BMC Cancer

RESEARCH

Open Access

The real-world safety profile of pemetrexed and platinum with or without pembrolizumab: insights from a comparative analysis of FAERS database

Shun Li[1,2†], Zhifei Huang[1,2†], Xiaoyu Zhong[1,2], Yan Zhou[1,2*] and Hao Jiang[1,2*]

Abstract

Background Lung cancer (LC) is a leading cause of cancer-related mortality worldwide. The combination of immune checkpoint inhibitors (ICIs) with chemotherapy significantly extends survival but increases the risk of treatment-related toxicity. To explore the impact of adding pembrolizumab to pemetrexed and platinum on treatment-related toxicity, this study utilized the FDA Adverse Event Reporting System (FAERS) to assess the safety of pemetrexed and platinum with or without pembrolizumab in LC patients.

Methods We collected data from FAERS database between the second quarter of 2017 and the third quarter of 2024. Disproportionality analysis was conducted using the Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-Item Gamma Poisson Shrinker (MGPS). Additionally, comparative analysis was performed using the ROR method.

Results Among LC patients receiving chemotherapy alone (pemetrexed + platinum) and combination therapy (pembrolizumab + pemetrexed + platinum), adverse event (AE) reports were 2871 and 5443 cases, respectively. Compared to chemotherapy alone, combination therapy was associated with a higher risk of renal and urinary disorders, hepatobiliary disorders, and interstitial lung disease (ILD), pneumonitis and other AEs. Subgroup analysis revealed that gender and age may be influential factors in the occurrence of AEs. Combination therapy prolonged the time to onset of AEs.

Conclusions In the real world, combination therapy increases the risk of certain AEs, particularly in specific patient subgroups. These findings emphasize the importance of personalized treatment strategies and AE monitoring, particularly during the first three months of therapy.

Keywords Immune checkpoint inhibitors, Pembrolizumab, Pemetrexed, Platinum, Cisplatin, Carboplatin, FAERS

†Shun Li and Zhifei Huang are contributed equally to the article.

*Correspondence:
Yan Zhou
30623491@qq.com

Hao Jiang
byyfyjh@bbmu.edu.cn

[1]Department of Radiation Oncology, The first affiliated hospital of Bengbu Medical University, Bengbu, Anhui 233000, China
[2]Joint Research Center for Regional Diseases of IHM, Bengbu Medical University, Bengbu, Anhui 233030, China

Introduction

Globally, lung cancer (LC) is one of the most common types of cancer, with approximately 2.5 million new cases in 2022, responsible for 1.8 million deaths [1]. In low- and middle-income countries where tobacco is endemic, LC incidence and mortality are on the rise [2]. While smoking rates in economically developed countries peaked decades ago and subsequently led to a decline in LC incidence, the incidence of LC in these countries continues to be high [2]. Between 2020 and 2050, LC are expected to cost the world $3.9 trillion (at 2017 international prices) [3]. LC is categorized into two main types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC constitutes approximately 85% of all LC cases and includes various subtypes such as lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC), with LUAD being the most prevalent subtype [4].

LC is extremely malignant, with the highest incidence and mortality rates among all types of cancer worldwide, posing a severe threat to human health [5]. Furthermore, the majority of patients are diagnosed at an advanced stage, having missed the opportunity for radical surgical resection and radiotherapy, thereby significantly reducing their survival rates [6]. In patients with advanced NSCLC, chemotherapy has provided limited survival benefits. Therefore, there is an urgent need for more effective treatment strategies. Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of malignant tumors worldwide, playing an important role in the therapy of various metastatic and locally advanced cancers [7]. At more than 5 years of follow-up, first-line pembrolizumab monotherapy was associated with significantly longer overall survival (OS) in patients with non-squamous non-small cell lung cancer (nsNSCLC) compared with pemetrexed combined with carboplatin chemotherapy [8]. In addition, the combination of pembrolizumab with pemetrexed and platinum showed advantages in both progression free survival (PFS) and OS compared to the regimen of pemetrexed and platinum, but pemetrexed and platinum plus pembrolizumab may increase treatment-related toxicities such as renal toxicity [9]. Randomized controlled trials (RCTs) are often conducted under strictly controlled conditions, limiting the generalizability of their results, whereas real-world studies are carried out in actual clinical settings, making their findings more readily applicable to a broader range of patient populations [10].

Recently, the FDA Adverse Event Reporting System (FAERS) has caught our attention, enabling us to conduct a real-world study. This database comprises post-marketing adverse event reports for drugs and biological products. FAERS is specifically designed to support the FDA's post-market safety monitoring of drugs and therapeutic biologics by collecting reports of adverse drug events that occur globally, and its data is publicly accessible.

In this study, we analyzed data from FAERS to compare adverse events (AEs) associated with two treatment regimens: pemetrexed and platinum with or without pembrolizumab. The purpose of this study was to provide clinicians with information on treatment-related toxicity when faced with the choice of these two treatment options.

Materials and methods

Data collection and processing

Medication records for pemetrexed and platinum plus pembrolizumab have primarily been reported since the second quarter of 2017 (Q2 2017). Consequently, this study collected AE data from FAERS spanning from Q2 2017 to the third quarter of 2024 (Q3 2024). The inclusion criteria for this study are as follows: (1) PP Group (pemetrexed and platinum): Each primaryid (a unique identifier for each case in FAERS) corresponding to a medication record must include pemetrexed and platinum (cisplatin or carboplatin), with at least one drug being the primary suspect drug (PS - the drug considered most likely to have caused the AE). Additionally, to minimize confounding factors, we excluded patients whose medication records included ICIs such as pembrolizumab, atezolizumab, and cemiplimab, and others. Because these drugs are often used in combination with chemotherapy for the treatment of LC and could potentially affect the reliability of the results. (2) PPP Group (pemetrexed and platinum plus pembrolizumab): Each primaryid corresponding to a medication record must include pembrolizumab, pemetrexed and platinum, with at least one of these drugs being the PS. In order to get more AE reports, all LC patients are included in the study. AEs are coded using preferred terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA). The system organ classes (SOCs - categories of medical terms based on organ systems.) is used to classify AEs into various systems. We follow the FDA's recommended methods to remove duplicate reports. The data used in this study can be freely accessed from the FAERS database on the FDA website (http://www.fda.gov).

Statistical analysis

Signal detection is based on a two-by-two contingency table (Supplementary Table 1) for disproportionality analysis. Four methods were used in this study for disproportionality analysis: Reporting Odds Ratio (ROR) [11], Proportional Reporting Ratio (PRR) [12], Multi-item Gamma Poisson Shrinker (MGPS) [13], and Bayesian Confidence Propagation Neural Network (BCPNN) [14]. These methods were used to calculate the ROR and its 95% Confidence Interval (CI), PRR and chi-square,

empirical Bayesian geometric mean (EBGM) along with the lower bound of its 95% CI (EBGM05), as well as the lower bound of the 95% CI for the information component (IC) for each AE. ROR and PRR indicate the ratio between the observed and expected reporting rates of AEs. Higher values indicate a stronger link. Bayesian methods like EBGM and BCPNN are used, with EBGM providing a more stable estimate and reducing false-positive signals, while BCPNN calculates the IC reflecting the drug-AE association strength [15]. To identify more potential drug adverse reactions, we chose the ROR method, which has higher sensitivity, for preliminary screening. Therefore, a potential drug adverse reaction should meet the criteria of the ROR method at least. The formulas for these disproportionality analyses and the criteria for positive signals are outlined in Supplementary Table 2. The onset time of an AE is defined as the period from the treatment start date (START_DT) to the AE occurrence date (EVENT_DT). The Kaplan-Meier method was used to draw the cumulative incidence curves of AEs, with the horizontal axis representing time and the vertical axis showing the cumulative incidence of AEs. The log-rank test is a non-parametric statistical method that can be used to compare whether there are significant differences between the cumulative incidence curves of AEs in two groups. If the p-value is less than the significance level (set at $p < 0.05$), it is considered that there are statistically significant differences between the cumulative incidence curves of each group. The FAERS database is large with many variables. R software can handle this data and has packages to help clean it. Also, R software is strong in statistical analysis and visualization. So, all analyses in this study were done using R software (version 4.3.2).

Results

Descriptive analysis

From Q2 2017 to Q3 2024, among LC patients receiving chemotherapy alone (pemetrexed + platinum) and combination therapy (pembrolizumab + pemetrexed + platinum) had 2,871 reports (8,434 AEs) and 5,443 reports (16,612 AEs), respectively. The number of AEs was higher in males than females across both treatment regimens. Despite incomplete weight records, most AEs occurred in patients weighing 50–100 kg. AEs were most frequent in patients aged 18–85 years. Notably, the combination therapy group had more AEs in elderly patients (≥ 65 years), while the chemotherapy alone group showed a slight predominance in younger patients (< 65 years). AE reports were primarily submitted by healthcare professionals. In the chemotherapy alone group, AE reports peaked in 2018, declined gradually, then rebounded from 2021. In contrast, the combination therapy group exhibited a steady upward trend in AE reports since 2017 (Fig. 1). AE reports were predominantly concentrated in seven countries: France, the United States, Italy, China, Japan, Germany, and Canada, with specific data detailed in Table 1.

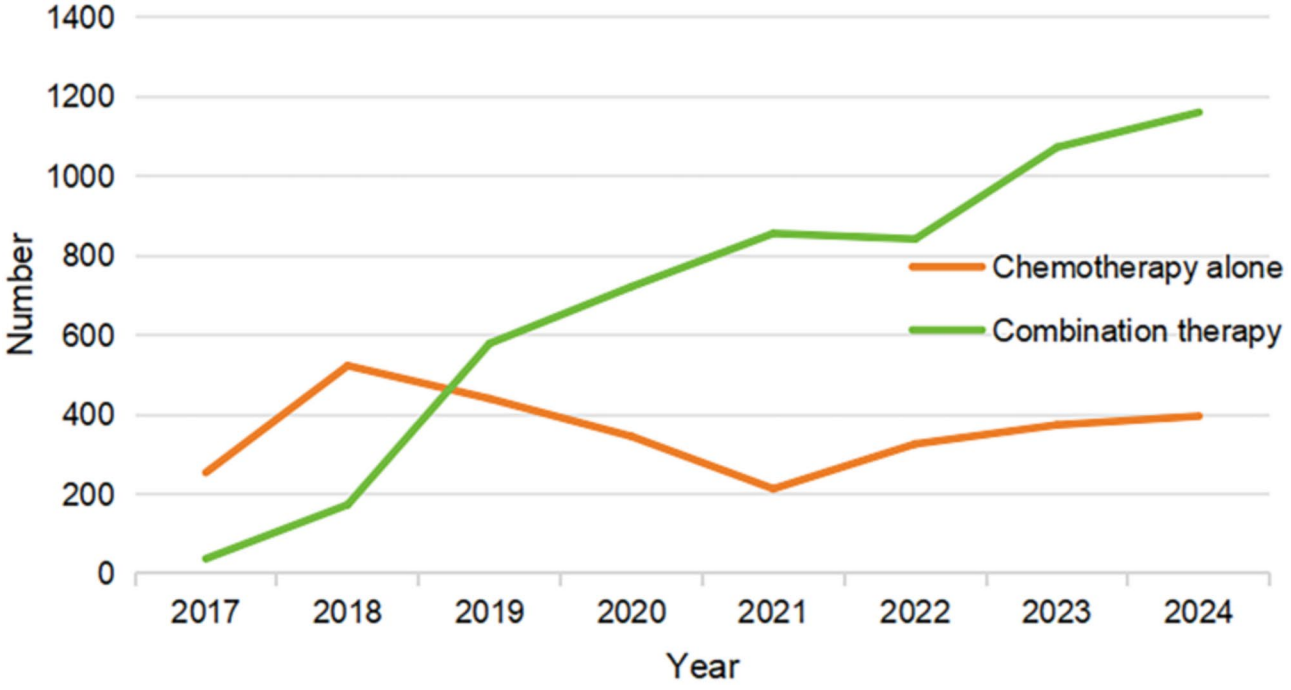

Fig. 1 Number of reports of chemotherapy alone (pemetrexed and platinum) and combination therapy (pemetrexed and platinum plus pembrolizumab) from the second quarter of 2017 to the third quarter of 2024

