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ORIGINAL ARTICLE

Retrospective Study

Proton pump inhibitors and all-cause mortality risk among cancer patients

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Abstract

BACKGROUND

Proton pump inhibitors (PPIs) are widely used, including among cancer patients, to manage gastroesophageal reflux and other gastric acid-related disorders. Recent evidence suggests associations between long-term PPI use and higher risks for various adverse health outcomes, including greater mortality.

AIM

To investigate the association between PPI use and all-cause mortality among cancer patients by a comprehensive analysis after adjustment for various confounders and a robust methodological approach to minimize bias.

METHODS

This retrospective cohort study used data from the TriNetX research network, with electronic health records from multiple healthcare organizations. The study employed a new-user, active comparator design, which compared newly treated PPI users with non-users and newly treated histamine2 receptor antagonists (H2RA) users among adult cancer patients. Newly prescribed PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole) users were compared to non-users or newly prescribed H2RAs (cimetidine, famotidine, nizatidine, or ranitidine) users. The primary outcome was all-cause mortality. Each patient in the main group was matched to a patient in the control group using 1:1 propensity score matching to reduce confounding effects. Multivariable Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence interval (CI).

RESULTS
During the follow-up period (median 5.4 ± 1.8 years for PPI users and 6.5 ± 1.0 years for non-users), PPI users demonstrated a higher all-cause mortality rate than non-users after 1 year, 2 years, and at the end of follow up (HRs: 2.34-2.72). Compared with H2RA users, PPI users demonstrated a higher rate of all-cause mortality HR: 1.51 (95%CI: 1.41-1.69). Similar results were observed across sensitivity analyses by excluding deaths from the first 9 months and 1-year post-exposure, confirming the robustness of these findings. In a sensitivity analysis, we analyzed all-cause mortality outcomes between former PPI users and individuals who have never used PPIs, providing insights into the long-term effects of past PPI use. In addition, at 1-year follow-up, the analysis revealed a significant difference in mortality rates between former PPI users and non-users (HR: 1.84; 95%CI: 1.82-1.96).

CONCLUSION
PPI use among cancer patients was associated with a higher risk of all-cause mortality compared to non-users or H2RA users. These findings emphasize the need for cautious use of PPIs in cancer patients and suggest that alternative treatments should be considered when clinically feasible. However, further studies are needed to corroborate our findings, given the significant adverse outcomes in cancer patients.

Key Words: All-cause mortality; Cancer; Histamine-2 receptor antagonists; Mortality; Malignancy; Proton pump inhibitors; Carcinoma; Outcome

Core Tip: Proton pump inhibitors (PPIs) are commonly used medications. Recent studies have raised concerns regarding increased all-cause and cause-specific mortality with PPIs. However, limited studies have addressed this issue in cancer patients. In addition, an association between PPIs and the mortality risk in unselected cancer populations remains uncertain. We investigated the association between PPI use and all-cause mortality in patients diagnosed with cancer. PPI use among cancer patients was associated with a higher risk of all-cause mortality compared to non-users or histamine-2 receptor antagonist users. These results strongly suggest the need for cautious use of PPIs in cancer patients and indicate that alternative treatments should be considered when clinically feasible.

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INTRODUCTION

Proton pump inhibitors (PPIs) are the most widely prescribed drug groups and are also available for sale over the counter without a prescription in several countries[1]. PPI use has increased rapidly over the past decade[2]. They are considered very safe in the general population, but there is growing concern regarding long-term safety. Noninterventional studies have shown associations between the use of PPIs and various outcomes, including alcoholic liver disease, cancer, cardiovascular disease, chronic kidney disease, dementia, and pneumonia[3]. Furthermore, recent studies have raised concerns regarding increased all-cause and cause-specific mortality with PPIs[3-5].

