Survival outcomes of patients with nonsmall cell lung cancer concomitantly receiving proton pump inhibitors and immune checkpoint inhibitors

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Abstract
Recent evidence suggests that gut microbiota dysbiosis adversely affects the efficacy of immune checkpoint inhibitors (ICIs). Our objective was to investigate the association between concomitant use of proton pump inhibitors (PPIs) and ICIs, and poor prognosis in patients with nonsmall cell lung cancer (NSCLC). We conducted a cohort study using a completely enumerated lung cancer cohort from a nationwide healthcare database in South Korea. We identified 2963 patients treated with ICIs as second-line or later therapy for stage ≥IIIb NSCLC. PPI use was ascertained within 30-days before and on the date of ICI initiation, and nonuse was defined as no prescription of PPIs during this period. Using national vital statistics in South Korea, we assessed the risk of all-cause mortality associated with concomitant PPI use through a propensity score-matched Cox proportional hazard model. Among 1646 patients included after 1:1 propensity score-matching, concomitant PPI use was associated with a 28% increased risk of all-cause mortality, compared to nonuse (adjusted hazard ratio [HR] 1.28; 95% confidence intervals [CIs], 1.13-1.46). We observed an increased risk when we restricted the analysis to new users of PPI (adjusted HR = 1.64; 95% CI = 1.25-2.17). Subgroup analysis showed that PPI use was associated with high mortality risk among patients with viral hepatitis (adjusted HR = 2.72; 95% CI = 1.54-4.78; Pinteraction = .048). Our study indicates that PPI use is associated with poor prognosis in NSCLC patients treated with ICIs. Further prospective studies are required to determine the risk-benefit balance of concomitant use of PPIs and ICIs.

KEYWORDS
immune checkpoint inhibitors, nonsmall cell lung cancer, prognosis, proton pump inhibitors, survival

What’s new?
The efficacy of immune checkpoint inhibitors (ICIs) in the treatment of non-small cell lung cancer (NSCLC) is potentially affected by imbalances in the human gut microbiota. Such imbalances may be induced by proton pump inhibitors (PPIs), though whether concomitant PPI and ICI use affects ICI
Immune checkpoint inhibitors (ICIs) have emerged as a mainstay in the treatment of advanced nonsmall cell lung cancer (NSCLC); however, their clinical outcomes are highly heterogeneous with only 20% to 30% of patients achieving an objective response. Emerging evidence shows that the gut microbiome modulates tumor response to ICIs, and an altered gut microbiota can negatively affect survival outcomes. Concerns have been raised that the use of proton pump inhibitors (PPIs) may induce gut microbiota dysbiosis and thus negatively impact ICI efficacy by disturbing gastric acidity and targeting bacterial and fungal proton pumps.

Alternatively, it has been suggested that PPIs possess anticancer properties. The acidic extracellular microenvironment of tumors promotes cancer progression and induces immune escape. It has been hypothesized that PPIs can neutralize the acidity of the tumor microenvironment and enhance the activity of tumor-infiltrating lymphocytes, suggesting the clinical potential of PPIs in T cell-based cancer immunotherapy. A phase II randomized controlled trial involving metastatic breast cancer patients showed a significant clinical benefit of concomitant esomeprazole use with chemotherapy in terms of the objective response rate (67.7% vs 46.9%, P = .049), compared to that of chemotherapy without PPIs.

In light of these two contradictory hypotheses, there is a high demand for further clinical research. To date, several studies have reported conflicting findings regarding the impact of PPI use on the outcomes of ICI therapy, including positive effects, non-association, and detrimental effects. These inconsistencies may be due to small sample sizes and differences in cancer types. Furthermore, the generalizability of the findings of post hoc analyses from RCTs to a real-world setting is uncertain. Given the lack of robust population-based studies, we analyzed a completely enumerated lung cancer cohort in South Korea to assess if the concomitant use of PPIs with ICIs is associated with reduced survival.

