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Impact of antitumor regimens on the outcomes of cancer patients with COVID-19: a pooled analysis

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Since the outbreak of coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) discovered in December 2019, the disease has emerged as a global pandemic (Shi et al., 2020; World Health Organization, 2020). Several studies have shown a higher incidence of COVID-19, as well as related poor outcomes in patients with malignancies as compared with those without them (Liang et al., 2020; Tian et al., 2020). The impact of cancer on COVID-19 may be attributed to the use of antitumor treatments that may disturb the host response to SARS-CoV-2 infection (Wang et al., 2020), while the current studies on this topic have drawn controversial conclusions. Some implied that anticancer treatments might elevate the risk of death (García-Suárez et al., 2020; Liu et al., 2020). On the contrary, others pointed out that this association is not significant (Brar et al., 2020; Lee et al., 2020a). Although previous systematic reviews have investigated this important issue (Wang and Huang, 2020), the heterogeneity of findings is obvious and the general conclusion has remained unclear. Considering this ambiguity, it is difficult for clinicians to make therapeutic decisions when facing patients with both cancer and COVID-19; therefore, a high-quality and accurate evaluation of the impact of anticancer treatments on COVID-19 patients is necessary. Accordingly, we conducted a pooled analysis with the original data of each patient for the first time to provide a comprehensive perspective into the association between anticancer regimens and the outcomes of cancer patients with COVID-19.

The study was carried out according to a predefined protocol submitted to the PROSPERO registry (CRD42020209305). After performing a search on PubMed, Embase, and Cochrane library for the period of January 1, 2019 to October 17, 2020, 5306 citations were identified, of which 1374 duplicate records were excluded. The review of titles and abstracts led to the exclusion of 3762 irrelevant citations, leaving 170 for further assessment. After reviewing the full texts of these citations, 11 studies were included for the final pooled analysis. The detailed inclusion criteria were listed in Appendix S1. The selection process is shown in Fig. 1, and the search strategy is detailed in Appendix S2.

During the assessment of the full texts, the studies that possibly reported on the same patients were carefully checked by the reviewers. Potential duplicate patients who were identified according to the information provided by the articles were removed. Finally, 11 studies with 394 participants were included in our research (Bertuzzi et al., 2020; Biernat et al., 2020; Bogani et al., 2020; Booth et al., 2020; Dai et al., 2020; Frey et al., 2020; Joharatnam-Hogan et al., 2020; Kalinsky et al., 2020; Wu et al., 2020; Zhang HY et al., 2020; Zhang L et al., 2020). In addition, 45 patients from three studies (Booth et al., 2020; Kalinsky et al.,

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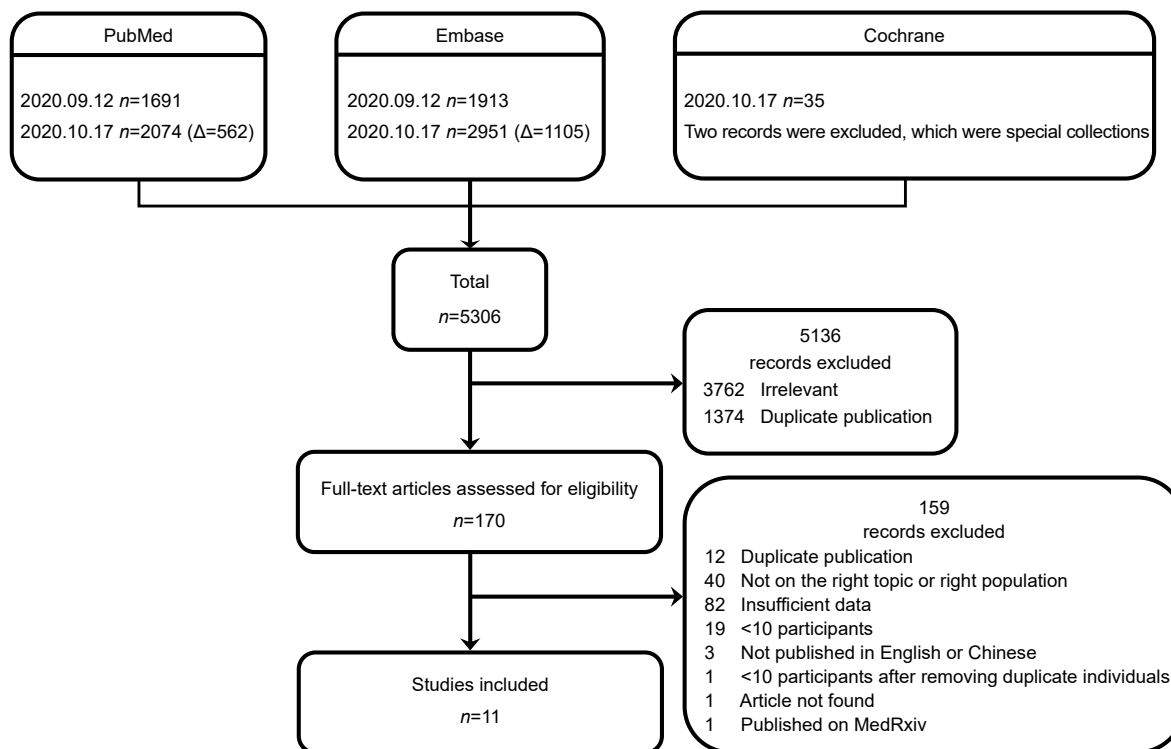 Dajing XIA, https://orcid.org/0000-0003-1645-9046

Fig. 1 Flow diagram of the study selection process. Δ: the remaining records after excluding the overlap between two rounds of literature search.