In a recent prospective study, more than 25% of cancer patients undergoing anticancer treatment used PPIs[6]. However, this study suggests that the use of PPIs is prevalent in cancer patients. Recent studies found associations between PPIs and excess cause-specific and all-cause mortality[7-9]. Concerns have also been raised about the increase in all-cause and cause-specific mortality associated with PPI use[10]. Limited studies have addressed this issue; despite the available literature, several knowledge gaps persist. Notably, most studies focused on specific cancer types or lacked a robust design to assess the diverse landscape of cancer patients. Furthermore, one study showed that after adjusting for confounders, such as overall health status and longstanding diseases, regular PPI use was not associated with a greater risk of all-cause mortality[11].

An association between PPIs and the mortality risk in unselected cancer populations remains uncertain. Additionally, pharmacoepidemiologic studies are susceptible to protopathic bias. First, methodological limitations and heterogeneity across individual studies are a challenge. Second, the potential influence of confounding factors, such as cancer stage, comorbidities, and concomitant medications, has been inconsistently addressed[8,9]. Third, the duration and cumulative effect of PPI use on mortality outcomes require further exploration. These discrepancies highlighted the need for a comprehensive and well-designed study to clarify the relationship of PPIs to all-cause mortality in cancer.

Studies are required to bridge this gap by providing a broad analysis of the association between chronic PPI use and all-cause mortality in cancer patients. Hence, addressing the link between PPIs and all-cause mortality in cancer patients is essential for optimizing treatment strategies. In addition, understanding the potential risks or benefits of PPIs in cancer

is necessary for adjusting patient care. Therefore, this study aimed to investigate the association between PPI use and all-cause mortality in patients diagnosed with cancer.

MATERIALS AND METHODS

Study design and population

This large, population-based, retrospective cohort study was conducted using the TriNetX research network (Cambridge, MA, United States). TriNetX is a federated multicenter research network that provides real-time access to an anonymized dataset from participating healthcare organizations' electronic health records (EHR). Details of the data source, quality checks, and diagnosis codes used for selection [according to a predefined international classification of diseases (ICD)-9 and ICD-10 codes] are described in the Supplementary Material. Details of the TriNetX network are described in previous studies[12,13]. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Cohort design

We identified all adult (aged ≥ 18 years) patients with a cancer diagnosis between January 1, 2010 and December 31, 2022. We adopted a new-user, active comparator design for our study, comparing patients who were newly treated with PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole) with non-users. We used non-users as primary analysis controls, defined as either histamine-2 receptor antagonists (H2RAs) or PPIs. We matched new PPI users to non-users by propensity scores. If we were to consider individuals on PPIs as exposed at the time of cancer diagnosis, it could introduce an immortal time bias because mortality cannot occur before the first use of PPI after diagnosis. At cohort entry, all patients were required to have at least 1 year follow-up. Finally, as recommended, we used a lag time of 6 months to allow for a sufficient latency period and to minimize reverse causality (protopathic bias)[14,15].

Outcome

The primary outcome was all-cause mortality.

Matching process

The propensity score matching (PSM) was performed using 1:1 to reduce the confounding effects. The covariates were adjusted in the PSM model for priori-identified potential confounders, such as age, sex, race/ethnicity, nicotine dependence, alcohol dependence, body mass index, cancer type, comorbidities, cancer treatment, and medications (Table 1). Logistic regression was used to obtain the propensity scores, and a greedy nearest-neighbor matching algorithm performed the matching with a caliper of 0.1 pooled SD. The balance of potential confounding variables was evaluated using standardized mean differences (SMD) with a threshold set a priori at 0.10. We used SMD to measure the magnitude of differences between the groups (rather than the *P* value) due to their insensitivity to sample size. Logistic regression using both Python (Python Software Foundation, Wilmington, Delaware, United States) and R 3.4.4 software (R Foundation for Statistical Computing, Vienna, Austria) to ensure the outputs matched and the order of the rows in the covariate matrix was randomized to eliminate this bias.

Secondary analyses

We used new users of an alternative acid suppression drug, H2RAs (cimetidine, famotidine, nizatidine, or ranitidine), as a control in the secondary analysis. We deliberately chose H2RAs as the comparator because H2RAs are a clinically relevant cohort used for indications similar to PPIs; hence, H2RAs were chosen as it was aimed to minimize confounding by therapeutic indication. Patients with a history of concurrent prescription of PPIs and H2RAs at cohort entry were excluded to ensure a clear distinction between exposure groups. Furthermore, the study cohort included individuals who switched to or added on treatment between the study drug classes (PPI to H2RA or vice versa).

