Supplementary Materials

Supplementary Methods

Description of Data Sources Used to Identify Systemic Therapy

The initiation of systemic treatment was determined using evidence from one or more of four data sources: 1) Ontario Health Insurance Plan (OHIP) physician billing codes for systemic therapy administration; 2) procedure codes for systemic therapy administration within the National Ambulatory Care Reporting System (NACRS), which collects data from hospital- and community-based outpatient procedures; 3) receipt of systemic therapy within the Cancer Care Ontario Activity Level Reporting dataset, which captures all systemic therapy administered in regional cancer centers; and 4) records within the New Drug Funding Plan, which covers the cost of newer systemic therapies. The latter two datasets provided information on the specific drugs or therapy regimens administered. OHIP and NACRS billing codes are shown in Supplementary Table 4. Common systemic therapies observed in the Cancer Care Ontario and New Drug Funding Plan datasets are shown in Supplementary Tables 5 and 6.

Time-Varying Covariate Analysis for the Effect of Recent Systemic Therapy

After initiation of systemic therapy, many patients received additional courses of systemic therapy during follow-up. We examined the effect of recent receipt of systemic therapy on AKI risk using a separate Cox proportional hazards model. The 90-day period after chemotherapy exposure has been suggested as a period of increased risk for AKI [1]. We therefore defined recent exposure to systemic therapy as the 90-day

period following each treatment during follow-up. Exposures to therapy during follow-up were ascertained using the same data sources used to determine the initiation of systemic therapy. We compared these periods of 'active treatment' during follow-up to periods in which patients had not recently been exposed to any systemic therapy (for at least the preceding 90 days). If patients received multiple systemic therapies within 90 days, the exposure period was extended to include the 90-day period following the most recent treatment. After the 90-day period following treatment had elapsed the time-varying covariate would revert to being 'unexposed'. In this way, patients contributed person-time to 'exposed' and 'unexposed' periods during the course of their follow-up. The hazard ratio from this analysis therefore compares the hazard of AKI during exposed person-time relative to unexposed person-time. The other covariates used in this model were the same (time-fixed) variables used in the primary model. We accounted for the competing risk of death using cause-specific hazard ratios in this model. Supplementary Figure 1 provides an illustrative example of patient exposure status in this time-varying covariate analysis.

Effect of Co-Prescriptions Subcohort Analysis

We evaluated the effect of commonly co-prescribed medications on AKI risk, including angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARB), beta-blockers, calcium channel blockers, diuretics, and statins in the subcohort of patients 66 years of age and older who receive outpatient drug benefits. We used the Ontario Drug Benefits database to ascertain prescription drug exposure in the 120-days preceding systemic therapy initiation. This database records prescription

drug dispensing and has an error rate of <1% [2]. We fitted a multivariable Fine and Gray model in this subcohort and reported subdistribution HRs for the risk of AKI associated with each drug class.

Temporal Trends in Annual AKI Incidence Rates

We reported annual AKI and AKI-D incidence rates from 2007 to 2014 in terms of event rate per 1,000 patient-years. AKI/AKI-D events were attributed to the year in which patients initiated systemic therapy (i.e. the year of cohort entry), rather than the year in which AKI occurred. In this way, we avoided over-attribution of AKI events to the later years of the study period due to disease progression over time or episodes associated with end-of-life care. The Cochran-Armitage test was used to assess two-sided p-value for trends.

AKI Risk Associated with Therapies in High-risk Cancers (Post hoc analysis)

We assessed the association between specific cancer therapies and AKI risk in separate models for three cancers with frequent incidence of AKI: bladder cancer, multiple myeloma and leukemia. We reviewed and manually categorized the initial treatments recorded in the Cancer Care Ontario Activity Level Reporting dataset for patients with each of these cancers.

In bladder cancer, we categorized the initial treatments as regimens including cisplatin, carboplatin, or other (i.e., non-platinum-based therapies). In multiple myeloma, therapies were primarily recorded as receipt of individual drugs, and as such, we

analyzed AKI risk associated with each agent (e.g., bortezomib, cyclophosphamide, immunomodulatory drugs, etc.). For leukemia, we compared treatments for acute versus chronic leukemia. These three models were also adjusted for all other (time-fixed) covariates used in the primary model.