Table 1 Clinical characteristics of treatment-related adverse events (AEs)

Characteristics	Chemotherapy alone (*n*, %)	Combination therapy (*n*, %)
Gender		
Female	1088 (37.9)	2024 (37.2)
Male	1441 (50.2)	3206 (58.9)
Missing	342 (11.9)	213 (3.9)
Weight		
<50 kg	84 (2.9)	201 (3.7)
50~100 kg	759 (26.4)	1797 (33.0)
>100 kg	38 (1.3)	33 (0.6)
Missing	1990 (69.3)	3412 (62.7)
Age		
<18 years	3 (0.1)	43 (0.8)
18-64.9 years	1200 (41.8)	2103 (38.6)
65–85 years	1122 (39.1)	2404 (44.2)
>85 years	11 (0.4)	9 (0.2)
Missing	535 (18.6)	884 (16.2)
Type of reporter		
Consumer	481 (16.8)	1203 (22.1)
Health-professional	596 (20.8)	916 (16.8)
Physician	1076 (37.5)	2600 (47.8)
Other health-professional	453 (15.8)	155 (2.8)
Pharmacist	253 (8.8)	568 (10.4)
Missing	12 (0.4)	1 (0.0)
Reported countries		
France	708 (24.7)	1199 (22.0)
United States	405 (14.1)	701 (12.9)
Italy	321 (11.2)	321 (5.9)
China	255 (8.9)	77 (1.4)
Japan	227 (7.9)	972 (17.9)
Germany	102 (3.5)	612 (11.2)
Canada	85 (3.0)	144 (2.7)
Other countries	768 (26.7)	1417 (26.0)
Reported year		
2017	254 (8.9)	37 (0.7)
2018	523 (18.2)	173 (3.2)
2019	440 (15.3)	579 (10.6)
2020	345 (12.0)	722 (13.3)
2021	213 (7.4)	856 (15.7)
2022	326 (11.4)	842 (15.5)
2023	374 (13.0)	1073 (19.7)
2024	396 (13.8)	1161 (21.3)

Distribution of AEs at the system organ class (SOC) level

After the removal of 3 clearly irrelevant SOCs (such as product issues), AEs associated with these two treatment regimens spanned 24 out of the 27 SOCs (Supplementary Tables 3 and 4). The three most common SOCs related to chemotherapy alone and combination therapy were, in order: general disorders and administration site conditions, blood and lymphatic system disorders, and gastrointestinal disorders. Disproportionality analysis indicated that in both treatment regimens, blood and lymphatic system disorders, renal and urinary disorders, and hepatobiliary disorders all exhibited positive signals. ROR analysis demonstrated statistically significant differences in these three SOCs between chemotherapy alone and combination therapy (Fig. 2). These results suggest that, compared with chemotherapy alone, combination therapy increased the risk of renal and urinary disorders and hepatobiliary disorders. Conversely, compared with combination therapy, chemotherapy alone increased the risk of blood and lymphatic system disorders.

AE signals mining at the preferred term (PT) level

Tables 2 and 3 list the top 50 most common AEs associated with chemotherapy alone and combination therapy, respectively. AEs related to chemotherapy alone include: anaemia, thrombocytopenia, pancytopenia, neutropenia, acute kidney injury, nausea, febrile neutropenia, diarrhoea, and vomiting. AEs related to combination therapy include: pancytopenia, acute kidney injury, neutropenia, anaemia, diarrhoea, febrile neutropenia, nausea, interstitial lung disease, and pyrexia. It is evident that the common AEs associated with chemotherapy alone and combination therapy are very similar. To identify more potential adverse reactions, we used the highly sensitive ROR method to screen for AEs with positive signals, which are presented in Supplementary Tables 5 and 6, respectively. To directly compare AE risks between the regimens, we first screened for AEs with positive signals in both the combination therapy group and chemotherapy alone group. Subsequently, we quantified risk differences for these AEs using the ROR method. Compared with chemotherapy alone, combination therapy significantly increased the risk of the following AEs: interstitial lung disease, pneumonitis, tubulointerstitial

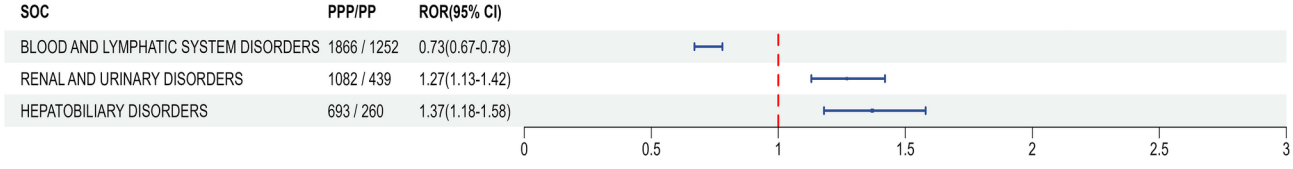

Fig. 2 Safety signals (ROR) of combination therapy (pembrolizumab + pemetrexed + platinum) and chemotherapy alone (pemetrexed + platinum) were compared at the SOC level. The confidence interval to the right of the null effect line (ROR = 1) indicates a higher risk of adverse events in the combination therapy group. Abbreviations: SOC, system organ class; PPP, pemetrexed and platinum with pembrolizumab; PP, pemetrexed and platinum; ROR, reporting odds ratio; CI, confidence interval

Table 2 The 50 most common adverse events for chemotherapy alone at the preferred term (PT) level

PT name	*N*	ROR(95%CI)	PRR(χ^2)	EBGM(EBGM05)	IC(IC025)
Anaemia*	211	2.74(2.38–3.15)	2.70(213.87)	2.60(2.31)	1.38(1.17)
Thrombocytopenia*	185	3.95(3.39–4.60)	3.88(365.73)	3.65(3.21)	1.87(1.64)
Pancytopenia*	182	6.86(5.86–8.03)	6.73(771.13)	5.96(5.22)	2.57(2.35)
Neutropenia*	167	3.22(2.75–3.77)	3.17(233.20)	3.03(2.65)	1.60(1.36)
Acute Kidney Injury*	163	3.69(3.14–4.34)	3.64(289.28)	3.43(3.00)	1.78(1.54)
Nausea	158	1.27(1.09–1.49)	1.27(8.87)	1.26(1.10)	0.33(0.10)
Febrile Neutropenia*	126	2.50(2.08–2.99)	2.47(105.37)	2.39(2.06)	1.26(1.00)
Diarrhoea	120	0.58(0.48–0.69)	0.58(36.53)	0.59(0.50)	-0.77(-1.03)
Vomiting	110	1.37(1.14–1.66)	1.37(10.76)	1.36(1.16)	0.44(0.16)
Death	109	0.33(0.27–0.39)	0.34(148.20)	0.34(0.29)	-1.55(-1.83)
Fatigue	105	0.84(0.69–1.02)	0.84(3.01)	0.85(0.72)	-0.24(-0.52)
Dyspnoea	95	0.91(0.74–1.12)	0.91(0.80)	0.91(0.77)	-0.13(-0.43)
Decreased Appetite	89	0.97(0.79–1.20)	0.97(0.08)	0.97(0.81)	-0.04(-0.35)
Leukopenia*	80	3.69(2.94–4.64)	3.67(143.39)	3.46(2.85)	1.79(1.46)
Asthenia	80	1.00(0.80–1.24)	1.00(0.00)	1.00(0.83)	-0.01(-0.33)
General Physical Health Deterioration	72	1.80(1.42–2.28)	1.80(24.51)	1.76(1.45)	0.82(0.47)
Sepsis	64	2.27(1.77–2.92)	2.26(42.99)	2.20(1.78)	1.14(0.77)
Bone Marrow Failure*	64	6.12(4.71–7.96)	6.08(238.41)	5.45(4.38)	2.45(2.07)
Respiratory Failure	60	1.93(1.49–2.50)	1.92(25.53)	1.88(1.52)	0.91(0.53)
Hepatocellular Injury*	59	10.54(7.92–14.02)	10.47(407.05)	8.62(6.79)	3.11(2.70)
Rash	58	0.39(0.30–0.51)	0.40(53.27)	0.40(0.32)	-1.31(-1.69)
Pneumonia	57	0.61(0.47–0.80)	0.62(13.63)	0.62(0.50)	-0.69(-1.07)
Pyrexia	55	0.59(0.45–0.77)	0.60(15.11)	0.60(0.48)	-0.74(-1.12)
Mucosal Inflammation*	50	3.43(2.57–4.58)	3.42(79.38)	3.24(2.54)	1.70(1.28)
Septic Shock*	48	3.48(2.59–4.68)	3.47(78.15)	3.28(2.57)	1.72(1.29)
Myelosuppression	46	1.33(0.99–1.78)	1.33(3.61)	1.32(1.03)	0.40(-0.03)
Interstitial Lung Disease	45	0.61(0.46–0.82)	0.61(10.79)	0.62(0.48)	-0.69(-1.12)
Haematotoxicity*	45	7.17(5.23–9.83)	7.14(203.87)	6.26(4.81)	2.65(2.19)
Nephropathy Toxic*	44	8.29(6.00-11.45)	8.25(235.52)	7.09(5.41)	2.83(2.36)
Pruritus	44	0.90(0.67–1.21)	0.9(0.48)	0.90(0.70)	-0.15(-0.58)
Platelet Count Decreased	43	1.15(0.85–1.56)	1.15(0.85)	1.15(0.89)	0.20(-0.24)
Dehydration	43	1.48(1.09–2.01)	1.48(6.44)	1.46(1.13)	0.55(0.10)
Blood Creatinine Increased	42	1.83(1.35–2.50)	1.83(15.20)	1.80(1.39)	0.84(0.39)
Renal Failure	41	1.95(1.43–2.67)	1.95(18.13)	1.91(1.47)	0.93(0.47)
Hypertransaminasaemia*	39	6.65(4.74–9.32)	6.62(161.51)	5.87(4.43)	2.55(2.07)
Hyponatraemia	35	1.63(1.16–2.29)	1.63(8.24)	1.61(1.21)	0.68(0.19)
Abdominal Pain	35	1.28(0.91–1.79)	1.28(2.04)	1.27(0.96)	0.34(-0.15)
Haemoglobin Decreased	34	2.23(1.58–3.15)	2.23(21.94)	2.17(1.62)	1.12(0.62)
Weight Decreased	34	0.79(0.56–1.11)	0.79(1.83)	0.80(0.60)	-0.33(-0.82)
Febrile Bone Marrow Aplasia*	34	12.37(8.44–18.12)	12.32(275.24)	9.81(7.13)	3.29(2.75)
Pulmonary Embolism	33	1.15(0.82–1.63)	1.15(0.67)	1.15(0.86)	0.20(-0.30)
Toxicity To Various Agents	33	2.37(1.67–3.37)	2.36(24.67)	2.29(1.71)	1.20(0.69)
Pleural Effusion	31	0.67(0.47–0.95)	0.67(5.11)	0.67(0.50)	-0.57(-1.09)
Constipation	31	0.57(0.40–0.81)	0.57(10.06)	0.57(0.43)	-0.80(-1.31)
Rash Maculo-Papular*	31	3.46(2.40-5.00)	3.45(50.12)	3.27(2.41)	1.71(1.18)
Headache	30	0.87(0.61–1.25)	0.87(0.58)	0.87(0.64)	-0.20(-0.72)
Renal Impairment	30	1.09(0.76–1.56)	1.09(0.21)	1.09(0.80)	0.12(-0.41)
Hypotension	27	1.16(0.79–1.69)	1.16(0.55)	1.15(0.84)	0.20(-0.35)
Hypertension	27	1.05(0.72–1.55)	1.05(0.08)	1.05(0.77)	0.08(-0.48)
Gamma-Glutamyltransferase Increased	27	2.83(1.91–4.17)	2.82(29.79)	2.71(1.95)	1.44(0.87)