Sensitivity analyses

We conducted three sensitivity analyses to ensure robustness due to the heterogeneous nature of the study outcomes. In the first sensitivity analysis, we estimated study outcomes by excluding patients with outcomes 6 months and 1 year after the index event. This analysis was performed using the same methods as the primary analysis. The second analysis evaluated the influence of PPI on mortality using Cox proportional hazards models with a lag time of 9 and 12 months. In the third analysis, we compared former users based on whether they had a history of PPIs before cancer diagnosis.

Statistical analyses

All analyses were performed using the TriNetX real-time analytics platform. This approach involves dynamic and immediate data analysis, enabling continuous processing and interpretation of data as it is generated. Categorical variables were compared using the Pearson χ^2 test and continuous variables by an independent-sample *t*-test. Continuous variables were expressed as mean ± SD and categorical variables as frequency and percentage. Analyses examined the outcome using Cox proportional hazards models. HRs and CIs, along with proportionality tests, were calculated using the R Survival package 3.2-3. The results were validated by comparing them with the output from SAS version 9.4. Patients were censored when the time window ended or the day after the last fact in their record. We utilized a 1:1 propensity matching strategy to establish comparable groups. In addition, we used this strategy to balance the covariates

Table 1 Demographic and clinical characteristics of patients with cancer by proton pump inhibitor use and non-users, *n* (%)/mean ± SD

