyroiditis, acute and subacute
E06.3	Thyroiditis	Chronic lymphocytic thyroiditis
E06.5	Thyroiditis	Thyroiditis
E06.9	Thyroiditis	Thyroiditis
E10.10	DM	Type 1 diabetic ketoacidosis
E10.21	DM	Type 1 diabetes nephropathy
E10.29	DM	Type 1 diabetes nephropathy
E10.311	DM	Type 1 diabetic retinopathy
E10.319	DM	Type 1 diabetic retinopathy
E10.36	DM	Type 1 diabetic retinopathy
E10.37X1	DM	Type 1 diabetic retinopathy
E10.37X2	DM	Type 1 diabetic retinopathy
E10.37X3	DM	Type 1 diabetic retinopathy
E10.37X9	DM	Type 1 diabetic retinopathy
E10.39	DM	Type 1 diabetic retinopathy
E10.40	DM	Type 1 diabetic neuropathy
E10.42	DM	Polyneuropathy in diabetes
E10.51	DM	Type 1 diabetic peripheral circulatory disorders
E10.65	DM	Type 1 diabetes
E10.8	DM	Type 1 diabetes
E10.9	DM	Type 1 diabetes
I73.00	443.1	Raynaud's syndrome
I73.01	443.1	Raynaud's syndrome
K50.00	IBD	Crohn's disease
K50.10	IBD	Crohn's disease
K50.80	IBD	Crohn's disease
K50.90	IBD	Crohn's disease
K51.00	IBD	Ulcerative colitis
K51.20	IBD	Ulcerative colitis
K51.30	IBD	Ulcerative colitis
K51.40	IBD	Ulcerative colitis
K51.50	IBD	Ulcerative colitis
K51.80	IBD	Ulcerative colitis
K51.90	IBD	Ulcerative colitis
K74.3	571.6	Biliary cirrhosis
K74.4	571.6	Biliary cirrhosis
K74.5	571.6	Biliary cirrhosis
K75.4	70.4	Chronic hepatitis
K90.0	557.11	Celiac disease

Table A4-3: ICD-9 code for autoimmune diseases and syndromes included in the database (part 3).

icd	Super PheWAS Code	PheWASString
L40.0	696.41	Psoriasis vulgaris
L40.1	696.41	Psoriasis vulgaris
L40.2	696.41	Psoriasis vulgaris
L40.3	696.41	Psoriasis vulgaris
L40.4	696.41	Psoriasis vulgaris
L40.50	696.42	Psoriatic arthropathy
L40.54	696.42	Psoriatic arthropathy
L40.59	696.42	Psoriatic arthropathy
L40.8	696.41	Psoriasis vulgaris
M06.9	RA	Rheumatoid arthritis
M08.00	RA	Juvenile rheumatoid arthritis
M32.10	695.42	Systemic lupus erythematosus
M34.0	709.3	Systemic sclerosis
M34.1	709.3	Systemic sclerosis
M34.2	709.3	Systemic sclerosis
M34.81	510.1	Lung involvement in conditions classified elsewhere
M34.82	709.3	Systemic sclerosis
M34.83	709.3	Systemic sclerosis
M34.89	709.3	Systemic sclerosis
M34.9	709.3	Systemic sclerosis
M35.00	709.2	Sicca syndrome
M35.01	709.2	Sicca syndrome
M35.02	709.2	Sicca syndrome
M35.03	709.2	Sicca syndrome
M35.04	709.2	Sicca syndrome
M35.09	709.2	Sicca syndrome
M35.3	717	Polymyalgia Rheumatica
M35.9	709	Diffuse diseases of connective tissue
M45.9	715.2	Ankylosing spondylitis
M60.9	770	Myalgia and myositis NOS
M79.7	770	Myalgia and myositis NOS
R76.8	279.7	Other immunological findings
R76.9	279.7	Other immunological findings
99.3	711.2	Reiter's disease
136.1	711.3	Behcet's syndrome
242	242	Thyrotoxicosis with or without goiter
242.01	242.1	Graves' disease
242.9	242	Thyrotoxicosis with or without goiter
242.91	242	Thyrotoxicosis with or without goiter
244.9	244.4	Hypothyroidism NOS
255.41	255.21	Glucocorticoid deficiency
258.1	259	Other endocrine disorders
287.31	287.31	Primary thrombocytopenia
323.51	Encephalitis	Encephalitis
323.61	Encephalitis	Encephalitis
323.62	Encephalitis	Encephalitis
323.81	Encephalitis	Encephalitis, non-infectious
323.82	Encephalitis	Encephalitis, non-infectious
323.9	Encephalitis	Encephalitis, non-infectious
340	335	Multiple sclerosis
341	Other CNS demyelinating diseases	Other demyelinating diseases of central nervous system
341.8	Other CNS demyelinating diseases	Other demyelinating diseases of central nervous system
341.9	Other CNS demyelinating diseases	Other demyelinating diseases of central nervous system

