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Mortality in adult patients with solid or hematological malignancies and SARS-CoV-2 infection with a specific focus on lung and breast cancers: A systematic review and meta-analysis

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ABSTRACT

Background: A systematic review and meta-analysis was performed to estimate mortality in adult patients with solid or hematological malignancies and SARS-CoV-2 infection.
Methods: A systematic search of PubMed, up to 31 January 2021, identified publications reporting the case-fatality rate (CFR) among adult patients with solid or hematological malignancies and SARS-CoV-2 infection. The CFR, defined as the rate of death in this population, was assessed with a random effect model; 95% confidence intervals (CI) were calculated.
Results: Among 135 selected studies (N = 33,879 patients), the CFR was 25.4% (95% CI 22.9%–28.2%). At a sensitivity analysis including studies with at least 100 patients, the CFR was 21.9% (95% CI 19.1%–25.1%). Among COVID-19 patients with lung (N = 1,135) and breast (N = 1,296) cancers, CFR were 32.4% (95% CI 26.5%–39.6%) and 14.2% (95% CI 9.3%–21.8%), respectively.
Conclusions: Patients with solid or hematological malignancies and SARS-CoV-2 infection have a high probability of mortality, with comparatively higher and lower CFRs in patients with lung and breast cancers, respectively.

1. Background

Since the start of the coronavirus disease 2019 (COVID-19) pandemic, the global cumulative number of cases all over the world has reached more than 108 million, with over 2.6 million cases of deaths as of March 2, 2021 (World Health Organization, 2021).

Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and a diagnosis of cancer are at high risk of severe symptomatic disease and death (Xia et al., 2020). Several efforts have been made to prevent SARS-CoV-2 infection among patients with cancer, as well as to ensure continuity of cancer care during the pandemic (Lambertini et al., 2020; Tagliamento et al., 2020a).

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Cancer has been shown to be an independent adverse prognostic factor on COVID-19-related mortality (de Azambuja et al., 2020; Saini et al., 2020). However, its effect across different patient subgroups is uncertain, and wide variability seems to exist according to different tumor types. In particular, patients with lung cancer have been reported to have disproportionally higher mortality rates from COVID-19, while those with breast cancer showed relatively lower mortality rates (Luo et al., 2020; Garassino et al., 2020; Vuagnat et al., 2020).

Since the outbreak of the pandemic, several case-series and cohort studies describing the clinical outcomes and mortality of SARS-CoV-2 infection in patients with cancer have been published. However, the relatively small sample size of most reports, their retrospective design and the restriction to hospitalized patients represent important limitations to interpret the reported mortality rates, and the extent to which they can be extrapolated to the wider population of patients with solid or hematological malignancies.

A systematic review and pooled analysis assessing the mortality rate of patients with SARS-CoV-2 infection and underlying cancer was published in 2020, but it included a relatively limited number of studies (n = 52) and did not provide pooled data on mortality according to tumor types (Saini et al., 2020). Moreover, to the best of our knowledge, no systematic review and meta-analyses focusing specifically on lung and breast malignancies are available to date.

To provide updated evidence on this important topic, we performed a systematic review and meta-analysis aiming to estimate the case-fatality rate (CFR) of patients with solid or hematological malignancies and SARS-CoV-2 infection. In addition, we also focused separately on patients with lung and breast cancers, in order to evaluate the CFR associated with these common tumors.

2. Materials and methods

2.1. Literature search

A systematic search of PubMed up to 31 January 2021 was performed by two authors (M.T. and F.P.); any disagreement was discussed among all authors and resolved. The search strategy included different combinations of terms: (covid OR coronavirus OR sars) AND (cancer OR tumor OR tumour OR tumors OR tumours OR malignancy OR malignancies OR neoplasia OR neoplasm) AND (mortality OR death). Duplicated results were not included. Only the most recent and updated version of a same study was considered.

2.2. Study selection

The following inclusion criteria were considered: i) publications reporting the mortality rate in patients with cancer and SARS-CoV-2 infection and/or specifically the mortality rate among patients with lung or breast cancers; ii) any type of study (observational, randomized controlled trials or case series); iii) studies involving patients with solid or hematological malignancies; iv) studies involving adult patients; v) studies including at least 10 patients; vi) publications in English.

2.3. Data extraction

Data extracted from every publication were: name of the first author, reported number of patients with cancer and SARS-CoV-2 infection, reported number of deaths among patients with cancer and SARS-CoV-2 infection, reported number of patients with lung cancer and SARS-CoV-2 infection, reported number of deaths among patients with lung cancer and SARS-CoV-2 infection, reported number of patients with breast cancer and SARS-CoV-2 infection, reported number of deaths among patients with breast cancer and SARS-CoV-2 infection. Data extraction was performed by two authors (M.T and E.A.).