We conducted a retrospective cohort study to determine if the concomitant use of PPIs and ICIs is associated with reduced survival among patients treated with ICIs for advanced NSCLC. We identified patients with pathologically confirmed stage IIIB-IV NSCLC who started receiving programmed cell death 1 (PD-1) and PD-L1 inhibitors as second-line or later therapy between 21 August 2017 (when PD-1 inhibitors were first reimbursed) and 31 December 2018. The study ICIs were the PD-1 inhibitors nivolumab, pembrolizumab, and atezolizumab. Cohort entry was defined as the date of incident ICI use. We excluded the following patients: (a) those <18 years of age at cohort entry and (b) those who initiated PD-1 inhibitors after 1 October 2018, to ensure at least 3 months of follow-up (Figure S1). PPI users and nonusers were further matched in a 1:1 ratio using propensity scores to address the imbalance of potential confounders.

We ascertained exposure to PPIs in both inpatient and outpatient settings using an intention-to-treat approach. Exposure to PPIs was ascertained within 30 days before or on the date of ICI initiation (cohort entry). Patients who received PPIs during this period were classified as PPI users, while those who did not were classified as nonusers. To avoid immortal time bias, patients were followed-up from the cohort entry. In addition to the analysis of the entire cohort with all study population, we restricted other analysis to new PPI users to minimize potential carryover effect. We applied 180-day new-user washout windows before the exposure ascertainment window (Figure S2A). The new user analysis included patients who did not receive any PPI treatment during the 180-day washout window. Among these PPI naïve patients, new PPI users were those who received PPIs within 30 days.
before or on the date of ICI initiation (cohort entry), whereas PPI nonusers were those who did not.

2.4 | Outcome

Our study outcome was all-cause mortality, based on data linked to national vital statistics. In the national vital statistics database, all death records are coded based on medical death certificates or police reports that are transmitted to Statistics Korea. The date of death was defined as the date of the event. Each patient was followed up from cohort entry until the occurrence of the outcome of interest (all-cause mortality) or the end of the study period (31 December 2018).

2.5 | Potential confounders

We assessed demographic information (age at cohort entry, sex and income level). The use of comediations that may potentially modulate gut microbiota, including antibiotics, metformin, corticosteroids and opioids, was assessed within 30 days before cohort entry. We assessed baseline characteristics within 1 year before cohort entry for patient medical history (including diabetes, cardiovascular disease, stroke, respiratory disease, sepsis, autoimmune disease and dementia; listed in Table S1), other comediations (chemotherapies, antibiotics, immunomodulators [conventional and targeted disease-modifying antirheumatic drugs and immunosuppressants], and opioids [listed in Table S2]) and Charlson comorbidity index. Additionally, we included lifestyle factors using up to 3 years of health screening records from cohort entry, including smoking (never, ex-smoker and current smoker), alcohol consumption (never, ≥1 time a week) and body mass index (BMI) categorized into the Asian standard (underweight [<18.5 kg/m²], normal [18.5-22.9 kg/m²], overweight [23.0-24.9 kg/m²] and obese [≥25.0 kg/m²]). The percentages of missing data for smoking, alcohol consumption and BMI were 21.6%, 27.7% and 21.6%, respectively.

2.6 | Statistical analysis

We estimated the propensity scores for receiving PPIs by fitting a multivariable logistic regression model using all predefined covariates assessed before cohort entry. The propensity score was estimated by fitting a logistic regression model including age, sex, income level, smoking status, alcohol consumption, BMI, medical history and medications. PPI users were matched to nonusers in a 1:1 ratio with propensity scores, using the greedy matching macro. Descriptive statistics were used to summarize patient characteristics, with frequencies and percentages for categorical variables and means (SDs) for continuous variables. Potential imbalances in covariates were assessed using the absolute value of standardized difference, with a value ≥0.1 considered as significant.

We used a Cox proportional hazard model to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality risk with the concomitant use of PPIs with ICIs, compared to nonuse, among patients treated with ICIs for NSCLC. The model was adjusted for age, sex, respiratory disease, viral hepatitis, antibiotics and corticosteroid use. These covariates were also used in the propensity score-matched cohort for a doubly robust estimation of the causal effect. We used the Kaplan-Meier method to estimate overall survival and assessed the median survival time. Kaplan-Meier survival curve was used to measure the probability of surviving over a period of time with the consideration of time in each small interval. It involves computing the probabilities of event occurrence at a certain point of time and then multiplying all the prior survival probabilities to compute the final estimate (Supplementary Method S1). Log-rank test was used to statistically compare the survival functions of two groups (PPI users vs nonusers).