In multiple myeloma and leukemia, we also analyzed AKI risk associated with receipt of HSCT as a time-varying exposure and assessed the hazard of AKI in the 30-day, 31-90-day, and 91-day to 1-year periods after HSCT (versus not having undergone HSCT, or having undergone HSCT more than 1-year prior).

Missing Data

Demographic data (e.g., age and sex) were required for cohort entry and were therefore complete in our data. Missing rural or long-term facility residence indicators were interpreted to reflect non-rural and non-long-term care facility residence, respectively (<0.5% of the cohort). Other comorbidity covariates have been well-validated in Institute for Clinical Evaluative Sciences administrative data and absent diagnostic indicators were interpreted as non-presence of the comorbid conditions [3].

Cancer staging data was missing in 28.6% of patients. Given this proportion, use of single or multiple imputation-based methods, missing value indicators, or complete case analysis may all lead to biased effect estimates [4, 5]. The latter would also be associated with loss of statistical power. Notwithstanding the limitations of this approach, we opted to model this covariate with inclusion of a ‘missing’ stage category and therefore reported associated adjusted hazard ratios for patients without available data on cancer stage at diagnosis.

Supplementary Tables

Supplementary Table 1. REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement*

Section	Item No.	STROBE items	RECORD items	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	(1.1) The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. (1.2) If applicable, the geographic region and time frame within which the study took place should be reported in the title or abstract. (1.3) If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title Page/Abstract
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported.	--	Abstract
Objectives	3	State specific objectives, including any prespecified hypotheses.	--	Abstract
Methods				
Study design	4	Present key elements of study design early in the paper.	--	Study Design and Setting
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	--	Study Design and Setting
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. (b) For matched studies, give matching criteria and number of exposed and unexposed.	(6.1) The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. (6.2) Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. (6.3) If the study involved linkage of databases, consider use of a flow	Population and Data Sources, Outcomes, Figure 1

			diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	(7.1) A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Outcomes, Statistical Analyses, Appendix 1-4
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	--	Population and Data Sources, Appendix 1-4
Bias	9	Describe any efforts to address potential sources of bias.	--	Statistical Analyses
Study size	10	Explain how the study size was arrived at.	--	Population and Data Sources
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.	--	Statistical Analyses
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) If applicable, explain how loss to follow-up was addressed. (e) Describe any sensitivity analyses.	--	Statistical Analyses
Data access and cleaning methods	--	N/A	(12.1) Authors should describe the extent to which the investigators had access to the database population used to create the study population. (12.2) Authors should provide information on the data cleaning methods used in the study.	Population and Data Sources
Linkage	--	N/A	(12.3) State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Population and Data Sources

Results				
Participants	13	(a) Report numbers of individuals at each stage of study--e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed. (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	(13.1) Describe in detail the selection of the persons included in the study (i.e., study population selection), including filtering based on data quality, data availability, and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Study Population and Setting, Figure 1
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate number of participants with missing data for each variable of interest. (c) Summarize follow-up time (e.g. average and total amount).	--	Results
Outcome data	15	Report numbers of outcome events or summary measures over time.	--	Results, AKI incidence across Cancer Types
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	--	Results, AKI incidence across Cancer Types
Other analyses	17	Report other analyses done (e.g. analyses of subgroups and interactions, and sensitivity analyses).	--	Effect of Recent Systemic Therapy, Effect of Co-prescription, Temporal Trends in AKI Incidence
Key results	18	Summarize key results with reference to study objectives.	--	Results, Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	(19.1) Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time,	Discussion

			as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	--	Discussion
Generalizability	21	Discuss the generalizability (external validity) of the study results.	--	Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.	--	Acknowledgements
Accessibility of protocol, raw data, and programming code	--	N/A	(22.1) Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Appendices 1-4

*Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. (2015) The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLoS Med 12(10): e1001885. doi:10.1371/journal.pmed.1001885