Asterisks (*) indicate that the signal is statistically significant in all four formulas. Abbreviations: N, the number of reports; ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of the 95% CI of EBGM; IC, information component; IC025, the lower limit of the 95% CI of the IC; CI, confidence interval; PT, preferred term

Table 3 The 50 most common adverse events for combination therapy at the preferred term (PT) level

PT name	*N*	ROR(95%CI)	PRR((χ^2))	EBGM(EBGM05)	IC(IC025)
Pancytopenia*	355	7.80(6.90–8.81)	7.65(1517.80)	5.90(5.33)	2.56(2.39)
Acute Kidney Injury*	294	3.54(3.13–4.01)	3.49(452.52)	3.14(2.83)	1.65(1.47)
Neutropenia*	281	2.82(2.49–3.20)	2.79(287.60)	2.58(2.33)	1.37(1.19)
Anaemia	273	1.78(1.57–2.01)	1.76(84.15)	1.71(1.54)	0.77(0.59)
Diarrhoea	272	0.66(0.58–0.75)	0.67(45.42)	0.68(0.61)	-0.57(-0.74)
Febrile Neutropenia	213	2.18(1.89–2.51)	2.16(121.55)	2.06(1.83)	1.04(0.83)
Nausea	204	0.82(0.71–0.94)	0.82(7.88)	0.83(0.73)	-0.27(-0.48)
Interstitial Lung Disease	204	1.46(1.27–1.69)	1.46(27.61)	1.43(1.27)	0.51(0.30)
Death	197	0.29(0.26–0.34)	0.30(324.54)	0.31(0.28)	-1.68(-1.89)
Pyrexia	189	1.05(0.91–1.22)	1.05(0.44)	1.05(0.93)	0.07(-0.15)
Thrombocytopenia	188	1.97(1.70–2.29)	1.96(81.73)	1.88(1.66)	0.91(0.69)
Pneumonitis	181	1.41(1.21–1.64)	1.41(20.09)	1.38(1.22)	0.47(0.24)
Vomiting	173	1.09(0.93–1.27)	1.09(1.21)	1.08(0.95)	0.12(-0.11)
Fatigue	170	0.68(0.59–0.80)	0.69(23.92)	0.70(0.61)	-0.52(-0.75)
Tubulointerstitial Nephritis*	159	7.84(6.53–9.40)	7.77(689.24)	5.97(5.12)	2.58(2.32)
General Physical Health Deterioration	157	2.05(1.74–2.42)	2.04(76.81)	1.95(1.70)	0.97(0.73)
Pneumonia	156	0.86(0.73–1.01)	0.86(3.59)	0.86(0.75)	-0.21(-0.45)
Rash	154	0.53(0.45–0.62)	0.53(62.77)	0.54(0.48)	-0.88(-1.11)
Asthenia	153	0.97(0.82–1.14)	0.97(0.18)	0.97(0.84)	-0.05(-0.29)
Drug Ineffective	139	0.92(0.78–1.09)	0.92(0.85)	0.93(0.80)	-0.11(-0.36)
Dyspnoea	124	0.59(0.49–0.71)	0.59(33.80)	0.61(0.52)	-0.72(-0.99)
Renal Impairment	116	2.26(1.86–2.74)	2.25(73.06)	2.13(1.81)	1.09(0.81)
Decreased Appetite	111	0.60(0.50–0.73)	0.60(28.29)	0.62(0.53)	-0.70(-0.98)
Colitis	110	2.25(1.85–2.74)	2.24(68.92)	2.13(1.80)	1.09(0.80)
Hepatitis*	105	3.81(3.10–4.70)	3.80(184.05)	3.38(2.84)	1.75(1.45)
Sepsis	100	1.81(1.48–2.22)	1.81(33.40)	1.74(1.47)	0.80(0.50)
Renal Failure	98	2.47(2.01–3.05)	2.46(76.71)	2.31(1.94)	1.21(0.90)
Hypothyroidism	95	1.79(1.45–2.21)	1.79(30.39)	1.72(1.45)	0.79(0.48)
Renal Tubular Necrosis*	90	13.54(10.4-17.63)	13.47(638.14)	8.65(6.94)	3.11(2.76)
Platelet Count Decreased	87	1.19(0.96–1.48)	1.19(2.51)	1.18(0.98)	0.24(-0.08)
Mucosal Inflammation*	84	3.02(2.40–3.80)	3.01(99.13)	2.76(2.28)	1.47(1.13)
Pulmonary Embolism	79	1.43(1.14–1.79)	1.42(9.41)	1.40(1.16)	0.48(0.15)
Pleural Effusion	76	0.83(0.66–1.04)	0.83(2.56)	0.84(0.69)	-0.26(-0.59)
Toxic Epidermal Necrolysis*	72	6.61(5.07–8.61)	6.59(261.08)	5.27(4.22)	2.40(2.02)
Blood Creatinine Increased	71	1.58(1.24–2.02)	1.58(14.17)	1.54(1.26)	0.62(0.27)
Myocarditis*	69	3.06(2.38–3.94)	3.05(83.42)	2.80(2.26)	1.48(1.12)
Immune-Mediated Enterocolitis*	69	3.36(2.60–4.33)	3.35(98.44)	3.03(2.45)	1.60(1.23)
Septic Shock	66	2.45(1.89–3.16)	2.44(50.43)	2.29(1.85)	1.20(0.83)
Immune-Mediated Lung Disease*	66	3.61(2.78–4.68)	3.59(105.97)	3.22(2.59)	1.69(1.31)
Toxicity To Various Agents	64	2.40(1.86–3.11)	2.40(47.04)	2.26(1.82)	1.18(0.80)
Malaise	64	0.70(0.55–0.90)	0.71(7.66)	0.71(0.58)	-0.48(-0.85)
Nephritis*	63	8.10(6.06–10.83)	8.07(283.73)	6.14(4.81)	2.62(2.21)
Leukopenia	62	1.39(1.07–1.79)	1.38(6.22)	1.36(1.10)	0.44(0.070)
Hepatic Function Abnormal	61	0.91(0.70–1.17)	0.91(0.55)	0.91(0.74)	-0.13(-0.51)
Constipation	60	0.55(0.43–0.71)	0.55(21.22)	0.56(0.46)	-0.82(-1.20)
Haemophagocytic Lymphohistiocytosis*	60	8.76(6.49–11.84)	8.74(292.08)	6.49(5.05)	2.70(2.28)
Pruritus	58	0.59(0.46–0.77)	0.59(15.90)	0.60(0.49)	-0.73(-1.11)
Immune-Mediated Hepatic Disorder*	58	4.32(3.26–5.73)	4.31(122.87)	3.76(2.97)	1.91(1.50)
Respiratory Failure	57	0.90(0.69–1.18)	0.90(0.55)	0.91(0.73)	-0.14(-0.53)
Cough	56	0.55(0.42–0.72)	0.55(19.60)	0.57(0.45)	-0.82(-1.21)

Asterisks (*) indicate that the signal is statistically significant in all four formulas. Abbreviations: N, the number of reports; ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of the 95% CI of EBGM; IC, information component; IC025, the lower limit of the 95% CI of the IC; CI, confidence interval; PT, preferred term

nephritis, renal impairment, colitis, hepatitis, hypothyroidism, renal tubular necrosis, toxic epidermal necrolysis, drug eruption, lichenoid keratosis, C-reactive protein increased, rheumatoid arthritis, Stevens-Johnson syndrome, and others (Fig. 3).

Subgroup analysis

To explore whether gender and age affect the occurrence of AEs, we used the ROR method for subgroup analysis at the SOC and PT levels. At the SOC level, men receiving chemotherapy alone are prone to blood and lymphatic system disorders and metabolism and nutrition disorders, while women are more affected by hepatobiliary disorders and eye disorders (Supplementary Fig. 1).