2.7 | Subgroup, sensitivity and exploratory analyses

We conducted subgroup analyses using the interaction terms by age group, sex, preexisting respiratory disease, viral hepatitis, ICI subtypes and gene driver mutations (epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK]). A subgroup analysis by EGFR and ALK driver mutation was conducted to assess if these mutations altered the observed association between concomitant PPI use with ICIs and reduced survival. EGFR or ALK mutation was defined as prior exposure to the respective targeted therapies. Only those who received EGFR tyrosine kinase inhibitors as first-line treatment were considered as EGFR mutant as these treatments can be prescribed irrespective of the status of EGFR mutations in second-line or later treatment settings. On the contrary, ALK tyrosine kinase inhibitors were only indicated for those with ALK mutations.

We performed three sensitivity analyses. First, we redefined new PPI users, given the great variability in time between studies to restore the gut microbiome after PPI or antibiotic use. We applied 30-day and 90-day washout windows before the exposure ascertain-ment window (30 days before and on the date of ICI initiation [cohort entry]; Figure S2B,C). Second, we redefined the exposure ascertain-ment period to 180 days before and on cohort entry to explore the long-term impact of PPI use on ICI efficacy. We then assessed the dose-duration response according to cumulative PPI duration (duration ≤14 days, 14 days < duration ≤30 days and duration > 30 days) and the cumulative defined daily dose of PPI (DDD; dose ≤14 DDD, 14 DDD < dose ≤30 DDD and dose > 30 DDD). Finally, we conducted a post hoc sensitivity analysis by calculating the E-value to quantify the effect of an unmeasured confounder that would have affected our findings (Supplementary Method S2).

In the exploratory analysis, we also evaluated the influence of histamine 2 receptor antagonists (H2RAs), which also can theoretically alter and induce the compositional changes of gut microbiota. To investigate this association, an exploratory analysis with three exposure groups (PPI users, H2RA users and nonusers) was conducted. Exposure to either PPIs or H2RAs was assessed within 30 days before and on the cohort entry. Patients who were exposed to both PPIs and H2RAs during this period were excluded for accurate exposure group assignment. Patients naive to
these drugs were classified as nonusers. Additionally, given that subsequent cancer treatments after the initial ICI treatment may modify survival in NSCLC patients, we conducted stratified analyses by subsequent post-ICI treatment options, including palliative radiation, single-agent chemotherapy and platinum-based doublet chemotherapy.

All statistical analyses were performed using SAS Enterprise software (version 7.1; SAS Institute, Cary, North Carolina). A two-tailed value of $P < .05$ indicated statistical significance.

### RESULTS

Of the 112,870 patients with lung cancer, we identified 2963 NSCLC patients who used ICI as second-line or later therapy, which comprised 936 concomitant PPI users (31.6%) and 2027 nonusers (68.4%; Figure S3). We included 1646 patients after propensity score-matching at a 1:1 ratio ($C$-statistic, 0.752). All variables were well-balanced after propensity score-matching (Table 1).