Variables	Before the propensity score match			After the propensity score match		
	PPI users (*n* = 48554)	Non-users (*n* = 2949116)	SMD	PPI users (*n* = 48452)	Non-users (*n* = 48452)	SMD
Age (years)	64.9 ± 12.2	62.4 ± 15.6	0.1803	64.9 ± 12.2	64.7 ± 12.8	0.0120
Sex (female)	20773 (428)	1494930 (50.67)	0.1590	20738 (42.8)	20146 (41.6)	0.0247
Ethnicity, Hispanic or Latino	2790 (5.7)	147470 (5.0)	0.0331	2785 (5.7)	2776 (5.7)	0.0008
Race						
White	32556 (67.05)	1930606 (65.4)	0.0336	32507 (67.1)	32345 (66.7)	0.0071
Black or African American	7694 (15.8)	227813 (7.7)	0.2539	7643 (15.8)	7491 (15.5)	0.0086
Asian	737 (1.5)	88263 (2.9)	0.0995	737 (1.5)	442 (0.9)	0.0556
Others	6502 (13.4)	586750 (19.9)	0.1753	6500 (13.4)	7517 (15.5)	0.0597
Nicotine dependence	9974 (20.5)	129401 (4.4)	0.5044	9872 (20.4)	9991 (20.6)	0.0061
Alcohol dependence	2220 (4.6)	19796 (0.7)	0.2460	2144 (4.4)	1866 (3.8)	0.0288
BMI (kg/m^2)	29 ± 6.64	28.1 ± 6.27	0.1473	29 ± 6.64	29.2 ± 6.73	0.0198
Cancer type						
Digestive organs	3890 (8.0)	1852 (0.64)	0.3683	3855 (7.9)	436 (0.9)	0.3482
Thyroid and other endocrine glands	511 (1.0)	11107 (0.4)	0.0803	506 (1.0)	156 (0.3)	0.0878
Neuroendocrine tumors	157 (0.3)	3812 (0.1)	0.0409	156 (0.3)	111 (0.2)	0.0177
Ovary	176 (0.4)	3878 (0.1)	0.0465	176 (0.3)	52 (0.1)	0.0528
Cervix uteri	206 (0.42)	3150 (0.1)	0.0617	204 (0.4)	250 (0.1)	0.0622
Corpus uteri	298 (0.6)	6055 (0.2)	0.0640	297 (0.6)	113 (0.2)	0.0585
Breast	2561 (5.3)	56312 (1.9)	0.1816	2541 (5.2)	887 (1.8)	0.1856
Urinary tract	1725 (3.5)	13303 (0.4)	0.2228	1719 (3.5)	296 (0.6)	0.2069
Kidney	3 816 (7.85)	95657 (3.2)	0.2026	3767 (7.8)	3117 (6.4)	0.0522
Malignant neoplasm of bronchus and lung	4034 (8.3)	67074 (2.3)	0.2720	3988 (8.2)	3369 (6.9)	0.0482
Malignant melanoma	3507 (7.2)	50881 (1.7)	0.2683	3473 (7.2)	1018 (2.1)	0.2428
Prostate	1969 (4.0)	30803 (1.0)	0.1919	1946 (4.0)	548 (1.1)	0.1830
Others	24704 (50.8)	2567897 (86.1)	0.4367	26679 (55.1)	26899 (55.5)	0.0134
Comorbidities						
Hypertension	21340 (43.9)	546208 (18.5)	0.5706	21238 (43.8)	21270 (43.9)	0.0013
Diabetes mellitus	10626 (219)	199682 (6.8)	0.4418	10529 (21.7)	10418 (21.5)	0.0056
Gastroesophageal reflux diseases	13540 (27.9)	126033 (4.3)	0.6788	13454 (27.8)	5132 (10.6)	0.4470
Peptic ulcers	1102 (2.3)	5925 (0.2)	0.1881	1051 (2.2)	374 (0.8)	0.1163
Gastroduodenitis	867 (1.8)	7790 (0.3)	0.1515	858 (1.8)	302 (0.6)	0.1057
Hyperlipidemia	14567 (30.0)	342093 (11.6)	0.4655	14480 (29.9)	13716 (28.3)	0.0347
Atrial fibrillation	4260 (8.8)	90521 (3.1)	0.2435	4228 (8.7)	3771 (7.8)	0.0343
Chronic lower respiratory diseases	11122 (22.9)	199314 (6.7)	0.4665	11021 (22.7)	10977 (22.6)	0.0022
Hypercholesterolemia	7075 (14.6)	174159 (5.9)	0.2888	7021 (14.5)	6663 (13.7)	0.0212
Cardiac arrhythmias	6421 (13.2)	107325 (3.6)	0.3502	6337 (13.1)	4982 (10.2)	0.0872
Coronary heart disease	3575 (7.4)	41413 (1.4)	0.2942	3513 (7.2)	2718 (5.6)	0.0669
Congestive heart failure	5089 (10.5)	63052 (2.1)	0.3483	5001 (10.3)	4704 (9.7)	0.0204
Cerebrovascular disease	6662 (13.7)	103190 (3.5)	0.3706	6570 (13.6)	6266 (12.9)	0.0185