Table A4-4: ICD-9 code for autoimmune diseases and syndromes included in the database (part 4).

icd	Super PheWAS Code	PheWASString
357	357	Inflammatory and toxic neuropathy
357.1	357	Inflammatory and toxic neuropathy
357.3	357	Inflammatory and toxic neuropathy
357.4	357	Inflammatory and toxic neuropathy
357.7	357	Inflammatory and toxic neuropathy
357.81	357	Inflammatory and toxic neuropathy
357.89	357	Inflammatory and toxic neuropathy
357.9	357	Inflammatory and toxic neuropathy
358	358	Myoneural disorders
358.01	358.1	Myasthenia gravis
359.6	359.2	Myopathy
390	41.21	Rheumatic fever / chorea
391	41.21	Rheumatic fever / chorea
391.1	420.3	Endocarditis
391.2	420.1	Myocarditis
391.8	394.4	Acute rheumatic heart disease
391.9	394.4	Acute rheumatic heart disease
392	41.21	Rheumatic fever / chorea
392.9	41.21	Rheumatic fever / chorea
446	446	Polyarteritis nodosa and allied conditions
446.1	446.2	Acute febrile mucocutaneous lymph node syndrome (Kawasaki disease)
446.4	446.4	Wegener's granulomatosis
446.5	446.5	Giant cell arteritis
446.6	446.8	Thrombotic microangiopathy
517.2	709.3	Systemic sclerosis
517.8	510	Other diseases of lung
580	Nephritis	Nephritis; nephrosis; renal sclerosis
580.4	Glomerulonephritis	Proliferative glomerulonephritis
580.89	Glomerulonephritis	Acute glomerulonephritis, NOS
580.9	Glomerulonephritis	Acute glomerulonephritis, NOS
582	Glomerulonephritis	Glomerulonephritis
582.1	Glomerulonephritis	Non-proliferative glomerulonephritis
582.2	Glomerulonephritis	Proliferative glomerulonephritis
582.4	Glomerulonephritis	Proliferative glomerulonephritis
582.89	Glomerulonephritis	Chronic glomerulonephritis, NOS
582.9	Glomerulonephritis	Chronic glomerulonephritis, NOS
583	Nephritis	Nephritis; nephrosis; renal sclerosis
583.1	Glomerulonephritis	Non-proliferative glomerulonephritis
583.2	Glomerulonephritis	Proliferative glomerulonephritis
583.81	Nephritis	Nephritis and nephropathy in diseases classified elsewhere
583.89	Nephritis	Nephritis and nephropathy with pathological lesion
694	695.2	Bullous dermatoses
694.2	695.21	Dermatitis herpetiformis
694.3	695.21	Dermatitis herpetiformis
694.4	695.22	Pemphigus and pemphigoid
694.5	695.22	Pemphigus and pemphigoid
694.6	695.22	Pemphigus and pemphigoid
695.15	695.1	Toxic erythema
704	704	Diseases of hair and hair follicles
704.09	704.1	Alopecia
709.01	694.1	Vitiligo
710.3	709.5	Dermatomyositis
710.4	709.4	Polymyositis

Table A4-5: ICD-9 code for autoimmune diseases and syndromes included in the database (part 5).