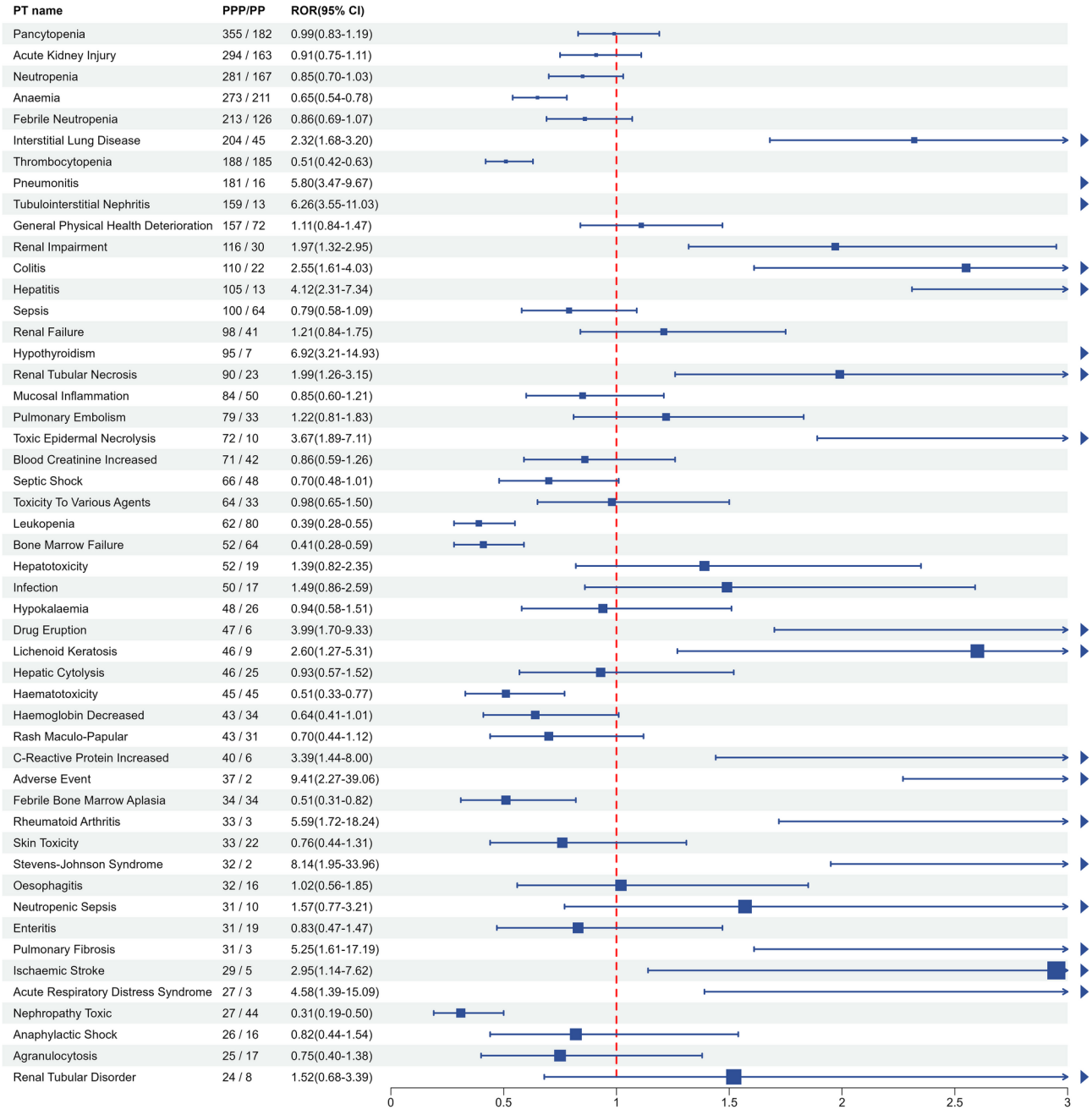

Fig. 3 Safety signals (ROR) of combination therapy (pembrolizumab + pemetrexed + platinum) and chemotherapy alone (pemetrexed + platinum) were compared at the PT level. The confidence interval to the right of the null effect line (ROR = 1) indicates a higher risk of adverse events in the combination therapy group. Abbreviations: PT, preferred term; PPP, pemetrexed and platinum with pembrolizumab; PP, pemetrexed and platinum; ROR, reporting odds ratio; CI, confidence interval

Blood and lymphatic system disorders, skin and subcutaneous tissue disorders, investigations, infections and infestations, cardiac disorders, and endocrine disorders are common in elderly patients. In contrast, general disorders and administration site conditions, respiratory, thoracic and mediastinal disorders, hepatobiliary disorders, ear and labyrinth disorders, and eye disorders occur more in younger patients (Supplementary Fig. 2).

Men receiving combination therapy are susceptible to blood and lymphatic system disorders, respiratory, thoracic and mediastinal disorders, infections and infestations, vascular disorders, and surgical and medical procedures. Renal and urinary system disorders, skin and subcutaneous tissue disorders, nervous system disorders, endocrine disorders, and eye disorders are more common in women (Supplementary Fig. 3). Blood and lymphatic system disorders, investigations, metabolic and nutritional disorders, and eye disorders often occur in elderly patients. In contrast, general disorders and administration site conditions, renal and urinary system disorders, nervous system disorders, surgical and medical procedures, and ear and labyrinth disorders are more common in younger patients (Supplementary Fig. 4).

To further explore the impact of gender and age on AEs, we screened 50 common ones at the PT level. In chemotherapy alone, AEs such as nausea, vomiting, hepatocellular injury, and renal tubular necrosis were more common in females; while males were more prone to pancytopenia, acute kidney injury, febrile neutropenia, general physical health deterioration, septic shock, febrile bone marrow aplasia, hyponatraemia, skin toxicity, ototoxicity, hypercreatininaemia, acute generalised exanthematous pustulosis, and rash vesicular. AEs such as anaemia, febrile neutropenia, acute kidney injury, general physical health deterioration, sepsis, septic shock, and platelet count decreased were more common in the elderly. Specific data are presented in Figs. 4 and 5. Supplementary Tables 7 and 8 show that gender and age have no significant impact on certain less common AEs with positive signals. This may be due to the reduced statistical power from the small subgroup sample size.

For patients undergoing combination therapy, AEs such as acute kidney injury, tubulointerstitial nephritis, hepatitis, and renal tubular necrosis were more likely to occur in female patients; while males needed to pay more attention to neutropenia, interstitial lung disease, renal impairment, sepsis, septic shock, haemophagocytic lymphohistiocytosis, immune-mediated hepatic disorder, haemoglobin decreased, myositis, pulmonary toxicity, immune-mediated hepatitis, enteritis, neutropenic sepsis, acute respiratory distress syndrome, pulmonary fibrosis, autoimmune hepatitis, and cytopenia. Moreover, compared to younger patients, the elderly were more likely to experience AEs including pancytopenia, neutropenia, interstitial lung disease, hypothyroidism, septic shock, drug eruption, bone marrow failure, immune-mediated hepatic disorder, hepatic cytolysis, myositis, and respiratory distress. More detailed information can be found in Figs. 6 and 7. Some less common AEs may be more common in the elderly, such as hypersensitivity pneumonitis, psoriasis, pneumocystis jirovecii pneumonia, and duodenitis. Gender may influence the occurrence of some less common AEs, such as eyelid ptosis, encephalopathy, and haematocrit decreased(Supplementary Tables 9 and 10).

Sensitivity analysis

To explore the impact of confounding factors on our findings, we conducted a sensitivity analysis. First, we identified 10 common concomitant medications through the FAERS database: acetaminophen, pantoprazole, atorvastatin, amlodipine, aspirin, bisoprolol, metformin, omeprazole, apixaban, and albuterol. Then, we excluded reports with these medications. Ultimately, we analyzed 2,451 chemotherapy alone reports (including 6,864 AEs) and 4,344 combination therapy reports (involving 13,261 AEs). Among the top 50 common AEs with positive signals in combination therapy group, only leukopenia, infection, and drug rash lost their positive signals. In chemotherapy alone group, general physical health deterioration, dehydration, hyponatremia, cerebrovascular accident, hypersensitivity, dyspnoea exertional, and urticaria no longer showed positive signals. In short, the vast majority of AEs retained positive signals. See Supplementary Tables 11 and 12 for details.

Time to AE onset

The median time to AE onset for chemotherapy alone was 17 (7–41) days. Compared with chemotherapy alone, combination therapy extended the median time to AE onset to 25 (8–81) days. We further identified three common SOCs and compared the cumulative incidence for the same SOC between the two treatment regimens. These three SOCs were blood and lymphatic system disorders, respiratory, thoracic and mediastinal disorders, and renal and urinary disorders. For the three SOCs, the median time to AE onset was longer with combination therapy (Table 4). Additionally, there was a statistically significant difference in the cumulative incidence of AEs between patients receiving these two treatment regimens (Fig. 8).

Discussion

Over the past decade, immunotherapy has revolutionized the treatment of solid tumors and hematological malignancies, significantly prolonging patient survival, with some patients achieving long-term remission [16]. Numerous studies have shown that, compared to chemotherapy alone, the combination of pemetrexed and

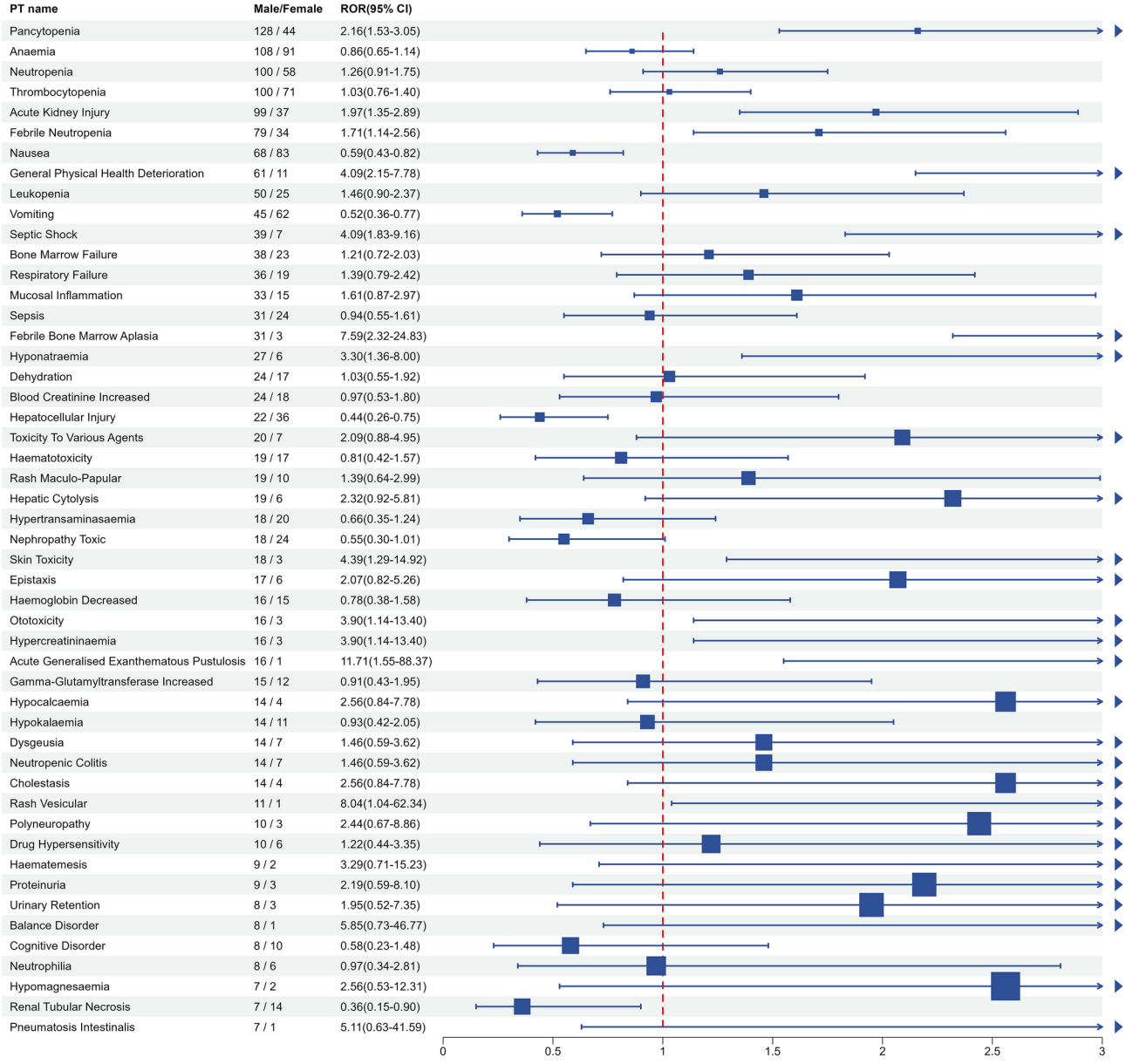

Fig. 4 At the preferred term (PT) level, the impact of gender on the occurrence of adverse events (AEs) in patients receiving chemotherapy alone (pemetrexed and platinum). The confidence interval to the right of the null effect line (ROR = 1) indicates a higher risk of adverse events in male patients, while one to the left indicates a higher risk for female patients. Abbreviations: PT, preferred term; ROR, reporting odds ratio; CI, confidence interval

platinum with pembrolizumab can significantly extend patient survival, and the incidence of AEs is within an acceptable range [17, 18, 19]. This study utilized real-world pharmacovigilance data from the FAERS database to comprehensively assess AEs associated with these two treatment regimens. Our findings indicate that AEs such as anemia, pancytopenia, thrombocytopenia, nausea, and neutropenia are commonly observed in both chemotherapy alone and combination therapy. The profiles of these common AEs between the two treatment regimens are similar. These AEs are consistent with the results of multiple studies [18, 19, 20, 21, 22]. Furthermore, we compared AEs related to these two treatment regimens and found that combination therapy may increase the risk of certain AEs, such as renal and urinary system disorders and hepatobiliary disorders. To explore the impact of gender and age on treatment-related AEs, we conducted subgroup analyses. The results of these analyses suggest that elderly patients may have a higher incidence of AEs, particularly in blood and lymphatic system disorders and renal and urinary system disorders. Lastly, we compared the time to onset of AEs associated with these two treatment regimens and found that combination therapy may delay the time to onset of AEs.