Diabetic polyneuropathy	1983 (4.1)	26801 (1.0)	0.2046	1945 (4.0)	2082 (4.3)	0.0142
Glomerular diseases	770 (1.6)	8865 (0.3)	0.1333	752 (1.5)	564 (1.2)	0.0335
Chronic kidney disease	6790 (13.9)	114526 (3.9)	0.3598	6708 (13.8)	6350 (13.1)	0.0216
Peripheral vascular diseases	4220 (8.7)	53718 (1.8)	0.3116	4149 (8.6)	3444 (7.1)	0.0542
Diabetic retinopathy	981 (2.0)	16162 (0.5)	0.1311	958 (1.9)	1232 (2.5)	0.0381
Diabetic nephropathy	1789 (3.7)	25585 (0.868)	0.1897	1754 (3.6)	2040 (4.2)	0.0304
Diseases of pancreas	1761 (3.6)	15,072 (0.5)	0.2202	1740 (3.6)	673 (1.38)	0.1417
Diseases of gallbladder	928 (1.9)	9746 (0.3)	0.1506	915 (1.9)	545 (1.1)	0.0627
Diseases of biliary tract	1371 (2.8)	9373 (0.3)	0.2026	1349 (2.8)	535 (1.1)	0.1219
Cirrhosis of liver	2259 (4.6)	15246 (0.5)	0.2629	2224 (4.6)	1047 (2.2)	0.1348
Osteoporosis	3338 (6.9)	77419 (2.6)	0.2008	3318 (6.8)	2465 (5.1)	0.0744
Obstructive sleep apnea	4034 (8.3)	67074 (2.3)	0.2720	3988 (8.2)	3369 (6.9)	0.0482
Liver diseases	5502 (11.3)	58923 (2.0)	0.3810	5403 (11.1)	5334 (11.0)	0.0045
Cancer treatment						
Chemotherapy	3922 (8.1)	112502 (3.8)	0.1810	3887 (8.0)	2419 (5.1)	0.1231
Antineoplastic and immunomodulating agents	7450 (15.3)	208407 (7.1)	0.2647	7400 (15.3)	4765 (9.8)	0.1647
Immunological agents	3816 (7.9)	95657 (3.2)	0.2026	3767 (7.8)	3117 (6.4)	0.0522
Radiotherapy	872 (1.8)	16379 (0.5)	0.1153	870 (1.8)	413 (0.8)	0.0826
Surgery	5480 (52.5)	769018 (26.1)	0.5615	25381 (52.4)	21120 (43.6)	0.1767
Targeted therapy	2092 (4.3)	9939 (0.3)	0.2660	2057 (4.2)	500 (1.0)	0.2015
Medications						
Beta-blockers	14581 (30.0)	285348 (9.7)	0.5277	14490 (29.9)	10814 (22.3)	0.1734
Aspirin	13275 (27.3)	240151 (8.1)	0.5192	13179 (27.2)	10192 (21.0)	0.1445
NSAIDs usage	20915 (43.1)	464565 (15.7)	0.6286	20813 (42.9)	14519 (29.9)	0.2724
Hypoglycemic drugs	6495 (13.4)	123497 (4.2)	0.3290	6424 (13.2)	6558 (13.5)	0.0081
Insulin	6951 (14.3)	89333 (3.0)	0.4094	6849 (14.1)	6551 (13.5)	0.0178
Antiarrhythmics	6274 (33.5)	329864 (11.2)	0.5564	16179 (33.4)	11097 (22.9)	0.2348
Antilipemic agents	16154 (33.3)	358588 (12.1)	0.5206	16064 (33.1)	13083 (27.0)	0.1345
ACE inhibitors	10817 (22.3)	218846 (7.42)	0.4273	10744 (22.2)	8770 (18.1)	0.1017
Angiotensin II inhibitors	6268 (12.9)	137747 (4.7)	0.2941	6232 (12.8)	5092 (10.5)	0.0733
Diuretics	4023 (28.9)	269083 (9.1)	0.5204	13928 (28.7)	10575 (21.8)	0.1597
Vitamin D supplement	8317 (17.1)	150002 (5.1)	0.3905	8261 (17.0)	5233 (10.8)	0.1813
Vitamin E supplement	1318 (2.7)	30518 (1.0)	0.1241	1309 (2.7)	1033 (2.1)	0.0371
Calcium channel blockers	0519 (21.7)	190886 (6.4)	0.4477	10437 (21.5)	7842 (16.1)	0.1372
Antihypertensive combinations	171 (0.3)	2229 (0.1)	0.0599	168 (0.3)	197 (0.4)	0.0098
Opioids	1369 (2.8)	23224 (0.8)	0.1531	1359 (2.8)	678 (1.4)	0.0981
Immunosuppressants	1958 (4.0)	36586 (1.2)	0.1749	1945 (4.0)	1056 (2.2)	0.1061
Antiemetics	16473 (33.9)	320517 (10.9)	0.5755	16382 (33.8)	9934 (20.5)	0.3026
Antidepressants	11404 (23.5)	230648 (7.8)	0.4415	11331 (23.4)	7563 (15.6)	0.1972
Anticonvulsants	8945 (18.4)	139173 (4.7)	0.4386	8875 (18.3)	5306 (10.9)	0.2095
Laxatives	17542 (36.1)	295981 (10.0)	0.6512	17440 (35.9)	10634 (21.9)	0.3134

PPI: Proton pump inhibitor; SMD: Standard mean difference; BMI: Body mass index; NSAID: Non-steroidal anti-inflammatory drugs.

between the groups effectively. We incorporated a robust variance estimator in the Cox regression model to account for clustering within the 1:1 propensity-matched sample and address the loss of independence among individuals due to the matching procedure[16]. The robust variance estimator was essential to enhance the accuracy of our analytical approach and ensure the validity of the study's findings. A priori-defined two-sided alpha of < 0.05 was used for statistical significance.