2020; Zhang HY et al., 2020) were excluded due to the uncertainty of the COVID-19 diagnostic results.

The following individual clinical data from each included study were extracted using a prospectively designed electronic data collection sheet: demographic information (gender, age, smoking habits, and comorbidities), the pattern of cancers, the details of antitumor regimens, the interval between anticancer treatments and COVID-19 onset, the primary outcome (all-cause mortality), and the secondary outcome (severe events, i.e., death, admission to an intensive care unit (ICU), and utilization of mechanical ventilation). The details of the involved studies are shown in Table 1.

Among the finally included 394 participants, the most commonly used antitumor regimen was chemotherapy (109 patients, 27.7%), followed by targeted therapy (56 patients, 14.2%), hormonal therapy (39 patients, 9.9%), radiotherapy (27 patients, 6.9%), immunotherapy (26 patients, 6.6%), and surgery (25 patients, 6.3%) (Fig. 2a).

The subgroup analysis revealed that the use of chemotherapy was the most common in patients with solid tumors and patients from each of the three different regions (Figs. 2b and 2c).

The analysis results indicated that, regardless of tumor type or geographic region, chemotherapy was the most common antitumor treatment. Therefore, among the various anticancer regimens, chemotherapy was attributed important status.

We calculated the crude and adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) to evaluate the impacts of antitumor regimens on the risks of primary (all-cause mortality) and secondary (severe events) outcomes. Based on the previous major studies (Lee et al., 2020a; Liu et al., 2021; Rüthrich et al., 2021), age, sex, smoking status, and comorbidities were regarded as potential confounders. According to our univariate analysis below, the covariables which were identified as significant risk factors were further included in multivariate analysis for adjustment. Moreover, we conducted a subgroup analysis by tumor type, gender, age, and the time period between treatments and the onset of COVID-19.

In total, 366 cancer patients with COVID-19 (ten studies) had a record of survival status, of which 91 patients (24.9%) died from any cause. The univariate analysis revealed that receiving chemotherapy (OR, 1.88; 95% CI, 1.13–3.13) and hormonal therapy (OR,

Table 1 Details of studies included in the analysis

Study	Sample size	Country	Age (year)	Gender	Regimen	Tumor type
Bertuzzi et al., 2020	26	Italy	43–89	Male/female	Chemotherapy, immunotherapy, hormonal therapy, and targeted therapy	Solid tumor
Bogani et al., 2020	19	Italy	49–84	Female	Surgery, chemotherapy, and targeted therapy	Gynecologic cancer*
Booth et al., 2020	66	UK	NA	Male/female	Chemotherapy, targeted therapy, and hormonal therapy	Haematologic malignancy
Dai et al., 2020	105	China	26–87	Male/female	Surgery, chemotherapy, immunotherapy, targeted therapy, and radiotherapy	Not specified
Zhang HY et al., 2020	107	China	36–98	Male/female	Surgery, chemotherapy, immunotherapy, targeted therapy, radiotherapy, and hormonal therapy	Not specified
Zhang L et al., 2020	28	China	24–80	Male/female	Surgery, chemotherapy, immunotherapy, targeted therapy, and radiotherapy	Solid tumor
Biernat et al., 2020	10	Poland	30–69	NA	Chemotherapy, targeted therapy, and hormonal therapy	Haematologic malignancy
Kalinsky et al., 2020	27	USA	32–80	Female	Chemotherapy, immunotherapy, targeted therapy, and hormonal therapy	Breast tumor
Wu et al., 2020	11	China	29–73	Male/female	Chemotherapy, immunotherapy, targeted therapy, and radiotherapy	Not specified
Frey et al., 2020	19	USA	NA	Female	Surgery, chemotherapy, immunotherapy, targeted therapy, radiotherapy, and hormonal therapy	Gynecologic cancer*
Joharatnam-Hogan et al., 2020	26	UK	24–91	Male/female	Surgery, chemotherapy, targeted therapy, radiotherapy, and hormonal therapy	Not specified

NA, not available. * Gynecologic cancer in these studies includes primary malignancies in cancers of the ovary, vulva, cervix, uterus, and endometrium.

2.98; 95% CI, 1.51−5.89) (Fig. 3) were associated with an increased risk of all-cause mortality. Besides, in the univariate analysis of 153 patients with relevant data (Bertuzzi et al., 2020; Dai et al., 2020; Kalinsky et al., 2020), age and a history of cardiovascular and cerebrovascular diseases were identified as significant variables ($P<0.05$; Table S1) and were further included in multivariate analysis, which was performed for cases from six studies (Bertuzzi et al., 2020; Bogani et al., 2020; Dai et al., 2020; Kalinsky et al., 2020; Wu et al., 2020; Zhang HY et al., 2020) that provided complete relevant clinical information. In the multivariate analysis, we found no association between chemotherapy or hormonal therapy and increased risk of death (Fig. 4). It seemed that the clinical characteristics, such as advancing age, or cardiovascular and cerebrovascular diseases, played a more important role in disease outcomes than the antitumor regimens.