**TABLE 1** Characteristics of nonsmall cell lung cancer patients treated with ICIs according to concomitant PPI use

| Characteristics                        | Overall ICI cohort (n = 2963) | PS-matched ICI cohort (n = 1646) |
|-----------------------------------------|-----------------------------|----------------------------------|
|                                         | PPI use, n (%) (n = 936) | PPI nonuse, n (%) (n = 2027) | aSD | PPI use, n (%) (n = 823) | PPI nonuse, n (%) (n = 823) | aSD |
| Age, years, mean (SD)                   | 65.5 (9.3) | 65.8 (9.8) | 0.03 | 65.8 (9.1) | 65.9 (9.1) | 0.01 |
| Male                                    | 744 (79.5) | 1582 (78.1) | 0.03 | 662 (80.4) | 661 (80.3) | 0.00 |
| **Lifestyle factors**                  |                |            |     |                |            |     |
| Smoking (ever)                          | 504 (53.9) | 1007 (49.7) | 0.12 | 437 (53.1) | 445 (54.1) | 0.03 |
| Alcohol consumption (>1 time per week) | 301 (32.2) | 602 (29.7) | 0.05 | 256 (31.1) | 262 (31.8) | 0.05 |
| **BMI (kg/m²)**                         |                |            |     |                |            |     |
| Underweight (<18.5)                    | 36 (3.9) | 65 (3.2) | 0.10 | 31 (3.8) | 31 (3.8) | 0.08 |
| Normal (18.5–22.9)                     | 268 (28.6) | 578 (28.5) | 0.08 | 233 (28.3) | 239 (29.0) | 0.04 |
| Overweight (23.0–24.9)                 | 425 (45.4) | 911 (45.0) | 0.08 | 376 (45.7) | 381 (46.3) | 0.05 |
| Radiation therapy                      | 395 (42.2) | 697 (34.4) | 0.16 | 327 (39.7) | 341 (41.4) | 0.03 |
| **Medical history**                    |                |            |     |                |            |     |
| Brain metastasis                       | 20 (2.1) | 49 (2.4) | 0.02 | 20 (2.4) | 27 (3.3) | 0.05 |
| Thyroid dysfunction                    | 166 (17.7) | 327 (16.1) | 0.04 | 137 (16.7) | 138 (16.8) | 0.00 |
| Respiratory disease                    | 746 (79.7) | 1521 (75.0) | 0.11 | 650 (79.0) | 656 (79.7) | 0.02 |
| Autoimmune disease                     | 96 (10.3) | 172 (8.5) | 0.06 | 89 (10.8) | 78 (9.5) | 0.04 |
| Diabetes mellitus                      | 364 (38.9) | 731 (36.1) | 0.06 | 318 (38.6) | 312 (37.9) | 0.01 |
| Renal disease                          | 44 (4.7) | 95 (4.7) | 0.00 | 39 (4.7) | 45 (5.5) | 0.03 |
| Hepatic disease                        | 377 (40.3) | 603 (29.8) | 0.22 | 317 (38.5) | 311 (37.8) | 0.02 |
| Dementia                               | 31 (3.3) | 61 (3.0) | 0.02 | 25 (3.0) | 25 (3.0) | 0.00 |
| Sepsis                                 | 66 (7.1) | 107 (5.3) | 0.07 | 57 (6.9) | 56 (6.8) | 0.00 |
| Hyperlipidemia                         | 487 (52.0) | 956 (47.2) | 0.10 | 422 (51.3) | 406 (49.3) | 0.04 |
| Cardiovascular disease                 | 362 (38.7) | 660 (32.6) | 0.13 | 310 (37.7) | 306 (37.2) | 0.01 |
| Stroke                                 | 91 (9.7) | 187 (9.2) | 0.02 | 79 (9.6) | 64 (7.8) | 0.06 |
| Viral hepatitis                        | 57 (6.1) | 120 (5.9) | 0.01 | 53 (6.4) | 55 (6.7) | 0.01 |
| Gastrointestinal disease               | 782 (83.6) | 1115 (55.0) | 0.65 | 670 (81.4) | 676 (82.1) | 0.02 |

| Comedication                           |                |            |     |                |            |     |
| Corticosteroids                        | 523 (55.9) | 813 (40.1) | 0.32 | 426 (51.8) | 422 (51.3) | 0.01 |
| Antibiotics                            | 349 (37.3) | 485 (23.9) | 0.29 | 276 (33.5) | 273 (33.2) | 0.02 |
| Metformin                              | 135 (14.4) | 233 (11.5) | 0.09 | 116 (14.1) | 109 (13.2) | 0.02 |
| Opioids                                | 557 (59.5) | 824 (40.7) | 0.38 | 454 (55.2) | 452 (54.9) | 0.00 |
| Beta blockers                          | 204 (21.8) | 342 (16.9) | 0.12 | 172 (20.9) | 173 (21.0) | 0.00 |
| Immunomodulators*                      | 57 (6.1) | 103 (5.1) | 0.04 | 47 (5.7) | 38 (4.6) | 0.05 |
| Antivirals                             | 120 (12.8) | 200 (9.9) | 0.09 | 100 (12.2) | 84 (10.2) | 0.06 |
| CCI, mean (SD)                         | 6.7 (2.9) | 6.4 (2.9) | 0.04 | 6.6 (2.9) | 6.7 (2.9) | 0.00 |

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; ICI, immune checkpoint inhibitor; PPI, proton pump inhibitor; PS, propensity score; aSD, absolute standard deviation.