RESULTS

Baseline characteristics

Following PSM, the PPI and non-user characteristics were well-balanced (Supplementary Figure 1). Age was comparable between PPI users and non-users after matching (64.9 ± 12.2 years *vs* 64.7 ± 12.8 years; SMD = 0.012, Table 1). Post-matching, racial distribution showed minimal differences, with White individuals comprising 67.1% of PPI users and 66.7% of non-users (SMD = 0.0071). The prevalence of nicotine and alcohol dependence was effectively matched (20.4% *vs* 20.6%, SMD = 0.0061 for nicotine; 4.4% *vs* 3.8%, SMD = 0.0288 for alcohol, Table 1). Significant baseline disease medication intake and chronic conditions were closely matched. The mean follow-up was 5.4 ± 1.8 years for the PPI group and 6.5 ± 1.0 years for non-users.

Outcome

The propensity score-matched analysis showed that PPI users had a higher mortality rate at all assessed time points compared to non-users. At 1 year, PPI users had a substantially higher mortality rate than non-users, with 8888 events in the PPI *vs* 3272 in the non-PPI group (HR = 2.72, 95%CI: 2.61-2.83, Table 2). After 2 years, there were higher than 13719 events in the PPI users *vs* 5276 in the non-users (HR = 2.66, 95%CI: 2.58-2.74, Table 2). Over the entire follow-up period, which averaged 5.4 ± 1.8 years for PPI users and 6.5 ± 1.0 years for non-users, the cumulative incidence of death was 23421 for PPI users and 11656 for non-users (HR = 2.34, 95%CI: 2.29-2.42, Table 2). The analysis revealed consistently elevated mortality risks across different time intervals in examining all-cause mortality concerning varying lag exposures for PPI compared to non-users.

Secondary analysis

A well-matched population was found in the PPI *vs* H2RA groups (n = 44, 834 each) after PSM (Supplementary Figure 2). The mean follow-up was 4.6 ± 1.3 years for PPIs and 3.8 ± 1.6 years for H2RAs. After 1 year, mortality was notably higher among PPI users (8393) than H2RA users (7980), HR 1.51 (95%CI: 1.41-1.69, Table 3). The difference in mortality rates between the two groups persisted for two years, with 12950 events for PPI users and 11989 for H2RA users (HR = 1.16, 95%CI: 1.04-1.39, Table 3). Over the entire follow-up, the cumulative mortality was 18304 for PPI users *vs* 17146 for H2RA users (HR = 1.17, 95%CI: 1.05-2.16).

Sensitivity analysis

Supplementary Tables 1-3 show the results of the sensitivity analyses. When extending the lag exposure to 9 months, the mortality risk remained significantly elevated, with HR = 2.45 (95%CI: 2.39-2.52). Further increasing the lag to 12 months resulted in 13898 mortality events for PPI users and 7009 for non-users, HR = 2.41 (95%CI: 2.34-2.48, Supplementary Table 1). The second analysis evaluated the impact of PPI use on all-cause mortality, excluding early outcomes. After excluding early events in the first six months, a similar pattern emerged when extending the exclusion to the first 6 months. The analysis included 44453 PPI and 48805 non-users, 17166 deaths in the PPI *vs* 8249 non-users during the follow-up. The HR remained consistent at 2.54 (95%CI: 2.43-2.61). We extended these sensitivity analyses by excluding the first 12 months from the index period. The mortality count was 12433 for PPI users and 5759 for non-users, HR = 2.48 (95%CI: 2.39-2.62, Supplementary Table 2). In the third analysis, we examined all-cause mortality between former PPI users and individuals who never used PPIs for insights into the long-term effects of past PPI use. At 1-year follow-up, a significant difference in mortality rates between former users and non-users (HR = 1.84, 95%CI: 1.82-1.96, Supplementary Table 3) was found. Former PPI users had an 84% higher mortality risk within one year compared to those who never used PPIs.