The OR for immunotherapy was significantly associated with an increased risk of all-cause mortality in solid tumor patients (OR, 2.66; 95% CI, 1.07−6.64; 10 studies; Fig. 5). In patients with haematologic malignancies, chemotherapy increased the risk of death (OR, 4.11; 95% CI, 1.59−10.60; 10 studies; Fig. 5). When stratified according to gender, hormonal therapy was significantly associated with death in male patients (OR, 8.09; 95% CI, 2.09−31.30; 9 studies; Fig. 5). As for age, both chemotherapy (OR, 3.47; 95% CI, 1.20−10.04; 8 studies) and immunotherapy (OR, 8.00; 95% CI, 1.78−35.89; 8 studies) were associated with increased mortality in patients younger than 65 years, but not in those older than 65 years (Fig. 5). The impact of immunotherapy on mortality seemed to be more evident in younger patients. In elder patients, this impact could be diluted by other well-known factors, such as age and comorbidities. The time interval between recent anticancer treatments and the onset of COVID-19 was divided into "within 3 months" and "within 50 d" before the onset of COVID-19. For the former, the risk of all-cause mortality was increased in patients who had gone through chemotherapy (OR, 2.34; 95% CI, 1.25−4.36; 6 studies), targeted therapy (OR, 2.37; 95% CI, 1.15−4.88; 6 studies), and hormonal therapy (OR, 6.43; 95% CI, 2.28−18.15; 6 studies) (Fig. 5). For the antitumor
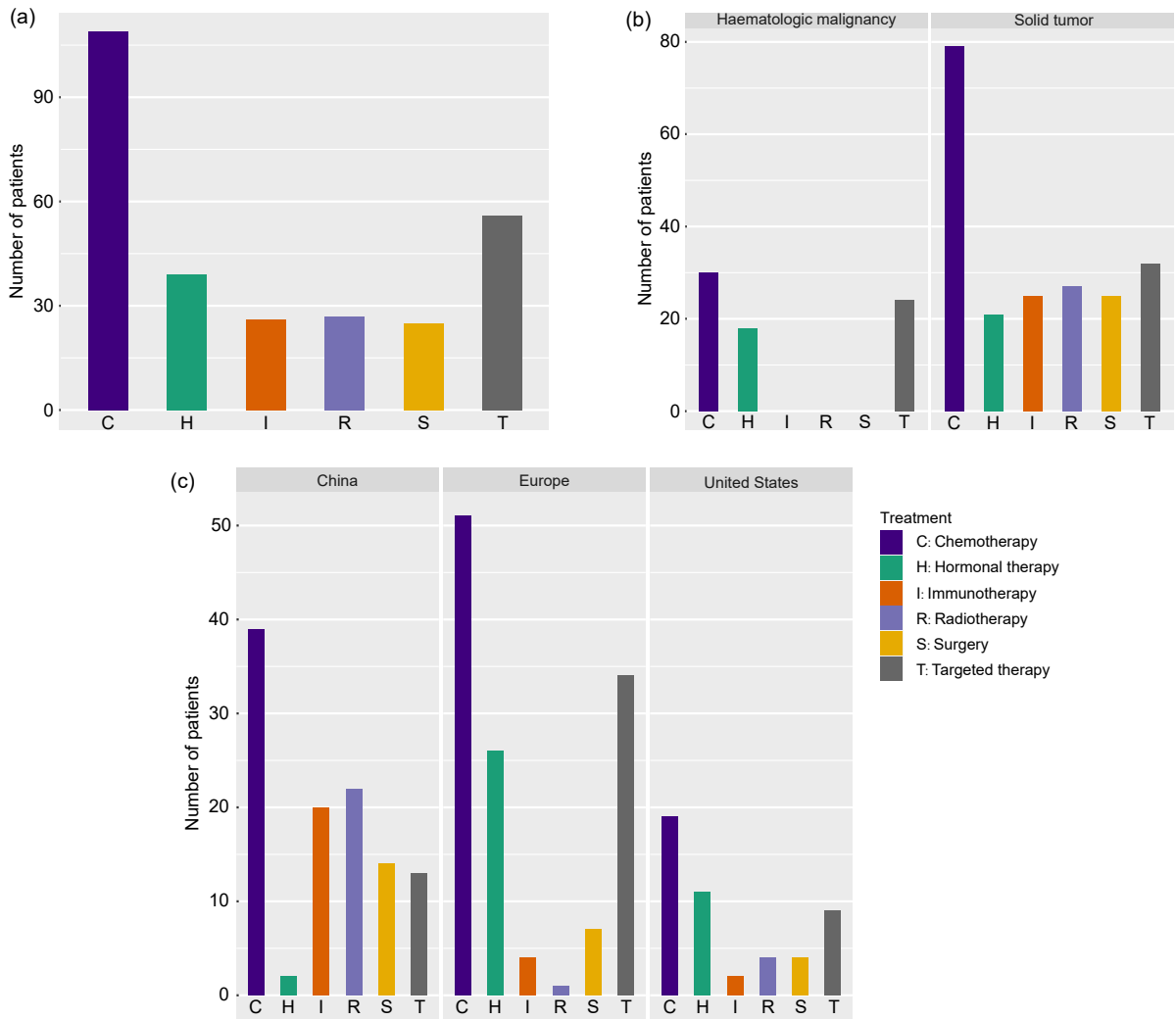
Fig. 2 Prevalence of different antitumor regimens in the overall population (a), and in patients stratified by tumor type (b) or geographic region (c).
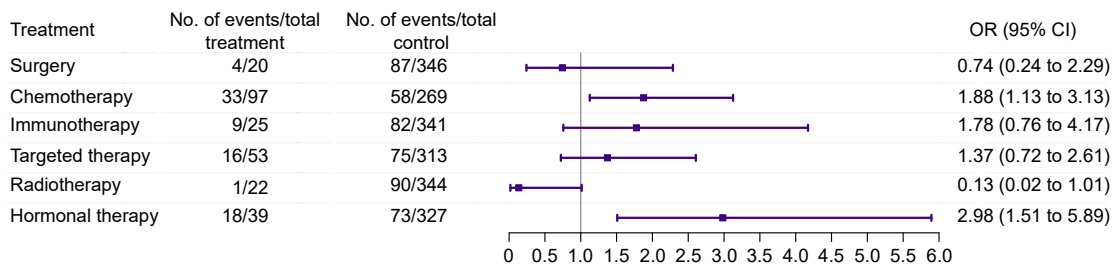
Fig. 3 Univariate analysis of the associations between antitumor regimens and the risk of death. OR: odds ratio; CI: confidence interval.