*Immunomodulators include conventional and biologic disease-modifying antirheumatic drugs and immunosuppressants.
**FIGURE 1** Mortality risk in the propensity score-matched ICI cohort according to concomitant PPI use. (A) Mortality risk in the entire propensity score-matched cohort (prevalent and new user cohorts). (B) Mortality risk in the propensity score-matched cohort of new PPI users. CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; PPI, protein pump inhibitor.
Figure 1 shows the survival curve for mortality in concomitant PPI users (comparison group: nonusers). Concomitant PPI use was associated with a 28% increased risk of all-cause mortality, compared to nonuse in the propensity score-matched cohort (adjusted HR = 1.28; 95% CI = 1.13-1.46; Figure 1A and Table 2). PPI users also had shorter median survival than nonusers (median [95% CI]: 5.1 months [4.6-6.0] vs 8.0 months [6.7-9.2], P < .001). The risk of mortality increased when we restricted the analysis to new PPI users (adjusted HR = 1.64; 95% CI = 1.25-2.17; Figure 1B and Table 2).

We observed an increased risk of mortality among concomitant PPI users regardless of subgroup (Figure 2). Interaction tests suggested that the effect of PPI on reduced survival differed between subgroups.

| TABLE 2 | Mortality risk among nonsmall cell lung cancer patients treated with ICIs according to concomitant PPI use |
|----------|--------------------------------------------------------------------------------------------------|
| Overall ICI cohort | PS-matched ICI cohort |
| No. of deaths/patients | IR | Unadjusted HR (95% CI) | Adjusted HR (95% CI) | No. of deaths/patients | IR | Unadjusted HR (95% CI) | Adjusted HR (95% CI) |
| PPI nonuse | 935/2027 | 76.3 | 1.00 (Ref) | 1.00 (Ref) | 448/823 | 98.9 | 1.00 (Ref) | 1.00 (Ref) |
| PPI use | 582/936 | 139.0 | 1.75 (1.58-1.94) | 1.59 (1.43-1.77) | 500/823 | 131.8 | 1.30 (1.14-1.47) | 1.28 (1.13-1.46) |

Abbreviations: CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; IR, incidence rate; PPI, proton pump inhibitor; PS, propensity score.

| Characteristics | No. of patients | IR (PPI use/ PPI nonuse) | Adjusted HR (95% CI) | P for interaction |
|-----------------|-----------------|--------------------------|----------------------|------------------|
| **Age group**   |                 |                          |                      | .1942            |
| 18-64           | 691             | 119.8/91.5               | 1.27 (1.04-1.56)     |                  |
| 65-74           | 640             | 134.9/117.6              | 1.12 (0.91-1.36)     |                  |
| ≥75             | 315             | 154.3/81.5               | 1.82 (1.34-2.47)     |                  |
| **Sex**         |                 |                          |                      | .0773            |
| Male            | 1323            | 126.6/101.2              | 1.21 (1.05-1.40)     |                  |
| Female          | 323             | 155.5/90                 | 1.64 (1.22-2.20)     |                  |
| **Respiratory disease** |  |                           |                      | .9197            |
| No              | 340             | 112.4/86.1               | 1.32 (0.98-1.79)     |                  |
| Yes             | 1306            | 137.5/102.3              | 1.27 (1.11-1.47)     |                  |
| **Viral hepatitis** |              |                          |                      | .0482            |
| No              | 1538            | 129.6/101.3              | 1.24 (1.08-1.41)     |                  |
| Yes             | 108             | 164.5/69.2               | 2.72 (1.54-4.78)     |                  |
| **ICI subtypes** |              |                          |                      | .245             |
| Nivolumab       | 779             | 139.8/100.4              | 1.38 (1.18-1.62)     |                  |
| Pembrolizumab   | 816             | 122.1/97.1               | 1.16 (0.99-1.36)     |                  |
| Atezolizumab    | 51              | 192.6/106.6              | 1.63 (1.03-2.60)     |                  |
| **EGFR mutation** |            |                          |                      | <.01             |
| EGFR mutant     | 155             | 209.2/123.7              | 1.47 (0.98-2.22)     |                  |
| EGFR wild type  | 1491            | 126.7/96.4               | 1.27 (1.11-1.46)     |                  |
| **ALK mutation** |              |                          |                      | <.01             |
| ALK mutant      | 24              | 196.5/113.2              | 1.66 (0.48-5.69)     |                  |
| ALK wild type   | 1622            | 131.1/88.7               | 1.28 (1.12-1.45)     |                  |

Abbreviations: CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; IR, incidence rate; PPI, proton pump inhibitor; PS, propensity score.