DISCUSSION

This large, retrospective cohort study conducted using a well-established research network revealed significant negative associations between PPI use and higher all-cause mortality among cancer patients. These findings contribute importantly to the growing body of evidence expressing concerns over the long-term use of PPIs, especially among vulnerable populations such as those undergoing cancer treatment.

Across all time points analyzed, PPI users had a significantly increased risk of the evaluated outcome than non-users and H2RA users. This consistent pattern highlights a potential association between PPI usage and death, warranting further investigation into the long-term effects of PPI therapy. These findings were persistent, even as the lag period increased. Although there was a trend of lower risk with longer lag times, the consistently high HRs emphasize the importance of cautious use and careful monitoring during long-term PPI therapy. The sensitivity analyses showed a persistent and significantly greater all-cause mortality with PPI use across various cohorts and timeframes, even when early mortality was excluded. Thus, it emphasizes the need for careful prescribing and ongoing management of PPI

Table 2 Hazard ratios (95%CIs) for all-cause mortality between new users of proton pump inhibitors compared with non-users

Outcome	PPI-users (*n* = 48452)	Non-users (*n* = 48452)	HR (95%CI)
At 1 year	8888	3272	2.72 (2.61-2.83)
At 2 years	13719	5276	2.66 (2.58-2.74)
Overall outcome during follow-up	23421	11656	2.34 (2.29-2.42)

PPI: Proton pump inhibitor; HR: Hazard ratio.

Table 3 Hazard ratios (95%CIs) for all-cause mortality between new users of proton pump inhibitors compared to histamine 2 receptor antagonists in a secondary analysis

Outcome	PPI-users (*n* = 44834)	H2RA-users (*n* = 44834)	HR (95%CI)
At 1-year	8393	7980	1.51 (1.41-1.69)
At 2-years	12950	11989	1.16 (1.04-1.39)
Overall outcome during follow-up	18304	17146	1.17 (1.05-2.16)

PPI: Proton pump inhibitor; HR: Hazard ratio; H2RA: Histamine2 receptor antagonist.

therapy, particularly around the duration of use and potential long-term health implications.

The substantially higher mortality rate among former PPI users *vs* non-users within the first year highlights a critical concern regarding the long-term health implications of PPI usage. This elevated risk accentuates the importance of monitoring and possibly re-evaluating the necessity and duration of PPI therapy in clinical practice, particularly considering the potential lasting effects even after discontinuation.

The results of our study are consistent with prior research indicating potential adverse outcomes associated with prolonged PPI use, including increased risks of cardiovascular disease[17], chronic kidney disease[18], and infections[19]. However, excess mortality risk among cancer patients, as indicated by our HRs, accentuates a potentially unique interaction between PPI use and cancer. The mechanisms may relate to the effects of PPIs on the absorption of vital nutrients[20], alterations of gut microbiota[21], and interference with the metabolism of chemotherapeutic agents[22]. Further research is needed to comprehensively understand the potential consequences of prolonged PPI usage in individuals undergoing cancer treatment.

Post-diagnostic PPI use is associated with higher cancer mortality, particularly in ovarian cancer[8]. In a cohort study, PPI use after colorectal cancer diagnosis or survivorship was associated with increased all-cause mortality[23]. Moreover, in the Veterans Affairs Cancer Center registry[24], post-diagnosis use of acid-suppressant medications, like PPIs, was associated with greater mortality in patients with gastric non-cardia cancer and hepatocellular carcinomas. Concomitant PPI use was also significantly associated with lower immune checkpoint inhibitor efficacy and greater risk of death in advanced cancer[22].