icd	Super PheWAS Code	PheWASString
710.8	Other diffuse CNT diseases	Other specified diffuse diseases of connective tissue
711.4	Arthropathy	Arthropathy associated with infections
711.41	Arthropathy	Arthropathy associated with infections
711.42	Arthropathy	Arthropathy associated with infections
711.43	Arthropathy	Arthropathy associated with infections
711.44	Arthropathy	Arthropathy associated with infections
711.45	Arthropathy	Arthropathy associated with infections
711.46	Arthropathy	Arthropathy associated with infections
711.47	Arthropathy	Arthropathy associated with infections
711.48	Arthropathy	Arthropathy associated with infections
711.49	Arthropathy	Arthropathy associated with infections
713.7	Arthropathy	Arthropathy associated with other disorders classified elsewhere
714.1	RA	Rheumatoid arthritis
714.2	RA	Rheumatoid arthritis
714.32	RA	Juvenile rheumatoid arthritis
714.81	RA	Rheumatoid arthritis
714.89	RA	Rheumatoid arthritis and other inflammatory polyarthropathies
M02.30	711.2	Reiter's disease
D86.0	697	Sarcoidosis
M35.2	711.3	Behcet's syndrome
E05.00	242	Thyrotoxicosis with or without goiter
E05.01	242.1	Graves' disease
E05.90	242	Thyrotoxicosis with or without goiter
E05.91	242	Thyrotoxicosis with or without goiter
E03.9	244.4	Hypothyroidism NOS
E10.11	DM	Type 1 diabetes
E10.618	DM	Type 1 diabetes
E27.1	255.21	Glucocorticoid deficiency
E31.0	259	Other endocrine disorders
D69.3	287.31	Primary thrombocytopenia
G04.02	Encephalitis	Encephalitis
G04.00	Encephalitis	Encephalitis
G04.30	Encephalitis	Encephalitis
G04.81	Encephalitis	Encephalitis, non-infectious
G04.89	Encephalitis	Encephalitis, non-infectious
G04.90	Encephalitis	Encephalitis, non-infectious
G35	335	Multiple sclerosis
G36.0	Other CNS demyelinating diseases	Other demyelinating diseases of central nervous system
G36.1	Other CNS demyelinating diseases	Other demyelinating diseases of central nervous system
G36.9	Other CNS demyelinating diseases	Other demyelinating diseases of central nervous system
G04.1	344	Other paralytic syndromes
G61.0	357	Inflammatory and toxic neuropathy
M05.50	357	Inflammatory and toxic neuropathy
G13.1	357	Inflammatory and toxic neuropathy
G61.1	357	Inflammatory and toxic neuropathy
G61.81	357	Inflammatory and toxic neuropathy
G61.89	357	Inflammatory and toxic neuropathy
G61.9	357	Inflammatory and toxic neuropathy
G70.00	358	Myoneural disorders
G70.01	358.1	Myasthenia gravis
M05.40	359.2	Myopathy
I00	41.21	Rheumatic fever / chorea
I01.0	41.21	Rheumatic fever / chorea

Table A4-6: ICD-9 code for autoimmune diseases and syndromes included in the database (part 6).