**Favors PPI use** | **Favors nonuse** |
|-------------------|------------------|
| 0.5               | 2                |

Figure 2 Subgroup analyses of mortality risk in the propensity score-matched ICI cohort by concomitant PPI use. ALK, anaplastic lymphoma kinase; CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; ICI, immune checkpoint inhibitor; IR, incidence rate; PPI, proton pump inhibitor; PS, propensity score. **Crude incidence per 100 person-years was calculated by dividing the number of events by the sum of person-years and then multiplying by 100.** **Adjusted for age, sex, respiratory disease, viral hepatitis, antibiotics and corticosteroid use before cohort entry.**
patients with and without viral hepatitis, in which PPI use was associated with a significantly higher risk of mortality among patients with viral hepatitis than among those without (adjusted HR = 2.72; 95% CI = 1.54-4.78; P for interaction = .048). Consistent results supporting the association were found in both EGFR/ALK mutant and EGFR/ALK wild-type patients, and the interaction analysis showed a trend toward an increased risk of mortality among the EGFR/ALK mutant patients (P interaction < .01).

Figure 3 shows the results of sensitivity analyses, where we redefined the new-user washout period and exposure ascertainment period. Consistent results were found when we redefined the new-user washout period to 30 and 90 days. When we ascertained PPI use 180 days before and including the date of cohort entry, PPI use was associated with an overall increased risk of mortality in all cumulative PPI duration and dose subgroups. However, we did not find a linear dose-duration response relationship. We applied our estimates for the association between new PPI use and the risk of mortality (adjusted HR = 1.64; 95% CI = 1.25-2.17), and the E-value was 2.17 (Supplementary Method S2).

As indicated by the results of the exploratory analysis, H2RA users had an increased risk of mortality, compared to nonusers of either PPIs or H2RAs (Figure S4). Table S3 shows the stratified analysis by post-ICI treatment subtype. In the PS-matched cohort, 26.9% of NSCLC patients received systemic chemotherapy after initial ICI treatment. We found similar trends indicating a negative prognostic effect of concomitant PPI use with ICI on survival outcomes in the analyses stratified by post-ICI treatment option, except for patients who received docetaxel or carboplatin plus gemcitabine, where HR estimates for mortality risk did not differ between PPI users and nonusers (Table S3).

4 | DISCUSSION

This large population-based cohort study provides clinical evidence indicating that the concomitant use of PPIs with ICIs is associated with reduced survival in patients with advanced NSCLC. Among 1646 ICI users with advanced NSCLC, PPI users had a 28% increased risk of all-cause mortality compared to PPI nonusers (adjusted HR = 1.28; 95% CI = 1.13-1.46). The risk was elevated when we restricted the analysis to new PPI users (adjusted HR = 1.64; 95% CI = 1.25-2.17). The association remained largely consistent when the exposure ascertainment period varied or when different new-user washout windows were applied.

While the impact of PPI use on ICI treatment outcomes is conflicting across studies,8-11 there are potential mechanisms underlying
the pathogenic link between PPI use and ICI response. The potent inhibition of gastric acid secretion by PPIs may increase gastric pH, leading to altered gut microbiota. PPIs reduced the load of Ruminococcus spp. in the gut microbiome, which are associated with a favorable response to ICIs. Alternatively, PPIs may directly suppress the immune system through the exertion of antiinflammatory effects by reducing the secretion of proinflammatory cytokines and adhesion molecules expressed by inflammatory cells. Notably, the negative impact of PPI use on survival was prominent among patients with viral hepatitis (adjusted HR = 2.72; 95% CI = 1.54-4.78; P value for interaction = .048). Given the pathogenic relationship between viral hepatitis and gut microbiota dysbiosis, it is possible that the gut microbiome-modulating effect of PPIs is particularly detrimental to patients who already have vulnerable gut microbiota conditions.