Supplementary Table 2. Administrative Cancer Diagnostic Codes*

ICD-O-3 Description	Codes
OCR Topographical Codes	
Head and Neck	C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C30, C31, C32
Esophageal	C15
Gastric	C16
Small Intestine	C17
Colorectal	C18, C19, C20
Anal	C21
Hepatobiliary	C22, C23, C24
Pancreatic	C25
Gastrointestinal – other	C26
Lung, tracheal and bronchogenic	C33, C34
Thymus	C37
Heart, mediastinal and pleural	C38
Intrathoracic – other	C39
Bones, joints and articular cartilage of limbs	C40, C41
Hematologic	C42
Skin	C44
Peripheral Nervous System	C47
Retroperitoneal/ peritoneal Tissues	C48
Muscle, connective and subcutaneous tissues	C49
Breast	C50
Female genital	C51, C52, C53, C54, C55, C56, C57, C58
Male genital	C60, C61, C62, C63
Renal	C64, C65
Ureterovesicular	C66, C67, C68
Ocular	C69
Central nervous system	C70, C71, C72
Thyroid	C73
Adrenal	C74
Endocrine gland	C75
Other	C76
Lymphoma	C77

Unknown primary site	C80
OCR Morphologic Codes	
Non-melanoma Skin	80500, 80502, 80503, 80510, 80513, 80513, 80520, 80522, 80523, 80530, 80600, 80702, 80703, 80706, 80713, 80723, 80733, 80743, 80753, 80762, 80763, 80812, 80823, 80833, 80843, 80901, 80903, 80913, 80923, 80933, 80943, 80953, 80960, 80973
Melanoma	87203, 87403, 87412, 87413, 87423, 87433, 87443, 87453, 87463, 87703, 87723, 87733, 87743
Lymphoma	95913, 95963, 96503, 96513, 96523, 96533, 96543, 96553, 96593, 96613, 96623, 96633, 96643, 96653, 96673, 96703, 96713, 96733, 96753, 96783, 96793, 96803, 96843, 96873, 96893, 96903, 96913, 96953, 96983, 96993, 97003, 97013, 97023, 97053, 97083, 97093, 97143, 97163, 97173, 97183, 97193, 97273, 97283, 97293, 99701
Myeloma	97313, 97323
Leukemia	98003, 98013, 98053, 98203, 98233, 98263, 98273, 98273, 98311, 98323, 98333, 98343, 98353, 98363, 98373, 98403, 98603, 98613, 98633, 98673, 98703, 98713, 98723, 98733, 98743, 98753, 98763, 98913, 98953, 98963, 98973, 99103, 99203, 99403, 99453, 99463, 99483, 99633, 99643

*Abbreviations: ICD-O-3, International Classification of Diseases for Oncology, third edition; OCR, Ontario Cancer Registry.

Supplementary Table 3: Acute Kidney Injury Codes

Diagnostic Code	Description
Acute Kidney Injury Diagnostic Codes (ICD-10)	
N17	Acute kidney failure
Acute Kidney Injury Requiring Dialysis Billing Codes*	
G082	Continuous venovenous haemodialfiltration
G083	Continuous venovenous haemodialysis
G085	Continuous venovenous haemofiltration
G090	Venovenous slow continuous ultrafiltration
G091	Continuous arteriovenous haemodialysis
G092	Continuous arteriovenous haemodiafiltration
G093	Haemodiafiltration - Contin. Init & Acute (repeat x3)
G095	Slow Continuous Ultra Filtration - Initial & Acute (repeat)
G295	Continuous aterivenous haemofiltration initial and acute
G294	Arteriovenous slow continuous ultrafiltration init and acute
R849	Dialysis – Heamodialysis - Initial & acute
R850	Dialysis-Haemodialysis-Insert Scribner Shunt
G323	Dialysis – Haemodialysis - Acute, repeat (max 3)
G325	Dialysis – Haemodialysis - Medical component (incl in unit fee)
G326	Dialysis - Chronic, contin. haemodialysis or haemofiltration each
G862	Hospital self care Chronic hemodialysis
G863	Chronic hemodialysis IHF location
G866	Intermittent hemodialysis treatment centre

* Ontario Health Insurance Plan fee code. Abbreviations: ICD-10, International Classification of Diseases, tenth edition.