regimens which were administered within 50 d before the onset of COVID-19, immunotherapy significantly increased the risk of all-cause mortality (OR, 3.57; 95% CI, 1.41–9.01; 5 studies; Fig. 5), which was consistent with the overall result of multivariate analysis.

Overall, the subgroup analysis demonstrated that the adverse impacts of chemotherapy mainly occurred in patients with haematologic malignancies. However, for patients with solid tumors, immunotherapy could lead to life-threatening outcomes, especially when
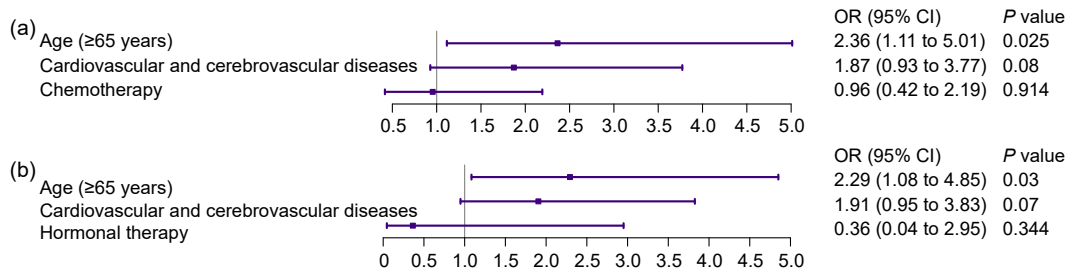
Fig. 4 Multivariate analysis of the associations between antitumor regimens (chemotherapy (a) and hormonal therapy (b)) and the risk of death. OR: odds ratio; CI: confidence interval.

administered within 50 d. Both chemotherapy and immunotherapy were reported to affect SARS-CoV-2 antibody levels in patients and could influence the immune response to SARS-CoV-2 (Yazaki et al., 2021). In fact, some previous studies even indicated that chemotherapy increased the risk of poor outcomes (Grivas et al., 2021; Sharafeldin et al., 2021), especially in patients with haematologic malignancies (Lee et al., 2020b), which is in agreement with our results. For patients with haematologic malignancies, myelosuppressive chemotherapy could disrupt the immune system and contribute to a more severe form of COVID-19 (Lin et al., 2021). Furthermore, it was conferred that lymphocytopenia following myelosuppressive chemotherapy or lymphocyte-reducing chemotherapy in patients with haematologic malignancies correlated with a greater risk of severe or even a life-threatening form of COVID-19 (Shi et al., 2020; Nakamura et al., 2021; Shumilov et al., 2021), which confirmed our finding for chemotherapy in patients with haematologic malignancies. Immunotherapy, including immune checkpoint blockage, chimeric antigen receptor (CAR) T-cell therapy, cancer vaccines, and tumor neoantigens, can reverse cancer immune evasion to eliminate cancer cells (Yang, 2015). Insufficient signaling through the programmed death-1 (PD-1) pathway following the administration of immune checkpoint inhibitors, which is commonly done in solid tumors, might lead to immunopathology in acute virus infection (Schönrich and Raftery, 2019). The pathological characteristics in a fatal case of COVID-19 revealed CD8 T-cells with high cytotoxicity (Xu et al., 2020), as observed in the toxicity of checkpoint inhibitors (Kennedy and Salama, 2020). Therefore, it can be speculated that the interplay between SARS-CoV-2 infection and immunotherapy might result in poor outcomes among special patients.