Our analysis showed that the highest HRs were predominantly seen in individuals who had used PPIs for less than two years. Interestingly, the HRs gradually decreased as the duration of PPI use extended beyond this period; this trend may be due to the underlying comorbidity conditions where PPIs are commonly prescribed for managing gastrointestinal symptoms and as a preventive measure against gastrointestinal damage from prolonged nonsteroidal anti-inflammatory drugs use among cancer patients[24-26].

Compared to earlier studies that often focused on specific cancer sites or smaller patient cohorts, our study has a robust sample size and diverse cancer patients. This enhances generalizability. For example, a previous study did not find an association between PPI use and increased mortality among general populations[10]; however, our cancer-specific patient population appears at higher risk, possibly due to their different baseline health status and unique metabolic and therapeutic contexts.

Our study had several strengths. First, methodological rigor allows a nuanced assessment of PPI impacts in real-world settings. It is the largest study to date to examine the association of PPI with all-cause mortality in cancer patients, consisting of 'real-world' data with long follow-up times. Second, the comprehensive cohort design and PSM minimized confounding variables with narrower CIs and higher precision. Third, the cohort was restricted to new users, eliminating bias associated with prevalent users[26]. Fourth, comparing PPIs with an HR2A comparator in secondary analysis likely minimized confounding by indication. Fifth, we used varying exposure times, eliminating immortal time bias by allowing a cohort to contribute time to different exposure categories during the follow-up period[27]; however, PPI use was still associated with higher mortality. Finally, our results remained consistent across several sensitivity analyses.

This study also has some limitations. First, the retrospective design and the reliance on an EHR-based database limited our results. Whenever patient information is translated into diagnosis codes, data from EHR-based databases are susceptible to errors in coding. Standardized measures identified cases to minimize documentation errors. Second, PPIs and H2RAs are available over the counter in the United States, potentially leading to some missing medication information. Third, residual confounding remains possible even after adjusting potential confounders in an observational study. However, we used new users as a cohort to reduce the potential for unmeasured confounding. Moreover, some residual confounding may be from imperfectly captured covariates, such as *Helicobacter pylori* infection. Fourth, we lacked information regarding disease stage and grade, family history, and genetic risk factors. In addition, information on cancer staging, chemotherapy, immunotherapy, or radiotherapy was not available for all the patients. The absence of staging information at diagnosis greatly impacts the study, critically influencing prognosis and treatment decisions. However, the comprehensive analysis of available data sheds light on potential associations and prompts further inquiry. Finally, the reliance on EHR data may introduce misclassification biases related to drug exposure and outcome assessment.

Clinicians should weigh the risks and benefits of prolonged PPI use in cancer patients, considering alternative management strategies for acid-related symptoms when feasible. This is particularly relevant during chemotherapy, where PPI use might negatively impact treatment efficacy or exacerbate adverse effects. Regular reassessment of the necessity of PPI therapy should focus on minimizing the duration of use. Further prospective studies and randomized controlled trials could clarify the causative mechanisms behind the observed higher cancer mortality associated with PPIs. Studies exploring the interaction between PPI use and specific cancer therapies could also provide insights into how best to manage individually[28].

CONCLUSION

In conclusion, our study highlights a notable link between the use of PPIs and increased overall mortality in individuals with cancer. This indicates the need for heightened caution when prescribing PPIs to this especially vulnerable group, considering alternative approaches for managing acid-related symptoms, such as lifestyle modifications, non-PPI medications, or complementary therapies whenever possible. Although our study provides novel information, randomized controlled trials, and additional observational studies are needed to corroborate our findings, given the significant adverse outcomes in cancer patients. Given the widespread use of PPIs, these findings have significant public health consequences and emphasize the important point that PPIs should be used only when therapeutically required and for the shortest duration possible. The findings advocate for a careful assessment of the risks and benefits of PPI therapy, highlighting the necessity for alternative therapeutic strategies and continuous patient monitoring.

FOOTNOTES

Author contributions: Krishnan A contributed to the concept of the study and study design and was responsible for data acquisition and statistical analysis; Krishnan A and Schneider CV drafted the manuscript; Walsh D participated in the review and editing. All authors were involved with interpreting the data and critically revising the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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