Supplementary Table 4. Evidence of Systemic Therapy

Dataset	Variable or Diagnostic Codes Used to Establish Systemic Therapy Receipt
Cancer Care Ontario – Activity Level Reporting	'Systemic Dataset': 'visit_date' variable
Ontario Health Insurance Plan (OHIP)	Fee codes: "G345", "G359", "G381", "G382", "G388"
New Drug Funding Plan (NDFP)	'treatment_date' variable
National Ambulatory Care Reporting System (NACRS)	ICD-10 codes: "Z511", "Z512"

Supplementary Table 5. Top 40 Most Frequently Observed Cancer Care Ontario (Activity Level Reporting Data) Systemic Treatment Entries (2007 to 2014)

Cancer Care Ontario Regimen Entry*	Frequency (n)	%
*PACLICARBO	27661	4.8
*CHOP-RITUXIMAB	27517	4.8
*FOLFOX	23385	4.0
*FEC 100	19281	3.3
*CRBPPACL	17436	3.0
*CHOP+R	15721	2.7
*CISP	14330	2.5
*GEM-CISP	11845	2.0
*ECF	11483	2.0
*FEC-T	11161	1.9
*FOLFIRI-BEVACIZUMAB	10749	1.9
*AC-TAXOL DD	10599	1.8
*ABVD	10254	1.8
*CISPETOP -3 DAYS	10215	1.8
*VINOCISP	10157	1.8
*AC-PACL(DD)	9481	1.6
*MFOLFOX6	9080	1.6
*CVP-RITUXIMAB	9061	1.6
*AC	8434	1.5
*FOLFIRI+BEVA	8189	1.4
*FEC100	7862	1.4
*TC	7407	1.3
*CISPGEMC	7013	1.2
*CYCLDOCE	5792	1
*FOLFIRI	5388	0.9
*CISPETOP(3D)	5319	0.9
*ETOPCARBO	5296	0.9
*FU-CISP	4791	0.8
*GEM-CARBO	4709	0.8
*FOLFOX4	4703	0.8
*CYCLO IV	4636	0.8
*GEMCIT	4442	0.8
*FOLFIRINOX	4414	0.8
*CISPVINO	4122	0.7
*FEC-D	3842	0.7
*ECX	3702	0.6
*CARBO	3701	0.6
*CVP+R	3632	0.6

*BEP-5-DAYS	3230	0.6
*BEND+RITU	2955	0.5

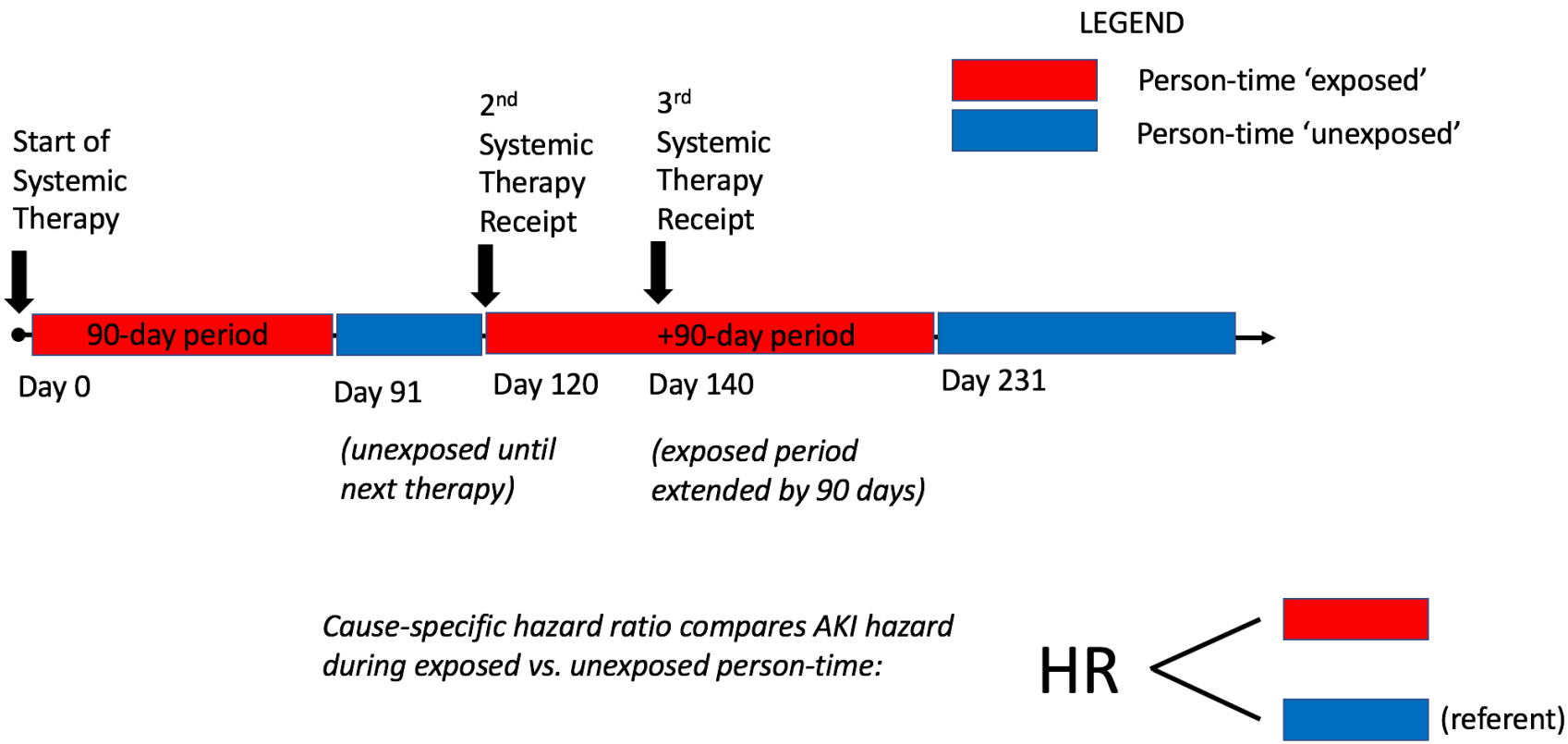
*Data entries presented as they appear in the Cancer Care Ontario Activity Level Reporting dataset