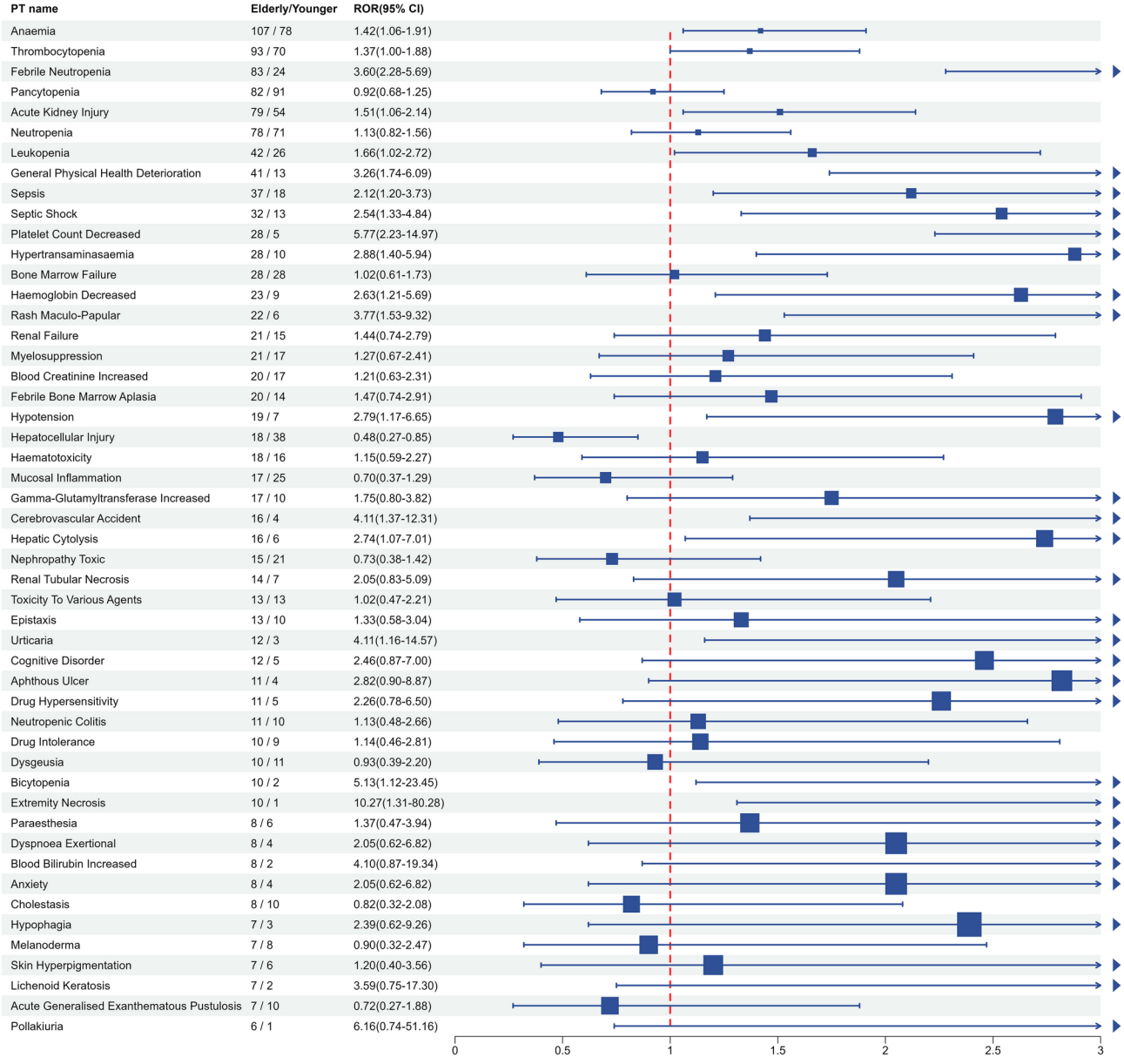

Fig. 5 At the preferred term (PT) level, the impact of age on the occurrence of adverse events (AEs) in patients receiving chemotherapy alone (pemetrexed and platinum). In this forest plot, a confidence interval for an adverse event to the right of the null effect line (ROR = 1) indicates a higher risk for elderly patients (≥ 65 years old), while one to the left indicates a higher risk for younger patients (< 65 years old). Abbreviations: PT, preferred term; ROR, reporting odds ratio; CI, confidence interval

Our study indicates that combination therapy is associated with an increased incidence of renal and urinary system disorders, compared to chemotherapy alone. Nephrotoxicity is a challenging and often underestimated safety issue that not only reduces patients' quality of life but also poses a potential negative impact on treatment outcomes [23]. Consistent with our results, combination therapy may increase nephrotoxicity [24]. Results from the phase 3 KEYNOTE-189 study suggest that combination therapy may increase the risk of nephritis and acute kidney injury (AKI) compared to chemotherapy alone [19]. Our study results suggest that combination therapy elevates the risk of AEs such as tubulointerstitial nephritis, renal impairment, and renal tubular necrosis, but it does not appear to increase the incidence of AKI. Notably, renal disorders such as tubulointerstitial nephritis, renal impairment, and renal tubular necrosis are all associated with AKI. In our analysis, the total number of reports for these renal disorders surpassed that for AKI. Some patients may experience both AKI and other renal disorders simultaneously, but their AKI may not have been reported, potentially underestimating

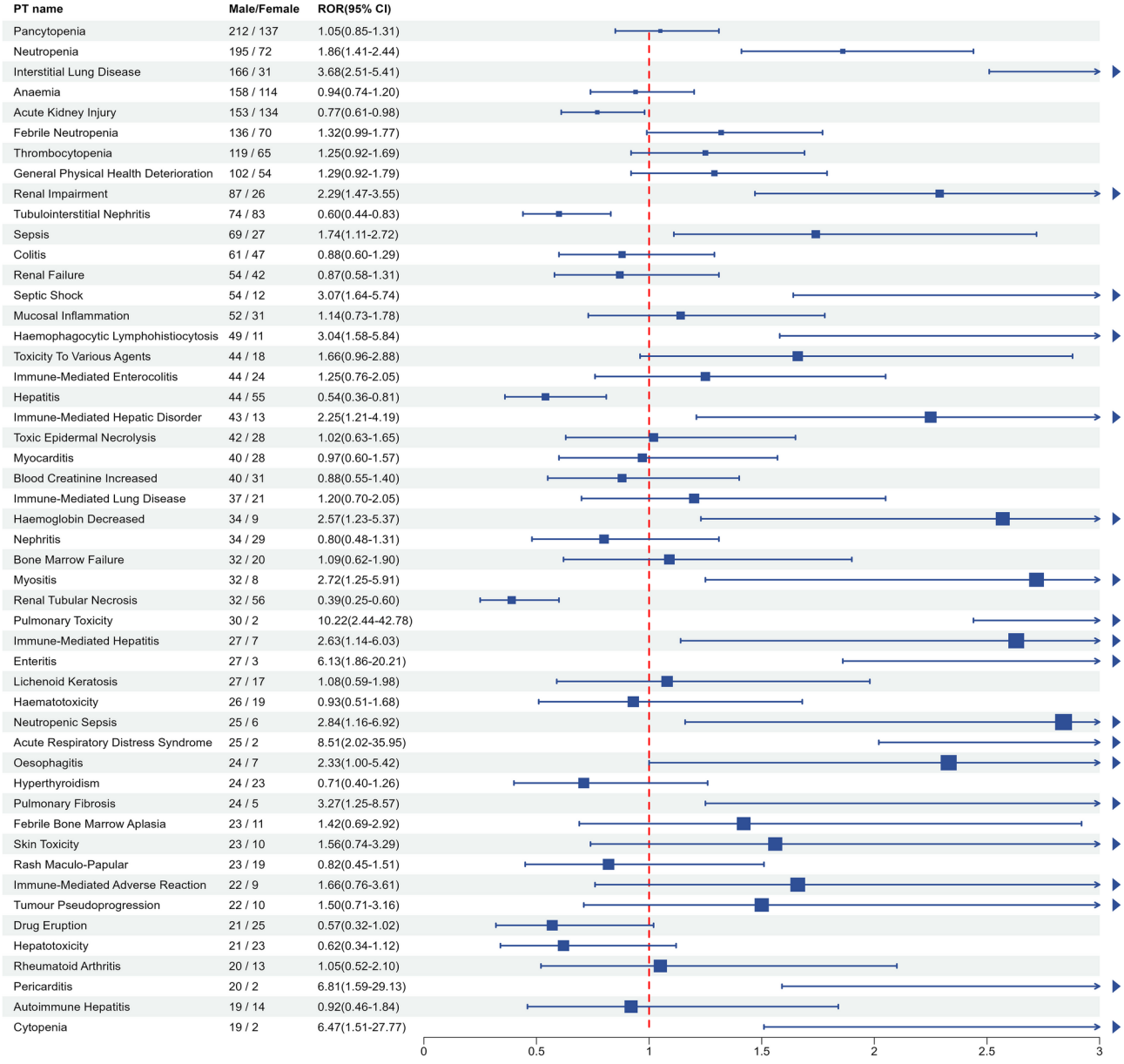

Fig. 6 At the preferred term (PT) level, the impact of gender on the occurrence of adverse events (AEs) in patients receiving combination therapy (pembrolizumab + pemetrexed + platinum). The confidence interval to the right of the null effect line (ROR = 1) indicates a higher risk of adverse events in male patients, while one to the left indicates a higher risk for female patients. Abbreviations: PT, preferred term; ROR, reporting odds ratio; CI, confidence interval

the risk of AKI in this study. Currently, there is a lack of specific research exploring the mechanisms by which combination therapy increases nephrotoxicity. Nephrotoxicity caused by ICIs is primarily associated with tubulointerstitial nephritis, which accounts for nearly 90% of immune-related acute injury [25, 26]. Tubulointerstitial nephritis may be caused by the loss of peripheral tolerance of self-reactive T cells to endogenous renal antigens [26]. ICIs, by blocking the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway, release the inhibition of cytotoxic T cells by tumor cells but may also trigger autoimmune reactions. The expression of PD-L1 in renal cells, particularly upregulated by IFN-g, may expose patients treated with ICIs to the risk of T cell-mediated kidney damage [27]. Furthermore, ICIs may activate drug-specific T cells, leading to aberrant immune responses and resulting in kidney inflammation and injury [28]. The combined action of these mechanisms may lead to the development of tubulointerstitial nephritis in patients treated with ICIs. Our study results indicate that among renal disorders with positive signals, the number of reports for tubulointerstitial