Considering the secondary outcome, 227 cancer patients with COVID-19 (four studies) had a record of severe events, in which 97 patients (42.7%) developed severe events during follow-up.

In these studies, we carefully reviewed the definitions of "severe events." Thus, in view of the similarity of the definition of "severe events" in these four studies (Dai et al., 2020; Joharatnam-Hogan et al., 2020; Zhang HY et al., 2020; Zhang L et al., 2020), for subsequent analysis, we defined severe events as death, admission to an ICU, and utilization of mechanical ventilation.

The univariate analysis indicated that immunotherapy was significantly associated with the risk of severe events (OR, 5.75; 95% CI, 1.19–27.73; Fig. S1). In addition, sex, age, and history of cardiovascular and cerebrovascular diseases with *P*<0.05 (Table S2) were included in multivariate analysis, which was conducted for cases in three studies (Dai et al., 2020; Zhang HY et al., 2020; Zhang L et al., 2020) providing sufficient relevant clinical information. When adjusted for the potential confounders (sex, age, and history of cardiovascular and cerebrovascular diseases), the effects of antitumor regimens on severe events became insignificant, while the effects of age and history of cardiovascular and cerebrovascular diseases remained significant (Fig. S2). Similar to the results of the primary outcome, the clinical characteristics seemed to be a more substantial risk factor in comparison with the antitumor regimens.