Heterogeneity has been observed in studies on the association between the concomitant use of PPIs and ICIs and reduced survival. A recent systematic review that included seven studies reported a null association between PPI use and mortality risk (HR = 1.05; 95% CI = 0.79-1.40); however, concomitant PPI use played contrary roles in patients with different cancer types, demonstrating a beneficial effect in melanoma patients and a negative effect in NSCLC patients. While the mechanisms underlying the inconsistent clinical consequences of PPI use in melanoma and NSCLC is yet to be elucidated, it has been hypothesized that the immunosuppressive effect of PPIs may have exerted an excessive influence on the prognosis of NSCLC patients who are already susceptible to infections, including pneumonia.

Consistent with our findings, three retrospective post hoc analyses of RCTs of atezolizumab also demonstrated negative survival outcomes associated with concurrent PPI use. One study identified 757 atezolizumab users (234 PPI users and 523 PPI nonusers) using pooled RCT data of patients with NSCLC and reported an increased mortality risk in PPI users (HR = 1.45; 95% CI = 1.20-1.75). Similar finding was reported in another RCT post hoc analysis of atezolizumab combination therapy (plus carboplatin and paclitaxel) among patients with nonsquamous NSCLC. The post hoc analysis of atezolizumab RCT among urothelial carcinoma patients reported that PPI use was a negative prognostic marker for mortality (HR = 1.52; 95% CI = 1.27-1.83). Another observational study involving 224 nivolumab users with NSCLC in the Czech Republic investigated the impact of several concomitant medications on mortality. However, the results were underpowered such that a significant association between PPI use and mortality risk could not be detected (HR = 1.22; 95% CI = 0.72-2.05). The generalizability of the results of previous studies to ICIs as a whole has remained unclear, as the study populations were limited to either atezolizumab or nivolumab users only. The results of our study indicated that concomitant PPI use had a negative impact on survival in the large real-world study population of PD-1 inhibitor users. Although PPI use was associated with elevated mortality risk across all cumulative PPI dose and duration subgroups in our study, a monotonic and linear dose-duration response relationship was not observed. Previous studies reported conflicting findings on the dose-duration effect of PPIs on reduced gut microbiome diversity. A study performed in the United States reported that PPI use decreased microbiome diversity. However, the study also did not detect the dose-duration response of PPI. The nonmonotonic dose-duration response in our study may have been influenced by time-varying effects of external risk factors for mortality during the follow-up, or alternatively, it possibly reflects the complexity of dose-duration responses in real-world settings due to the variability in individual susceptibility across patients (eg, underlying medical conditions or genetic factors) and synergistic or antagonistic effects of cumulative exposure. Nonetheless, this nonlinear association requires further investigation through prospective studies to determine the causal association between concomitant PPI use with ICIs and reduced survival.

Subgroup analysis by NSCLC histological type was not possible due to the unavailability of histological information in the NHS database. Previous studies reported conflicting evidence on the association between NSCLC histological types and survival. In East Asia where EGFR mutations are highly prevalent among adenocarcinoma patients, a shifting trend of survival has been observed with between squamous cell carcinoma and adenocarcinoma after the development of EGFR-targeted and ALK-targeted therapies in the early 2000s. A South Korean study reported a shift in survival rate trends for squamous cell carcinoma and adenocarcinoma from 1993 to 2012 (5-year survival [%] of squamous cell carcinoma and adenocarcinoma: 1993 to 1997 [13.6% vs 10.4%], 1998 to 2002 [16.4% vs 14.6%], 2003 to 2007 [19.5% vs 23.1%] and 2008 to 2012 [22.2% vs 32.1%]). This result reflects an improved survival rate for adenocarcinoma following the introduction of EGFR and ALK tyrosine kinase inhibitors. Our analysis by EGFR and ALK supported the association between concomitant PPI use with ICIs and reduced survival among both EGFR/ALK mutant and EGFR/ALK wild type patients.

In the stratified analysis by post-ICI treatment subtype, we did not find survival difference by PPI use among patients who received docetaxel or carboplatin plus gemcitabine. While the study was not designed specifically to measure the effectiveness of post-ICI treatment, this survival difference could either be reflective of post-ICI therapy or the type of patients who started therapy, which may have caused differential results among patients who received these therapies.