Fig. 7 At the preferred term (PT) level, the impact of age on the occurrence of adverse events (AEs) in patients receiving combination therapy (pembrolizumab + pemetrexed + platinum). In this forest plot, a confidence interval for an adverse event to the right of the null effect line (ROR = 1) indicates a higher risk for elderly patients (≥ 65 years old), while one to the left indicates a higher risk for younger patients (< 65 years old). Abbreviations: PT, preferred term; ROR, reporting odds ratio; CI, confidence interval

Table 4 Time to onset of adverse events

SOC	Chemotherapy alone Median time (IQR, days)	Combination therapy Median time (IQR, days)	Log-rank *p*-value
Blood and lymphatic system disorders	14 (8–32.5)	19 (7–50)	0.014
Respiratory, thoracic, and mediastinal disorders	31 (12–76)	40.5 (12–116)	0.013
Renal and urinary disorders	15 (8–42.5)	56 (13–92)	<0.0001
All adverse events	17 (7–41)	25 (8–81)	<0.0001

Abbreviation: SOC, system organ class; IQR, inter-quartile range

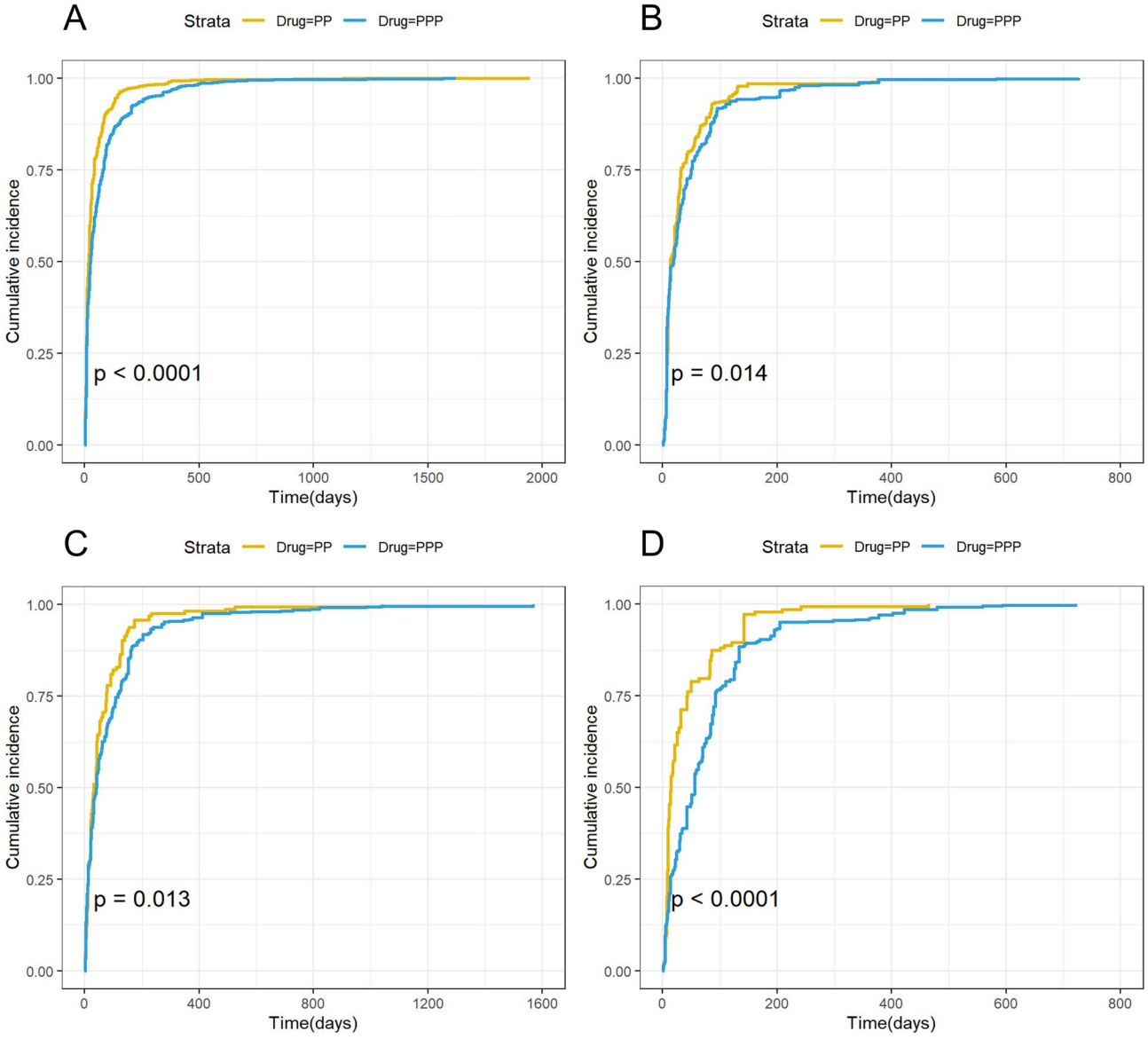

Fig. 8 Comparison of the cumulative incidence of adverse events related to combination therapy (pembrolizumab + pemetrexed + platinum) and chemotherapy alone (pemetrexed + platinum). (**A**) All adverse events (AEs). (**B**) blood and lymphatic system disorders. (**C**) respiratory, thoracic and mediastinal disorders. (**D**) renal and urinary disorders. Abbreviations: PPP, pemetrexed and platinum with pembrolizumab; PP, pemetrexed and platinum

nephritis ranks second. Another possible reason for increased nephrotoxicity is the interaction between pembrolizumab and pemetrexed or platinum, which may elevate the risk of certain renal disorders. Studies have shown that the use of cisplatin or carboplatin in patients receiving ICIs is a risk factor for kidney injury [29]. However, the combination of pembrolizumab with pemetrexed did not significantly increase the incidence of kidney injury [30]. Nephrotoxicity induced by chemotherapy is primarily associated with acute tubular injury or necrosis [27]. Our findings suggest that combination therapy may increase the risk of renal tubular necrosis.

Drug-induced interstitial lung disease (DIILD) is associated with a variety of anticancer drugs. Due to differences in patient cohorts, the incidence of DIILD ranges from less than 1–60% [31]. ILD induced by anticancer drugs is characterized by a low incidence rate but a high mortality rate [32]. Compared to PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, PD-1 inhibitors (including pembrolizumab) pose a higher risk of ILD, and the concurrent use of two or more pulmonary toxic drugs may increase the risk of DIILD [33]. Studies have shown that the risk of ILD induced by combined anti-PD-1/PD-L1 and anti-CTLA-4 therapies is higher than that of monotherapy [34]. In the combination

therapy group, ILD is one of the most common pulmonary AEs. Compared with chemotherapy alone, the combination therapy increases the risk of ILD. However, a meta-analysis found no statistically significant difference in the incidence of ILD induced by chemotherapy combined with ICIs compared to chemotherapy alone [35]. The incidence of DIILD in real-world studies is inconsistent with that in clinical trials, partly because real-world studies include more patients with poor physical status and older age, both of which increase the risk of DIILD [36]. This explanation is hypothetical and requires further confirmation. The pathogenic mechanisms of anticancer drug-induced ILD have not been clearly studied. One possible hypothesis is that drugs (most chemotherapy drugs) directly cause lung injury by damaging lung epithelial cells and alveolar capillary endothelial cells, leading to the release of cytokines, inflammatory responses, and apoptosis [37]. Another possible mechanism is that drugs directly modify pulmonary tissue proteins as haptens or deposit antibody-antigen immune complexes, thereby triggering immune responses, recruiting and activating inflammatory cells, releasing cytokines, and leading to inflammatory reactions and tissue damage in the alveoli and interstitium [37, 38]. Both mechanisms of lung injury may lead to DIILD. Compared to previous clinical trials, the combination therapy in real-world settings shows a higher incidence of pneumonitis and is associated with poor survival [39]. A meta-analysis including 22 clinical trials found that chemoimmunotherapy significantly increased the incidence of treatment-related pneumonitis ($p = 0.01$) with low heterogeneity [35]. Similarly, our study shows that the combination therapy increases the risk of treatment-related pneumonitis.

RCTs improve detection of treatment-related AEs in new therapies by using three key methods: randomization to reduce confounding factors, strict control of variables, and blinding to minimize bias in patient-provider interactions [40]. Gender medicine encourages the inclusion of sufficient samples of both males and females in clinical trials and research to ensure that results are applicable to all genders. Regrettably, previous RCTs on treatment safety have overlooked the significance of gender and age in the incidence of AEs. To fill this gap, this study screened AEs with positive signals to explore the influence of gender and age on these AEs. Our study results indicate that female patients undergoing chemotherapy alone seem to be more susceptible to AEs such as nausea, vomiting, hepatocellular injury, and renal tubular necrosis. De Francia and colleagues have considered that biological gender differences may influence the pharmacokinetics and pharmacodynamics, thereby affecting efficacy and safety. Their research indicates that among patients treated with DNA binding drugs, including platinum-based drugs, women are at a higher risk of experiencing nausea and vomiting compared to men [41]. In patients receiving combination therapy, women are more likely to experience AEs such as acute kidney injury, tubulointerstitial nephritis, hepatitis, and renal tubular necrosis. Tubulointerstitial nephritis and renal tubular necrosis are primarily caused by immunotherapy and chemotherapy, respectively [27]. Renal tubular necrosis is more prevalent in women regardless of chemotherapy alone or combination therapy, suggesting that female patients may be more susceptible to nephrotoxicity. Cisplatin-induced nephrotoxicity, which mainly damages renal tubular cells, is more severe in women, possibly due to higher glutathione S-transferase activity and estrogen influence, leading to prolonging drug retention and increasing toxicity in the kidneys [42]. In contrast, pemetrexed-induced nephrotoxicity is mainly related to cumulative dosage [43]. Qu et al. pointed out that immunotherapy-related nephrotoxicity predominantly occurs in males [44]. However, in our study, women who received combination therapy may become a high-risk group for nephrotoxicity. Among the 50 most common AEs, 17 were more likely to occur in males. It appears that males receiving combination therapy experienced a higher number of AEs that could be life-threatening, and a similar situation seems to exist among patients undergoing chemotherapy alone. For instance, compared to females, males receiving combination therapy are more prone to AEs such as sepsis, septic shock, and neutropenic sepsis. Additionally, males undergoing chemotherapy alone are more likely to experience febrile neutropenia, septic shock, and febrile bone marrow aplasia. Febrile neutropenia is a serious medical condition that can lead to severe infections affecting treatment outcomes and prognosis [45]. If not treated promptly, febrile neutropenia may progress to sepsis, causing shock, multi-organ failure, and even death [46]. Therefore, febrile neutropenia is a clinical condition that requires close monitoring and management, especially in immunocompromised patients.

