Proton Pump Inhibitors and All-Cause Mortality Risk Among Cancer Patients

Supplementary Material Online Content

SUPPLEMENTARY METHODS:

Data Source:

We used TriNetX (Cambridge, MA, USA), a global federated health research network providing real-time access to electronic health records (EHRs). TriNetX platform de-identifies and aggregates EHR data from 66 healthcare organizations (HCOs), most of which are large academic medical institutions with both inpatient and outpatient facilities at multiple locations across 50 states in the United States. The Real-time access to health insurance portability and accountability act– deidentified, compliant, and longitudinal clinical data to member HCOs is provided cloud-based. The deidentified clinical data, such as diagnoses, procedures, medications, laboratory values, and genomic information, are continuously aggregated directly from the EHR of the participating HCOs.

Participating HCOs include outpatient, inpatient, and specialty care services and provide care to a diverse patient population from different ethnicity, age groups, geographical region, and income levels. Both the patients and HCOs, as data sources, stay anonymous. As a federated network, TriNetX data have been granted a waiver from the Western institutional review board since only aggregated counts and statistical summaries of de-identified information without any protected health information were received from participating HCOs. In addition, no study-specific activities are performed in retrospective analyses.

Standardizing the terminology and data quality check:

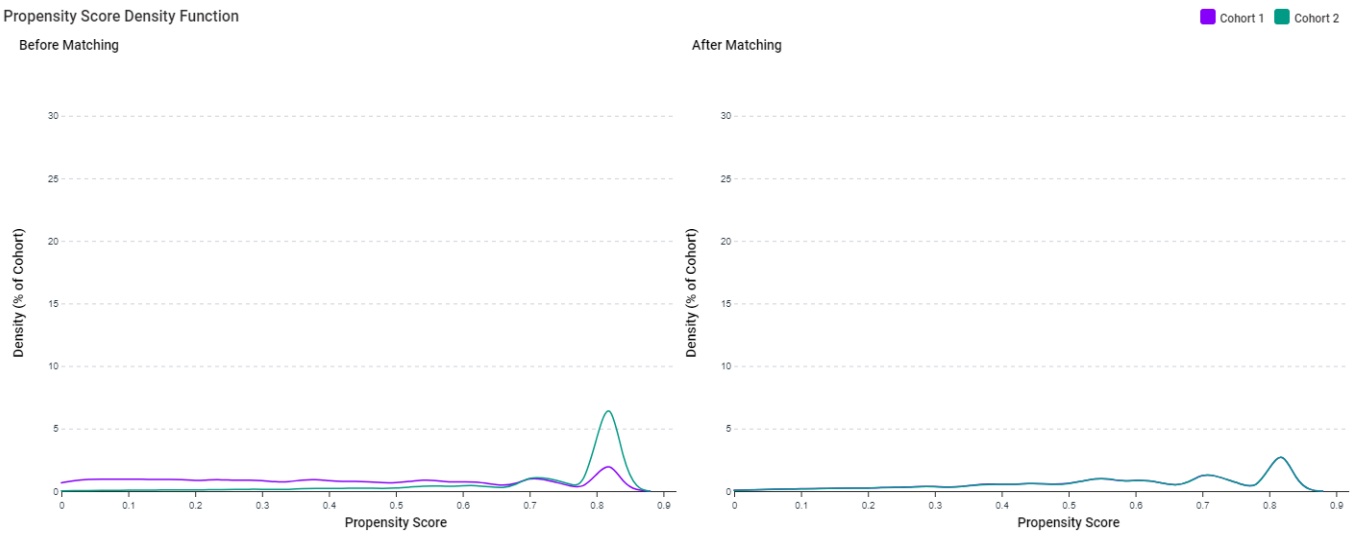
The TriNetX software verifies the basic formatting to confirm that data are appropriately characterized. Patient counts were rounded up to the nearest 10 in our analysis to safeguard protected health information. TriNetX has production capabilities that have been tested that map data extensively from each of these structures to the standard model within TriNetX and can extract details of interest from the narrative

content of clinical documents using natural language processing. The contributing EHR systems used United Medical Language System (UMLS) for coding. TriNetX maps the data to a standard and controlled set of clinical terminologies, for example, mapping disease terms from Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT) to International