A subgroup analysis was also performed, which indicated that, for tumor type, immunotherapy increased the risk of severe events in solid tumor patients (OR, 5.04; 95% CI, 1.02–24.86; 4 studies; Fig. 6). Considering the interval between antitumor treatments and the onset of COVID-19, immunotherapy given within 50 d significantly increased the risk of severe events (OR, 5.51; 95% CI, 1.14–26.72; Fig. 6). Therefore, the use of immunotherapy significantly increased the risk of severe events in patients with solid tumors, especially when
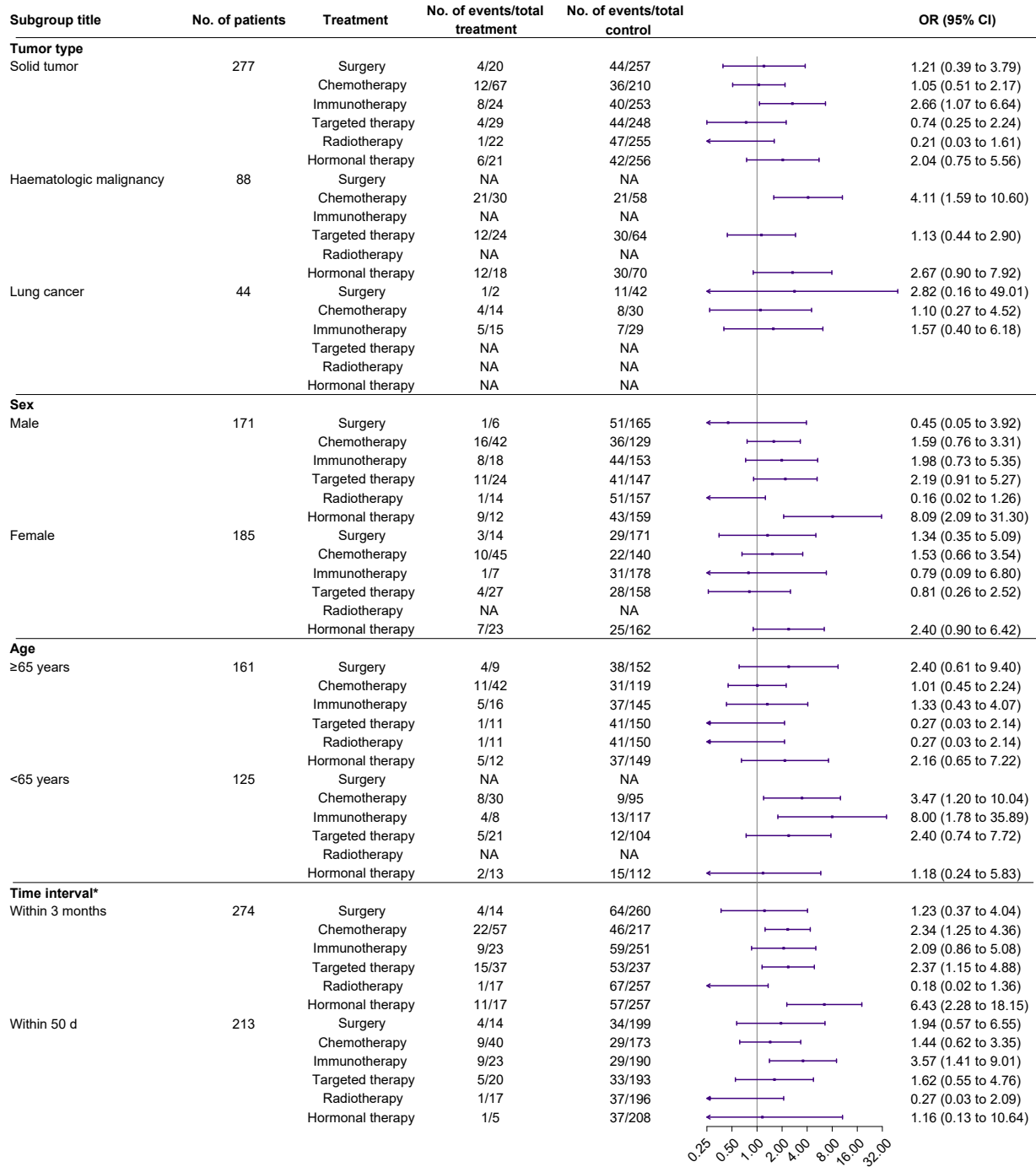
Subgroup title	No. of patients	Treatment	No. of events/total treatment	No. of events/total control		OR (95% CI)
Tumor type						
Solid tumor	277	Surgery	4/20	44/257		1.21 (0.39 to 3.79)
		Chemotherapy	12/67	36/210		1.05 (0.51 to 2.17)
		Immunotherapy	8/24	40/253		2.66 (1.07 to 6.64)
		Targeted therapy	4/29	44/248		0.74 (0.25 to 2.24)
		Radiotherapy	1/22	47/255		0.21 (0.03 to 1.61)
		Hormonal therapy	6/21	42/256		2.04 (0.75 to 5.56)
Haematologic malignancy	88	Surgery	NA	NA		
		Chemotherapy	21/30	21/58		4.11 (1.59 to 10.60)
		Immunotherapy	NA	NA		
		Targeted therapy	12/24	30/64		1.13 (0.44 to 2.90)
		Radiotherapy	NA	NA		
		Hormonal therapy	12/18	30/70		2.67 (0.90 to 7.92)
Lung cancer	44	Surgery	1/2	11/42		2.82 (0.16 to 49.01)
		Chemotherapy	4/14	8/30		1.10 (0.27 to 4.52)
		Immunotherapy	5/15	7/29		1.57 (0.40 to 6.18)
		Targeted therapy	NA	NA		
		Radiotherapy	NA	NA		
		Hormonal therapy	NA	NA		
Sex						
Male	171	Surgery	1/6	51/165		0.45 (0.05 to 3.92)
		Chemotherapy	16/42	36/129		1.59 (0.76 to 3.31)
		Immunotherapy	8/18	44/153		1.98 (0.73 to 5.35)
		Targeted therapy	11/24	41/147		2.19 (0.91 to 5.27)
		Radiotherapy	1/14	51/157		0.16 (0.02 to 1.26)
		Hormonal therapy	9/12	43/159		8.09 (2.09 to 31.30)
Female	185	Surgery	3/14	29/171		1.34 (0.35 to 5.09)
		Chemotherapy	10/45	22/140		1.53 (0.66 to 3.54)
		Immunotherapy	1/7	31/178		0.79 (0.09 to 6.80)
		Targeted therapy	4/27	28/158		0.81 (0.26 to 2.52)
		Radiotherapy	NA	NA		
		Hormonal therapy	7/23	25/162		2.40 (0.90 to 6.42)
Age						
≥65 years	161	Surgery	4/9	38/152		2.40 (0.61 to 9.40)
		Chemotherapy	11/42	31/119		1.01 (0.45 to 2.24)
		Immunotherapy	5/16	37/145		1.33 (0.43 to 4.07)
		Targeted therapy	1/11	41/150		0.27 (0.03 to 2.14)
		Radiotherapy	1/11	41/150		0.27 (0.03 to 2.14)
		Hormonal therapy	5/12	37/149		2.16 (0.65 to 7.22)
<65 years	125	Surgery	NA	NA		
		Chemotherapy	8/30	9/95		3.47 (1.20 to 10.04)
		Immunotherapy	4/8	13/117		8.00 (1.78 to 35.89)
		Targeted therapy	5/21	12/104		2.40 (0.74 to 7.72)
		Radiotherapy	NA	NA		
		Hormonal therapy	2/13	15/112		1.18 (0.24 to 5.83)
Time interval*						
Within 3 months	274	Surgery	4/14	64/260		1.23 (0.37 to 4.04)
		Chemotherapy	22/57	46/217		2.34 (1.25 to 4.36)
		Immunotherapy	9/23	59/251		2.09 (0.86 to 5.08)
		Targeted therapy	15/37	53/237		2.37 (1.15 to 4.88)
		Radiotherapy	1/17	67/257		0.18 (0.02 to 1.36)
		Hormonal therapy	11/17	57/257		6.43 (2.28 to 18.15)
Within 50 d	213	Surgery	4/14	34/199		1.94 (0.57 to 6.55)
		Chemotherapy	9/40	29/173		1.44 (0.62 to 3.35)
		Immunotherapy	9/23	29/190		3.57 (1.41 to 9.01)
		Targeted therapy	5/20	33/193		1.62 (0.55 to 4.76)
		Radiotherapy	1/17	37/196		0.27 (0.03 to 2.09)
		Hormonal therapy	1/5	37/208		1.16 (0.13 to 10.64)

Fig. 5 Subgroup analysis of the associations between antitumor regimens and all-cause mortality. * Time interval between the treatment and the onset of COVID-19. NA: not available; OR: odds ratio; CI: confidence interval.

administered within 50 d, which was in accordance with the result of the primary outcome.