In the chemotherapy alone group, the number of AEs was slightly higher in younger patients than in older patients. This may be due to the higher number of AEs clearly unrelated to treatment reported in younger patients. These AEs included malignant neoplasm progression, neoplasm progression, and lung adenocarcinoma, among others. To ensure the accuracy of the results as much as possible, these AEs were not included in the subsequent analysis. Subsequent subgroup analysis indicates that elderly patients aged 65 and above who receive chemotherapy alone or combination therapy seem to bear a higher burden of AEs compared to younger patients under 65. There may be four main reasons behind this finding: Age-related decline in hepatic

and renal function affects the clearance of many medications, thereby increasing the risk of AEs [47]. The physiological reserves of the organs and systems in the elderly decline, making them more likely to develop functional disorders when facing physiological stress such as cancer treatment [48]. The elderly often suffer from multiple chronic diseases and these comorbidities can increase the complexity and risks of treatment. Meanwhile, the use of multiple medications can increase the risk of drug interactions, further increasing the likelihood of AEs [49]. Immunosenescence may affect the interaction between the immune system and ICIs, which in turn may influence the efficacy and toxicity in elderly patients [50]. Studies have shown that elderly patients treated with pembrolizumab have a higher reporting rate of immune-related AEs, which involve multiple organ systems such as the cardiovascular, pulmonary, renal, and skin systems, as well as musculoskeletal and nervous tissues [51]. Moreover, the incidence of severe AEs and treatment discontinuation rates due to AEs increase with age in elderly patients [52]. Given the higher incidence of AEs in the elderly, it is essential to enhance monitoring, conduct thorough risk assessment, and implement personalized treatment strategies to optimize their treatment outcomes and quality of life.

Some rare AEs should also be noted. Hypersensitivity pneumonitis is an immune - mediated inflammatory lung disease, typically triggered by antigen inhalation in susceptible individuals [53]. Subgroup analysis suggests elderly patients may face higher risks, with case reports linking pembrolizumab to subclinical hypersensitivity pneumonitis exacerbation [54]. Thus, comprehensive pre-treatment assessments, especially for subclinical diseases, are recommended for high-risk groups. Pneumocystis jirovecii pneumonia is a rare fungal opportunistic infection in solid malignancy patients [55]. Xia S et al.'s study indicates that ICIs may be linked to pneumocystis jirovecii pneumonia, especially in elderly men [56], which is consistent with our research findings. Notably, ICIs might increase the mortality risk after pneumocystis jirovecii pneumonia infection [57]. Therefore, vigilance and early intervention, even prophylactic treatment, should be considered for these immunocompromised patients. However, results on rare AEs should be interpreted cautiously due to potential reduced statistical power from small sample sizes.

Sensitivity analysis shows that in patients receiving chemotherapy alone, most AEs retain positive signals. Among the top 10 AEs with positive signals, only general physical health deterioration lost its positive signal. This might be because excluding 10 common concomitant medications also excluded some patients with comorbidities like diabetes, peptic ulcer, and cardiovascular disease, which may be linked to general physical health deterioration. Notably, diabetes and cardiovascular disease may be related to poor prognosis in LC patients [58, 59]. In combination therapy group, top 10 AEs with positive signals persisted. These AEs included pancytopenia, AKI, neutropenia, anemia, febrile neutropenia, ILD, and thrombocytopenia, among others. Some could be life - threatening, such as febrile neutropenia, sepsis, and septic shock. Early detection and intervention can effectively reduce their negative impact on prognosis.

This study compared time to AEs onset and cumulative incidence of AEs between two treatment regimens. The results indicate that combination therapy prolonged time to AEs onset, and there was a significant difference in the cumulative incidence of AEs between patients receiving these two treatment regimens. Specifically, the majority of treatment-related AEs in patients undergoing chemotherapy alone occurred within the first six weeks, whereas for those receiving combination therapy, the majority occurred within the first three months. For patients undergoing combination therapy, particularly during the initial three months, enhanced monitoring of AEs is warranted to facilitate timely identification and intervention. Specifically, during the first month of treatment, emphasis should be placed on symptoms associated with hematologic AEs, such as bleeding, mucosal pallor, and fever. In the second month, priority shifts to symptoms correlated with respiratory AEs, such as chest tightness, cough, and sputum production. In the third month, vigilance should focus on symptoms related to renal and urinary AEs, such as frothy urine, hematuria, and abnormal urine output. Additionally, we propose developing an intelligent reminder application based on the timeline of AE occurrence. This tool could automatically deliver self-assessment questionnaires for specific AEs at key time points.

While the study may yield valuable conclusions, we must acknowledge some limitations. Firstly, the lack of both a control group and adjustments for confounding factors, despite observed temporal associations between drugs and AEs, limits the ability to infer causation. The core value of this study lies in identifying potential risks. Future research should verify our results through more rigorous retrospective cohort studies and further confirm causality through large - scale prospective studies or RCTs. Secondly, certain AEs may have higher reporting rates for various reasons (such as media attention, black box warnings, etc.), which could lead to overestimation of certain risks. Thirdly, the four disproportionality analysis methods used in this study all have inherent drawbacks. In rare AE scenarios, frequentist statistical methods (ROR/PRR) are susceptible to small fluctuations. Specifically, the addition of a single report may cause the ROR or PRR to shift from non-significant to significant. Bayesian methods (BCPNN/MGPS), while improving stability,

may suppress true signals, raising the risk of false negatives [60]. Frequentist statistical methods and Bayesian methods are highly consistent for high - frequency AEs but less so for low - frequency ones. Fourthly, the symptoms of underlying diseases may overlap with or mask treatment-related AEs, complicating the differentiation between symptoms attributable to the underlying disease and those triggered by the medication. Furthermore, concomitant medications may lead to drug-drug interactions increasing both the incidence and severity of AEs. Lastly, reports in the FAERS database may be incomplete, lacking key information such as dosage, duration of use, and patient demographic characteristics, which limits the analysis and interpretation of the data. The lack of dosage information makes it hard to assess the dose - response relationship precisely, and missing duration of use data may mix up acute and chronic toxicity. In subgroup analysis, missing demographic data can cut the effective sample size and weaken statistical power. The FAERS database's limits come from its passive surveillance nature. Future research could combine data from different sources, use advanced analysis methods, and apply active monitoring strategies to improve result reliability. Nonetheless, by analyzing a large amount of data, our study may still provide meaningful information for subsequent clinical practice and scientific research activities.

Conclusions

This study, based on the largest real-world dataset to date, comprehensively assessed the safety of pemetrexed and platinum with or without pembrolizumab in LC patients. Despite the inherent limitations of the FAERS database, our findings still provide valuable insights. We found that combination therapy may increase the risk of some AEs, such as renal and urinary system disorders, hepatobiliary disorders, and ILD, among others. Gender and age may influence the incidence and types of AEs, highlighting the importance of personalized treatment strategies. Combination therapy prolongs the time to AE onset, requiring enhanced surveillance during the initial three months of treatment. In light of the increased reporting rates of AEs in specific patient subgroups, healthcare providers must continue to conduct pharmacovigilance research and optimize treatment regimens to minimize the negative impact of AEs on prognosis.

Abbreviations

LC	Lung cancer
ICIs	Immune checkpoint inhibitors
FDA	Food and drug administration
FAERS	FDA adverse event reporting system
Q2 2017	The second quarter of 2017
Q3 2024	The third quarter of 2024
ROR	Reporting odds ratio
PRR	Proportional reporting ratio
BCPNN	Bayesian confidence propagation neural network
MGPS	Multi-item gamma poisson shrinker
AE	Adverse event
ILD	Interstitial lung disease
NSCLC	Non-small cell lung cancer
SCLC	Small cell lung cancer
LUAD	Lung adenocarcinoma
LUSC	Lung squamous cell carcinoma
nsNSCLC	Non-squamous non-small cell lung cancer
OS	Overall survival
PFS	Progression free survival
RCTs	Randomized controlled trials
PS	Primary suspect drug
PP	Pemetrexed and platinum
PPP	Pemetrexed and platinum plus pembrolizumab
PTs	Preferred terms
MedDRA	Medical dictionary for regulatory activities
SOCs	System organ classes
IQR	inter-quartile range
CI	Confidence interval
EBGM	Empirical bayesian geometric mean
EBGM05	The lower limit of the 95% CI of EBGM
AKI	Acute kidney injury
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
DIILD	Drug-induced interstitial lung disease
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14171-3.

Supplementary Material 1

Acknowledgements

The authors thank all the contributors of the FAERS database.

Author contributions

Shun Li: Data curation, Methodology, Visualization, Writing—original draft, Writing—review & editing. Zhifei Huang: Data curation, Methodology, Visualization, Writing—original draft, Writing—review & editing. Xiaoyu Zhong: Data curation, Visualization. Yan Zhou: Supervision, Conceptualization, Methodology, Writing—original draft, Writing—review & editing. Hao Jiang: Funding acquisition, Supervision, Conceptualization, Methodology, Writing—original draft, Writing—review & editing.

Funding

This study was supported by the Research Funds of Joint Research Center for Regional Diseases of IHM (2023bydjk003) and Anhui Provincial Key R&D Programmes (202304295107020078).

Data availability

The data analysed during the current study are available from the corresponding author on reasonable request. The raw data used in this study can be freely accessed from the FAERS database on the FDA website (http://www.fda.gov).

Declarations

Ethics approval and consent to participate

Not applicable. Ethical approval was not required for this study because we used the FAERS database, which is a free open-access database.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 23 January 2025 / Accepted: 16 April 2025
Published online: 24 April 2025