Supplementary Table 6. Top 35 Most Frequently Observed New Drug Funding Plan Systemic Treatment Entries (2007 to 2014)*

New Drug Funding Program Entry	Frequency (n)	%
Paclitaxel	13588	14.8
Epirubicin	11821	12.9
Rituximab	11455	12.5
Oxaliplatin	11394	12.4
Gemcitabine	9521	10.4
Docetaxel	7522	8.2
Irinotecan	5311	5.8
Pamidronate	4774	5.2
Vinorelbine	3590	3.9
Trastuzumab	3002	3.3
Bevacizumab	2450	2.7
Bortezomib	1570	1.7
Interferon	959	1.1
Zoledronic Acid	838	0.9
Azacitidine	824	0.9
Pemetrexed	691	0.8
Bendamustine	687	0.8
Denosumab	465	0.5
Cetuximab	287	0.3
Ipilimumab	283	0.3
Raltitrexed	178	0.2
Liposomal Doxorubicin	137	0.2
Fludarabine	67	0.1
Pertuzumab	64	0.1
Nab-Paclitaxel	59	0.1
Temsirolimus	55	0.1
Panitumumab	41	0.04
Brentuximab	34	0.04
Topotecan	23	0.03
Radium-223 Dichloride	20	0.02
Arsenic Trioxide	10	0.01
Obinutuzumab	9	0.01
Pembrolizumab	9	0.01
Eribulin	6	0.01

*Institute for Clinical Evaluative Sciences privacy regulations do not allow reporting of data with 5 or fewer individuals due to the potential risk of re-identification. For this reason, the table was truncated to 35 entries (those with frequency of ≥ 6 individuals).

Supplementary Figure



Supplementary Figure 1. Illustrative Example of Patient Exposure Status in the Time-varying Covariate Analysis for the Effect of Systemic Therapy Exposure. HR = hazard ratio.

Supplementary References

1. Siew ED, Parr SK, Abdel-Kader K*, et al.* Predictors of Recurrent AKI. J Am Soc Nephrol 2016;27(4):1190-200.
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4. Groenwold RH, White IR, Donders AR*, et al.* Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. CMAJ 2012;184(11):1265-9.
5. Sterne JA, White IR, Carlin JB*, et al.* Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393.