In summary, our work provided a comprehensive review of anticancer regimens and their impacts on cancer patients with COVID-19. The findings showed that chemotherapy was the most common treatment in

cancer patients with COVID-19. After adjustment, the effects of antitumor regimens on poor outcomes became insignificant, while the effects of advancing age and history of cardiovascular and cerebrovascular diseases remained significant, which indicated that crucial clinical characteristics such as age and comorbidity should
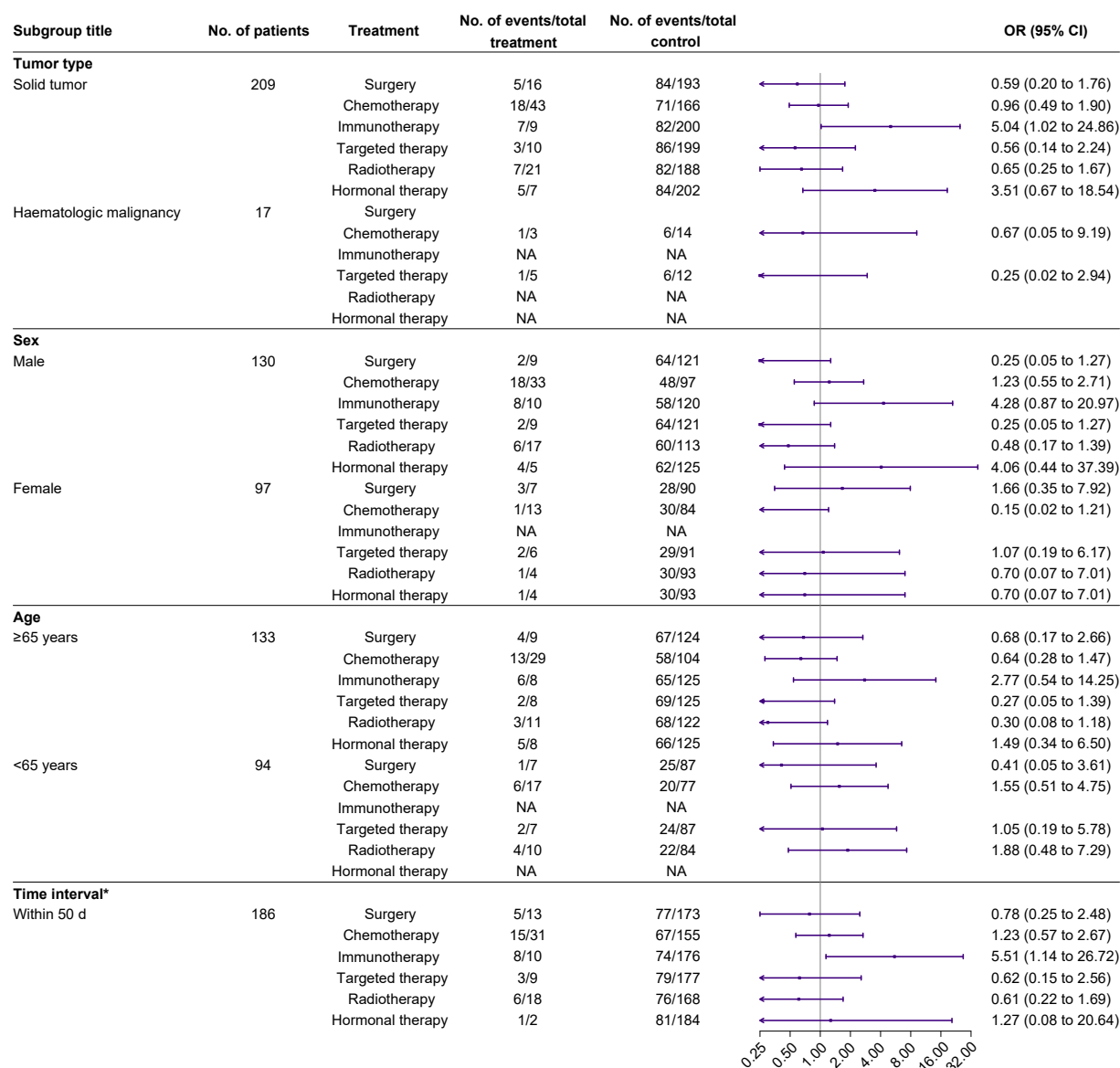
Subgroup title	No. of patients	Treatment	No. of events/total treatment	No. of events/total control		OR (95% CI)
Tumor type						
Solid tumor	209	Surgery	5/16	84/193		0.59 (0.20 to 1.76)
		Chemotherapy	18/43	71/166		0.96 (0.49 to 1.90)
		Immunotherapy	7/9	82/200		5.04 (1.02 to 24.86)
		Targeted therapy	3/10	86/199		0.56 (0.14 to 2.24)
		Radiotherapy	7/21	82/188		0.65 (0.25 to 1.67)
		Hormonal therapy	5/7	84/202		3.51 (0.67 to 18.54)
Haematologic malignancy	17	Surgery				
		Chemotherapy	1/3	6/14		0.67 (0.05 to 9.19)
		Immunotherapy	NA	NA		
		Targeted therapy	1/5	6/12		0.25 (0.02 to 2.94)
		Radiotherapy	NA	NA		
		Hormonal therapy	NA	NA		
Sex						
Male	130	Surgery	2/9	64/121		0.25 (0.05 to 1.27)
		Chemotherapy	18/33	48/97		1.23 (0.55 to 2.71)
		Immunotherapy	8/10	58/120		4.28 (0.87 to 20.97)
		Targeted therapy	2/9	64/121		0.25 (0.05 to 1.27)
		Radiotherapy	6/17	60/113		0.48 (0.17 to 1.39)
		Hormonal therapy	4/5	62/125		4.06 (0.44 to 37.39)
Female	97	Surgery	3/7	28/90		1.66 (0.35 to 7.92)
		Chemotherapy	1/13	30/84		0.15 (0.02 to 1.21)
		Immunotherapy	NA	NA		
		Targeted therapy	2/6	29/91		1.07 (0.19 to 6.17)
		Radiotherapy	1/4	30/93		0.70 (0.07 to 7.01)
		Hormonal therapy	1/4	30/93		0.70 (0.07 to 7.01)
Age						
≥65 years	133	Surgery	4/9	67/124		0.68 (0.17 to 2.66)
		Chemotherapy	13/29	58/104		0.64 (0.28 to 1.47)
		Immunotherapy	6/8	65/125		2.77 (0.54 to 14.25)
		Targeted therapy	2/8	69/125		0.27 (0.05 to 1.39)
		Radiotherapy	3/11	68/122		0.30 (0.08 to 1.18)
		Hormonal therapy	5/8	66/125		1.49 (0.34 to 6.50)
<65 years	94	Surgery	1/7	25/87		0.41 (0.05 to 3.61)
		Chemotherapy	6/17	20/77		1.55 (0.51 to 4.75)
		Immunotherapy	NA	NA		
		Targeted therapy	2/7	24/87		1.05 (0.19 to 5.78)
		Radiotherapy	4/10	22/84		1.88 (0.48 to 7.29)
		Hormonal therapy	NA	NA		
Time interval*						
Within 50 d	186	Surgery	5/13	77/173		0.78 (0.25 to 2.48)
		Chemotherapy	15/31	67/155		1.23 (0.57 to 2.67)
		Immunotherapy	8/10	74/176		5.51 (1.14 to 26.72)
		Targeted therapy	3/9	79/177		0.62 (0.15 to 2.56)
		Radiotherapy	6/18	76/168		0.61 (0.22 to 1.69)
		Hormonal therapy	1/2	81/184		1.27 (0.08 to 20.64)