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca Cancer J Clin. 2024;74:229–63.
2. Leiter A, Veluswamy RR, Wisnivesky JP. The global burden of lung cancer: current status and future trends. Nat Rev Clin Oncol. 2023;20:624–39.
3. Chen S, Cao Z, Prettner K, Kuhn M, Yang J, Jiao L, et al. Estimates and projections of the global economic cost of 29 cancers in 204 countries and territories from 2020 to 2050. JAMA Oncol. 2023;9:465–72.
4. Relli V, Trerotola M, Guerra E, Alberti S. Abandoning the notion of Non-Small cell lung Cancer. Trends Mol Med. 2019;25:585–94.
5. Chen K, He Y, Wang W, Yuan X, Carbone DP, Yang F. Development of new techniques and clinical applications of liquid biopsy in lung cancer management. Sci Bull. 2024;69:1556–68.
6. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature. 2018;553:446–54.
7. Gougis P, Jochum F, Abbar B, Dumas E, Bihan K, Lebrun-Vignes B et al. Clinical spectrum and evolution of immune-checkpoint inhibitors toxicities over a decade—a worldwide perspective. eClinicalMedicine. 2024;70.
8. de Castro G, Kudaba I, Wu Y-L, Lopes G, Kowalski DM, Turna HZ, et al. Five-Year outcomes with pembrolizumab versus chemotherapy as First-Line therapy in patients with Non–Small-Cell lung Cancer and programmed death Ligand-1 tumor proportion score ≥ 1% in the KEYNOTE-042 study. JCO. 2023;41:1986–91.
9. Borghaei H, Langer CJ, Gadgeel S, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. 24-Month overall survival from KEYNOTE-021 cohort G: pemetrexed and carboplatin with or without pembrolizumab as First-Line therapy for advanced nonsquamous Non–Small cell lung Cancer. J Thorac Oncol. 2019;14:124–9.
10. Sheldrick RC. Randomized trials vs real-world evidence: how can both inform decision-making? JAMA. 2023;329:1352.
11. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidem Dr S. 2004;13:519–23.
12. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidem Dr S. 2001;10:483–6.
13. Rivkees SA, Szarfman A. Dissimilar hepatotoxicity profiles of propylthiouracil and methimazole in children. J Clin Endocrinol Metab. 2010;95:3260–7.
14. Ang PS, Chen Z, Chan CL, Tai BC. Data mining spontaneous adverse drug event reports for safety signals in Singapore - a comparison of three different disproportionality measures. Expert Opin Drug Saf. 2016;15:583–90.
15. Wu S, Hu W, Chen M, Xiao X, Liu R. A real-world pharmacovigilance study of FDA adverse event reporting system events for lutetium-177-PSMA-617. Sci Rep. 2024;14:25712.
16. Pauken KE, Dougan M, Rose NR, Lichtman AH, Sharpe AH. Adverse events following cancer immunotherapy: Obstacles and opportunities. Trends Immunol. 2019;40:511–23.
17. Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, Domine M, et al. Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): A multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21:387–97.
18. Chu Q, Perrone F, Greillier L, Tu W, Piccirillo MC, Grosso F, et al. Pembrolizumab plus chemotherapy versus chemotherapy in untreated advanced pleural mesothelioma in Canada, Italy, and France: A phase 3, open-label, randomised controlled trial. Lancet. 2023;402:2295–306.
19. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, Angelis FD, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med. 2018;378:2078–92.
20. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: A randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016;17:1497–508.
21. Leonetti A, Perrone F, Puntoni M, Maglietta G, Bordi P, Bria E et al. Real-world outcomes of Italian patients with advanced non-squamous lung cancer treated with first-line pembrolizumab plus platinum-pemetrexed. Eur J Cancer. 2024;202.
22. Muehlenbein C, Kim S, Ryabko E, Oton A, Agg H, Smolyakova N, et al. Real-world safety of pemetrexed, carboplatin, and pembrolizumab in U.S. NSCLC patients. JCO. 2020;38 5suppl:50–50.
23. De Giglio A, Grandinetti V, Aprile M, Borelli G, Campus A, Croci Chiocchini AL, et al. Patterns of renal toxicity from the combination of pemetrexed and pembrolizumab for advanced nonsquamous non-small-cell lung cancer (NSCLC): A single-center experience. Lung Cancer. 2022;174:91–6.
24. Garon EB, Aerts J, Kim JS, Muehlenbein CE, Peterson P, Rizzo MT, et al. Safety of pemetrexed plus platinum in combination with pembrolizumab for metastatic nonsquamous non-small cell lung cancer: A post hoc analysis of KEYNOTE-189. Lung Cancer. 2021;155:53–60.
25. Cortazar FB, Marrone KA, Troxell ML, Ralto KM, Hoenig MP, Brahmer JR, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. Kidney Int. 2016;90:638–47.
26. Miao J, Sise ME, Herrmann SM. Immune checkpoint inhibitor related nephrotoxicity: advances in clinicopathologic features, noninvasive approaches, and therapeutic strategy and Rechallenge. Front Nephrol. 2022;2.
27. Dumoulin DW, Visser S, Cornelissen R, van Gelder T, Vansteenkiste J, Thusen J, von der, et al. Renal toxicity from pemetrexed and pembrolizumab in the era of combination therapy in patients with metastatic nonsquamous cell NSCLC. J Thorac Oncol. 2020;15:1472–83.
28. Moturi K, Sharma H, Hashemi-Sadraei N. Nephrotoxicity in the age of immune checkpoint inhibitors: mechanisms, diagnosis, and management. Int J Mol Sci. 2024;25:414.
29. Kanbay M, Yildiz AB, Siriopol D, Vehbi S, Hasbal NB, Kesgin YE, et al. Immune checkpoints inhibitors and its link to acute kidney injury and renal prognosis. Int Urol Nephrol. 2023;55:1025–32.
30. Patil T, Nie Y, Hu J, Schenk EL, Pacheco JM, Purcell WT, et al. Duration of pemetrexed maintenance therapy with or without pembrolizumab is associated with risk of renal toxicity in patients with metastatic nonsquamous NSCLC. JCO. 2021;39 15suppl:e21205–21205.
31. Zhang Y, Ma Z, Sun X, Zhang Y, Zhu M, Zhang S et al. Anticancer drug-induced interstitial lung disease: A critical appraisal of clinical practice guidelines and consensus statements. Expert Opin Drug Saf 2024;20:1–9.
32. Li X, Gu Y-L, Liu X-C, Sun Z-X, Sun Y. Analysis of 12 cases of antineoplastic agents-induced interstitial lung disease. Front Pharmacol. 2023;14:1218480.
33. Spagnolo P, Bonniaud P, Rossi G, Sverzellati N, Cottin V. Drug-induced interstitial lung disease. Eur Respir J. 2022;60:2102776.
34. Gu L, Khadaroo PA, Su H, Kong L, Chen L, Wang X, et al. The safety and tolerability of combined immune checkpoint inhibitors (anti-PD-1/PD-L1 plus anti-CTLA-4): A systematic review and meta-analysis. BMC Cancer. 2019;19:559.
35. Liu H, Luo SX, Jie J, Peng L, Wang S, Song L. Immune checkpoint inhibitors related respiratory disorders in patients with lung cancer: A meta-analysis of randomized controlled trials. Front Immunol. 2023;14.
36. Suzuki Y, Karayama M, Uto T, Fujii M, Matsui T, Asada K, et al. Assessment of immune-related interstitial lung disease in patients with NSCLC treated with immune checkpoint inhibitors: A multicenter prospective study. J Thorac Oncol. 2020;15:1317–27.
37. Harrison M, Kavanagh G, Corte TJ, Troy LK. Drug-induced interstitial lung disease: A narrative review of a clinical conundrum. Expert Rev Respir Med. 2024;18:23–39.
38. Conte P, Ascierto PA, Patelli G, Danesi R, Vanzulli A, Sandomenico F, et al. Drug-induced interstitial lung disease during cancer therapies: expert opinion on diagnosis and treatment. ESMO Open. 2022;7:100404.
39. Fujimoto D, Miura S, Yoshimura K, Wakuda K, Oya Y, Yokoyama T, et al. Pembrolizumab plus chemotherapy-induced pneumonitis in chemo-naïve patients with non-squamous non-small cell lung cancer: A multicentre, retrospective cohort study. Eur J Cancer. 2021;150:63–72.
40. Zabor EC, Kaizer AM, Hobbs BP. Randomized controlled trials. Chest. 2020;158:S79–87.
41. De Francia S, Berchialla P, Armando T, Storto S, Allegra S, Sciannameo V, et al. Colorectal cancer chemotherapy: can sex-specific disparities impact on drug toxicities? Eur J Clin Pharmacol. 2022;78:1029–38.
42. Marcu LG. Gender and sex-related differences in normal tissue effects induced by platinum compounds. Pharmaceuticals. 2022;15:255.
43. de Rouw N, Boosman RJ, van de Bruinhorst H, Biesma B, van den Heuvel MM, Burger DM, et al. Cumulative pemetrexed dose increases the risk of nephrotoxicity. Lung Cancer. 2020;146:30–5.

44. Qu J, Ding Y, Jiang K, Hao J, Li Y, Zhang A, et al. Nephrotoxicity of immune checkpoint inhibitors: A disproportionality analysis from 2013 to 2020. Tohoku J Exp Med. 2021;254:275–82.
45. Carmona-Bayonas A, Jimenez-Fonseca P, de Castro EM, Mata E, Biosca M, Custodio A, et al. SEOM clinical practice guideline: management and prevention of febrile neutropenia in adults with solid tumors (2018). Clin Transl Oncol. 2019;21:75–86.
46. Sloan WA, Kemmerly S, Jain S, Shreves A, Dauterive K. 787. Improving ED sepsis care. Open Forum Infect Dis. 2019;6 Supplement2:S348–9.
47. McLachlan AJ, Pont LG. Drug metabolism in older people—a key consideration in achieving optimal outcomes with medicines. Journals Gerontology: Ser A. 2012;67A:175–80.
48. Soto-Perez-de-Celis E, Li D, Yuan Y, Lau YM, Hurria A. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. Lancet Oncol. 2018;19:e305–16.
49. Mozaffari S, Mousavi T, Nikfar S, Abdollahi M. Common Gastrointestinal drug-drug interactions in geriatrics and the importance of careful planning. Expert Opin Drug Metab Toxicol. 2023;19:807–28.
50. Esen BH, Bektas SN, Topcu U, Köylü B, Kuvvet FBB, Bahat G, et al. Immune-related adverse events in older adults receiving immune checkpoint inhibitors: A comprehensive analysis of the food and drug administration adverse event reporting system. Age Ageing. 2025;54:afaf008.
51. Chen C, Zhang C, Wu B, Xu T. Immune-related adverse events in older adults: data mining of the FDA adverse event reporting system. J Geriatric Oncol. 2022;13:1017–22.
52. Fujimoto D, Miura S, Yoshimura K, Wakuda K, Oya Y, Haratani K et al. A real-world study on the effectiveness and safety of pembrolizumab plus chemotherapy for nonsquamous NSCLC. JTO Clin Res Rep. 2022;3.
53. Collins BF, Raghu G. Hypersensitivity pneumonitis: A high index of clinical suspicion is key for early diagnosis and successful treatment. Respirology. 2025;30:10–2.
54. Vu A, Vassallo R, Ryu JH. Exacerbation of previously undiagnosed bird Fancier's lung by pembrolizumab therapy. Chest. 2019;155:e79–82.
55. Jeon C-H, Kim S-H, Kim S, Bae M, Lee S-J, Lim S. Pneumocystis jirovecii pneumonia in patients with solid malignancies: A retrospective study in two hospitals. Pathogens. 2022;11:1169.
56. Xia S, Gong H, Wang Y, Liu L, Zhao Y, Guo L et al. Pneumocystis jirovecii pneumonia associated with immune checkpoint inhibitors: A systematic literature review of published case reports and disproportionality analysis based on the FAERS database. Front Pharmacol. 2023;14.
57. Fan B, Sun X, Han W, Zou Y, Chen F, Lan F et al. Immune checkpoint inhibitor increased mortality in lung cancer patients with Pneumocystis jirovecii pneumonia: A comparative retrospective cohort study. Front Oncol. 2024;14.
58. Cho IY, Chang Y, Sung E, Park B, Kang J-H, Shin H, et al. Glycemic status, insulin resistance, and mortality from lung cancer among individuals with and without diabetes. Cancer Metabolism. 2024;12:17.
59. Wang C, Lu D, Cronin-Fenton D, Huang C, Liew Z, Wei D et al. Cardiovascular disease and risk of lung cancer incidence and mortality: A nationwide matched cohort study. Front Oncol. 2022;12.
60. Li Q, Shan W, Wu S. Safety assessment of rosuvastatin-fenofibrate combination in the treatment of hyperlipidemia based on FDA's adverse event reporting system database. Front Pharmacol. 2025;16.

Publisher's note