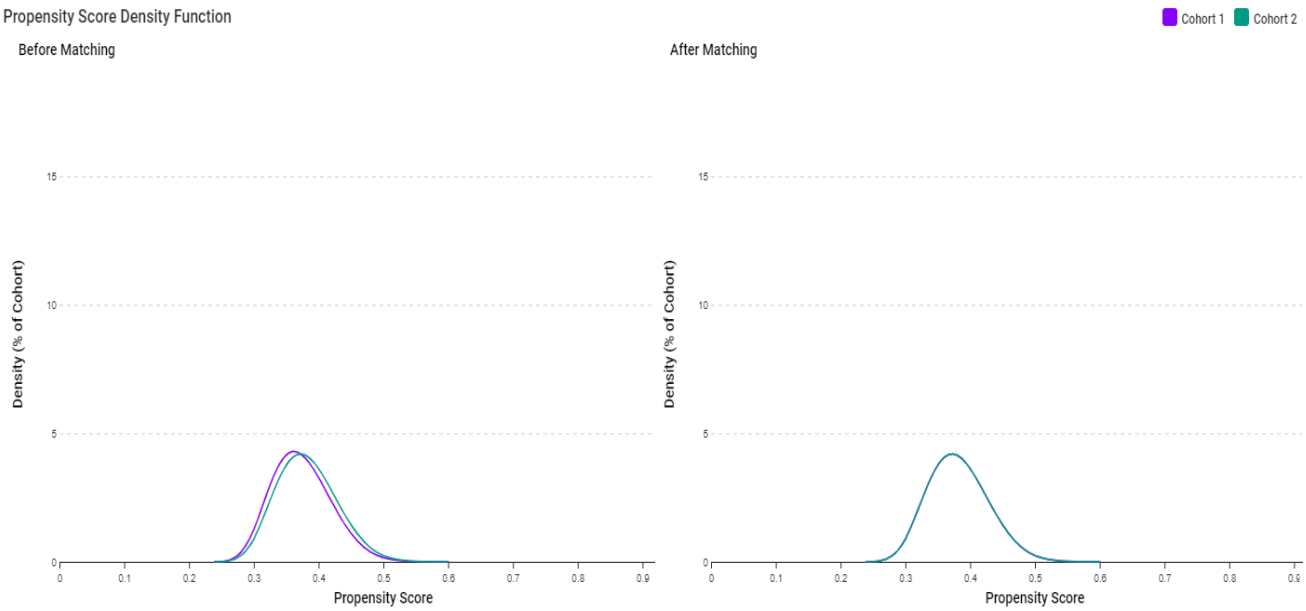
Classification of Diseases, and Clinical Modification (ICD-9 and 10 CM), drug terms from National Drug Codes (NDCs) to RxNorm. TriNetX enforces a list of required fields (e.g., patient identifier) and rejects those records where the required data is lacking. Referential integrity checking confirms that data spanning multiple database tables can be successfully joined together. TriNetX requires at least 1 non-demographic fact for a patient to be calculated in a given data set. Patient records with only demographic information are not included in data sets. As the data are refreshed, the TriNetX software monitors change in data volumes over time to ensure data validity.

Selection of Patients:

The search was conducted following the criteria provided by TriNetX to identify potential patients. These codes included the ICD-9, 10 CM. C00-C14 Malignant neoplasms of lip, oral cavity and pharynx; C15-C26 Malignant neoplasms of digestive organs; C30-C39 Malignant neoplasms of respiratory and intrathoracic organs; C43-C44 Melanoma and other malignant neoplasms of skin; C50-C50 Malignant neoplasms of breast; C51-C58 Malignant neoplasms of female genital organs; C60-C63 Malignant neoplasms of male genital organs; C64-C68 Malignant neoplasms of urinary tract; C69-C72 Malignant neoplasms of eye, brain and other parts of central nervous system; C73-C75 Malignant neoplasms of thyroid and other endocrine glands;C81-C96 Malignant neoplasms of lymphoid, hematopoietic and related tissue;;



Supplementary Figure 1: Propensity score density graph for the new users of proton pump inhibitors versus non-users among cancer before and after propensity score matching.



Supplementary Figure 2: Propensity score density graph for the new users of proton pump inhibitors versus histamine2 receptor antagonist among cancer before and after propensity score matching.

SENSITIVITY ANALYSES:

Sensitivity analysis 1: Hazard ratios (95% CIs) for all-cause mortality after extended lag exposure times between new users of proton pump inhibitors compared to non-users.

Outcome	PPI-Users	Non-users	HR (95% CI)
At 9 months, Lag exposure	16091	7849	2.45 (2.39 -2.52)
At 12 months, Lag exposure	13898	7009	2.41 (2.34 - 2.48)
Abbreviations: PPI, proton pump inhibitor; HR, hazard ratio; CI, confidence interval.			

Sensitivity analysis 2: Hazard ratios (95% CIs) for all-cause mortality after extended lag exposure times between new users of proton pump inhibitors compared to non-users after excluding early outcomes at 6 months and 1 year.

Outcome	**PPI-Users** (n=44453)	**Non-users** (n=48805)	**HR (95% CI)**
At 6 months	17166	8249	2.54 (2.43-2.61)
Outcome	**PPI-Users** (n=35739)	**Non-users** (n=40027)	**HR (95% CI)**
At 1 year	12433	5759	2.48 (2.39-2.62)

Abbreviations: PPI, proton pump inhibitor; HR, hazard ratio; CI, confidence interval.

Sensitivity Analysis 3: Hazard ratios (95% CIs) for all-cause mortality between former proton pump inhibitors users compared to non-users.

Outcome	Former PPI-Users (n=1360032	Non-users (n=1360032)	HR (95% CI)
At 1-year	125354	70472	1.84 (1.82 - 1.96)
Abbreviations: PPI, proton pump inhibitor; HR, hazard ratio; CI, confidence interval.			