0.25 0.50 1.00 2.00 4.00 8.00 16.00 32.00

Fig. 6 Subgroup analysis of the associations between antitumor regimens and severe events. * **Time interval between the treatment and the onset of COVID-19. NA: not available; OR: odds ratio; CI: confidence interval.**

deserve more attention. According to the subgroup analysis, chemotherapy increased the risk of all-cause mortality in patients with haematologic malignancies. Furthermore, immunotherapy was associated with all-cause mortality and severe events in patients with solid tumors, especially when given within 50 d before the onset of COVID-19. These findings can provide a basis for clinicians to tailor the regimens of anticancer treatments during the pandemic to minimize the impact of SARS-CoV-2 infection.

The present analysis has several limitations. Firstly, the number of studies with individual original data was insufficient, and the sample size was limited. Secondly, the quality and standard of data from different studies could not be fully controlled. Consequently, a multicenter study with a larger sample size and a unified standard of clinical data is strongly recommended. In addition, it appears that the combinational utilization of different treatments could reduce the side effects (Motz and Coukos, 2013). However, limited by the available clinical data, we did not investigate the effects of the combination of anticancer treatments on patients. Furthermore, as discussed above, the time interval between the recent anticancer treatments and the onset of COVID-19

was not fully analyzed. A more accurate investigation in this respect should therefore be conducted.

Author contributions

Yihua WU and Dajing XIA contributed to the conception and design of the study. Haohua LU, Yu SHI, Yihua WU, Kelie CHEN, and Yuequn NIU contributed to data extraction, statistical analysis, and data interpretation. Haohua LU, Yu SHI, and Yihua WU contributed to writing the manuscript. Dajing XIA, Zhi CHEN, and Haihong ZHU contributed to editing the manuscript. All authors have read and approved the final manuscript and, therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Haohua LU, Yu SHI, Kelie CHEN, Zhi CHEN, Haihong ZHU, Yuequn NIU, Dajing XIA, and Yihua WU declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Supplementary information

Appendixes S1 and S2; Tables S1 and S2; Figs. S1 and S2