icd	Super PheWAS Code	PheWASString
I01.1	420.3	Endocarditis
I01.2	420.1	Myocarditis
I01.8	394.4	Acute rheumatic heart disease
I01.9	394.4	Acute rheumatic heart disease
I02.0	41.21	Rheumatic fever / chorea
I02.9	41.21	Rheumatic fever / chorea
M32.12	420.21	Acute pericarditis
M32.11	395	Heart valve disorders
M30.0	446	Polyarteritis nodosa and allied conditions
M30.3	446.2	Acute febrile mucocutaneous lymph node syndrome
M30.1	446.4	Wegener's granulomatosis
M31.5	446.5	Giant cell arteritis
M31.1	446.8	Thrombotic microangiopathy
M32.13	510	Other diseases of lung
N00.0	Nephritis	Nephritis; nephrosis; renal sclerosis
N01.0	Glomerulonephritis	Proliferative glomerulonephritis
N00.8	Glomerulonephritis	Acute glomerulonephritis, NOS
N00.9	Glomerulonephritis	Acute glomerulonephritis, NOS
N03.2	Glomerulonephritis	Glomerulonephritis
N03.1	Glomerulonephritis	Non-proliferative glomerulonephritis
N03.4	Glomerulonephritis	Proliferative glomerulonephritis
N03.8	Glomerulonephritis	Proliferative glomerulonephritis
N03.0	Glomerulonephritis	Chronic glomerulonephritis, NOS
N03.9	Glomerulonephritis	Chronic glomerulonephritis, NOS
N05.9	Nephritis	Nephritis; nephrosis; renal sclerosis
N05.2	Glomerulonephritis	Non-proliferative glomerulonephritis
N05.3	Glomerulonephritis	Proliferative glomerulonephritis
M32.14	Nephritis	Nephritis and nephropathy in diseases classified elsewhere
N05.0	Nephritis	Nephritis and nephropathy with pathological lesion
L13.0	695.2	Bullous dermatoses
L12.2	695.21	Dermatitis herpetiformis
L10.0	695.22	Pemphigus and pemphigoid
L12.0	695.22	Pemphigus and pemphigoid
L12.1	695.22	Pemphigus and pemphigoid
L12.30	695.1	Toxic erythema
L64.9	704	Diseases of hair and hair follicles
L64.0	704.1	Alopecia
L80	694.1	Vitiligo
M32.0	709	Diffuse diseases of connective tissue
M33.00	709.5	Dermatomyositis
M33.20	709.4	Polymyositis
M35.1	Other diffuse CNT diseases	Other specified diffuse diseases of connective tissue
M02.80	Arthropathy	Arthropathy associated with infections
M02.811	Arthropathy	Arthropathy associated with infections
M02.821	Arthropathy	Arthropathy associated with infections
M02.831	Arthropathy	Arthropathy associated with infections
M02.841	Arthropathy	Arthropathy associated with infections
M02.851	Arthropathy	Arthropathy associated with infections
M02.861	Arthropathy	Arthropathy associated with infections
M02.871	Arthropathy	Arthropathy associated with infections
M02.88	Arthropathy	Arthropathy associated with infections
M02.89	Arthropathy	Arthropathy associated with infections
M02.9	Arthropathy	Arthropathy associated with other disorders classified elsewhere

Table A4-7: ICD-9 code for autoimmune diseases and syndromes included in the database (part 7).

ICD	Super PheWAS Code	PheWASString
M05.70	RA	Rheumatoid arthritis and other inflammatory polyarthropathies
M05.00	RA	Rheumatoid arthritis
M05.20	RA	Rheumatoid arthritis
M08.40	RA	Juvenile rheumatoid arthritis
M05.10	RA	Rheumatoid arthritis
M06.4	RA	Rheumatoid arthritis and other inflammatory polyarthropathies
M08.1	715	Other inflammatory spondylopathies
E03.5	348.7	Coma

Table A11: Cumulative incidence rate and hazard ratio under different matching criteria

	T (months)	CIR (immunotherapy)	CIR (chemotherapy)	Hazard ratio
Bisection	1	0.015 [0.012, 0.018]	0.0083 [0.0081, 0.0086]	1.77 [1.22, 2.53]
	2	0.032 [0.027, 0.036]	0.016 [0.015, 0.016]	2.18 [1.68, 2.86]
	3	0.045 [0.039, 0.050]	0.020 [0.019, 0.022]	2.31 [1.83, 2.89]
	6	0.070 [0.063, 0.076]	0.034 [0.033, 0.035]	2.32 [1.93, 2.77]
	12	0.098 [0.090, 0.106]	0.046 [0.045, 0.047]	2.41 [2.06, 2.76]
	24	0.118 [0.109, 0.126]	0.054 [0.052, 0.057]	2.51 [2.17, 2.87]
	36	0.119 [0.110, 0.127]	0.061 [0.058, 0.062]	2.47 [2.11, 2.82]
log-rank test		$p < 0.01$		
Quadrisection	1	0.015 [0.012, 0.018]	0.0086 [0.0083, 0.0088]	1.72 [1.20, 2.49]
	2	0.032 [0.027, 0.036]	0.019 [0.017, 0.019]	2.15 [1.63, 2.80]
	3	0.045 [0.039, 0.050]	0.023 [0.022, 0.024]	2.28 [1.83, 2.91]
	6	0.070 [0.063, 0.076]	0.035 [0.035, 0.036]	2.30 [1.91, 2.74]
	12	0.098 [0.090, 0.106]	0.051 [0.049, 0.053]	2.38 [2.03, 2.85]
	24	0.118 [0.109, 0.126]	0.059 [0.057, 0.061]	2.44 [2.13, 2.82]
	36	0.119 [0.110, 0.127]	0.062 [0.059, 0.062]	2.43 [2.11, 2.75]
log-rank test		$p < 0.01$		

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