First, to the best of our knowledge, this is the largest population-based study investigating the association between the concomitant use of PPIs and ICIs and reduced survival. Second, we obtained death records from the national vital statistics of South Korea to define our outcome of interest; thus, our outcome was well-validated, and artificial follow-up loss was unlikely to occur. In contrast, follow-up loss or patient withdrawal are frequent sources of outcome misclassification bias in the single-center electronic health record, leading to the under-detection of outcomes. Furthermore, loss to follow-up may give rise to selection bias, given that patients with incomplete follow-up have a higher risk of fatal complications. Third, our results have high generalizability as they were obtained by assembling a completely enumerated lung cancer cohort in South Korea. Fourth, we observed...
consistent results when we applied a new-user design and propensity score-matching.

Our study had several limitations. First, our study did not measure other clinical endpoints, such as objective response rate and progression-free survival, due to a lack of detailed clinical information in the health insurance claims data. Second, while our study provided a large amount of clinical evidence on the prognostic association of PPI use with survival outcomes in patients treated with ICIs, confounding by indication was not fully addressed in our study due to the limitation of retrospective healthcare database. The indication of PPI use (eg, gastroesophageal reflux disease) may have affected our study findings. Confounding by indication may have remained even after the propensity-score matching to increase comparability between PPI users and nonusers. Furthermore, concomitant use of PPI with chemotherapy may result in different prognostic effects, considering the ability of PPI to neutralize the acidity of the tumor microenvironment. This hypothetical association was examined in a phase II RCT, where a significant clinical benefit of concomitant PPI use with chemotherapy was shown among metastatic breast cancer patients.7 Thus, had our study repeated the analysis among the chemotherapy users as a negative control, our study would have provided more robust evidence on the specific treatment effect of ICI. Third, residual confounding from unmeasured confounders (eg, histology and Eastern Cooperative Oncology Group [ECOG] performance status score) may have affected our study findings. However, the calculated E-value suggests that the hypothetical unmeasured confounder has to be strongly associated with both the exposure and outcome with risk ratio estimates greater than 2.17 to affect our study conclusion (Supplementary Method S2). A recent study using the US SEER-Medicare linked database included 1256 ICI users with NSCLC to identify prognostic factors for survival.36 The value of association for mortality and major unmeasured confounders was lower than the E-value (ECOG 2-4 vs ECOG 0-1: HR = 1.10; 95% CI = 0.88-1.38; squamous NSCLC vs nonsquamous NSCLC: HR = 1.24; 95% CI = 1.05-1.45).36 Hence, we believe that it is implausible that neither such a strong confounder exists beyond what was adjusted for in the analyses, nor is such a confounder unevenly distributed between PPI users and PPI nonusers. Finally, PD-1 ICIs were only reimbursed for second-line or later treatment by the NSCLC patients in South Korea during the study period. Over the past few years, ICIs with/without chemotherapy have expanded their indication as a first-line treatment for NSCLC with favorable RCT results. Given that patients treated with ICIs as a first-line treatment are likely to survive longer than our study population, future studies exploring the association between concomitant use of PPI with ICI and survival outcomes in first-line treatment settings are necessary.

In conclusion, concomitant use of PPIs with ICIs indicated a negative prognostic association with survival outcomes in advanced NSCLC patients. Furthermore, PPI use was associated with a high mortality risk in patients with viral hepatitis, which warrants further investigation. However, given the limitation of retrospective data, there remains a need for additional prospective studies to investigate the causality of this association.

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CONFLICT OF INTEREST
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AUTHOR CONTRIBUTIONS
Yeon-Hee Baek: Conceptualization, methodology, investigation, data curation, software, formal analysis, visualization, writing—original draft, and writing—review & editing. Eun Joo Kang: Writing—review & editing. Soojung Hong: Writing—review & editing. Sohee Park: Formal analysis, validation, writing—review & editing. Ju Hwan Kim: Writing—review & editing. Ju-Young Shin: Supervision, methodology, funding acquisition, and writing—review & editing. The work reported in the article has been performed by the authors, unless clearly specified in the text.

DATA AVAILABILITY STATEMENT
Our study used the National Health Insurance Service—National Health Insurance Database (NHIS NHID), established by the NHIS of South Korea (Data number: NHIS-2020-1-227). Datasets used in the analysis are available upon request to the corresponding author, who obtained approval for the provided database.

ETHICS STATEMENT
Our study was approved by the Institutional Review Board of Sungkyunkwan University (approval number: SKKU-IRB-2019-011-001). The requirement for written informed consent was not applicable as our study used anonymized subject data.

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SUPPORTING INFORMATION
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