2.4. Statistical analysis

A meta-analysis of selected studies was performed in order to assess the CRF among adult patients with solid or hematological malignancies and SARS-CoV-2 infection, defined as the cumulative rate of deaths among patients with history of malignancy and SARS-CoV-2-infection. Moreover, the mortality rates among patients with lung and breast cancers and SARS-CoV-2 infection were separately computed. A random effect model was used to assess the CFR, and 95% confidence intervals (CI) were calculated. The likelihood of publication bias was assessed by Egger's test. The Higgins I^2 index was used to assess the heterogeneity between studies. Sensitivity analyses were carried out after excluding studies including less than 100 patients.

3. Results

The systematic search of the literature returned 1,727 records. In total, 1,551 were excluded on the basis of the title and 34 based on the abstract not fulfilling the inclusion criteria, while 7 were duplicates. A total of 135 studies were selected, including 33,879 patients with solid or hematological malignancies and SARS-CoV-2 infection (Table 1) (Lundon et al., 2020; Liu et al., 2020; Fuentes-Antrás et al., 2020; Wang et al., 2020a, 2021; Montopoli et al., 2020; Song et al., 2021; Huang et al., 2020; Sng et al., 2020; Li et al., 2020; Tagliamento et al., 2020a; de Melo et al., 2020; Bogani et al., 2020; Wang et al., 2020b; Cavanna et al., 2021; Rogado et al., 2020a; Mehta et al., 2020; Basse et al., 2021; Zhang et al., 2020a; Nakamura et al., 2021; Kalinsky et al., 2020; Jee et al., 2020; Engelhardt et al., 2020; Tian et al., 2020; Passamonti et al., 2020; Nie et al., 2021; Cattaneo et al., 2020; Zhang et al., 2020b; Sorouri et al., 2020; Yang et al., 2020a; Wu et al., 2020a; Sanchez-Pina et al., 2020; Alpert et al., 2021; Deng et al., 2020; Özdemir et al., 2020; Chari et al., 2020; Rogiers et al., 2021; Aries et al., 2020; Fox et al., 2020; Wu et al., 2020b; Guan et al., 2020; Wang et al., 2020c; Piper-Vallillo et al., 2021; Stroppa et al., 2020; Rubio et al., 2020; Singh et al., 2020; Lattenist et al., 2021; Ramachandran et al., 2020; Rüthrich et al., 2021; Luo et al., 2020; Tsimafeyeu et al., 2020; Garassino et al., 2020; He et al., 2020; Breccia et al., 2020; Hultcrantz et al., 2020; Boilève et al., 2020; Lara Álvarez et al., 2020; Mehta et al., 2021; Kathuria-Prakash et al., 2021; Lee et al., 2020; Nichetti et al., 2020; Scarfò et al., 2020; Brar et al., 2020; Rogado et al., 2020b; Ali et al., 2020; Ramaswamy et al., 2020; Shoumariyeh et al., 2020; Infante et al., 2020; Angelis et al., 2020; Robilotti et al., 2020; Ferrari et al., 2021; Miyashita et al., 2020; Ciceri et al., 2020; Borah et al., 2021; Kabarriti et al., 2020; Russell et al., 2020; Gupta et al., 2020; Docherty et al., 2020; Bhogal et al., 2021; Elkrief et al., 2020; Assaad et al., 2020; Barbui et al., 2021; Hanna et al., 2021; Kvåle et al., 2020; Antrim et al., 2021; García-Suárez et al., 2020; de Azambuja et al., 2020; Caffo et al., 2020; Lee et al., 2021; Nepogodiev et al., 2020; Martínez-López et al., 2020; Lunski et al., 2021; Biernat et al., 2020; Cherri et al., 2020; COVIDSurg Collaborative et al., 2020; Ganatra et al., 2020; Mato et al., 2020; Calles et al., 2020; Duarte et al., 2020; Zhang et al., 2020c; Wood et al., 2020; Joharatnam-Hogan et al., 2020; de Oliveira et al., 2021; Thompson et al., 2020; Dai et al., 2020; Ayhan et al., 2021; Pinato et al., 2020a; Fillmore et al., 2020; Ramtohul et al., 2020; Lara et al., 2020; Sun et al., 2021; Cui et al., 2020; Cook et al., 2020; Booth et al., 2020; Grasselli et al., 2020; Lièvre et al., 2020; Yang et al., 2020b; Yarza et al., 2020; Reale et al., 2020; Laurenge et al., 2021; Pinto et al., 2020; Yu et al., 2020; Westblade et al., 2020; Glenthøj et al., 2021; Martín-Moro et al., 2020; Wang et al., 2020d; Sadeghi et al., 2020; Morjaria et al., 2020; Erdal et al., 2021; Burn et al., 2021; Yigenoglu et al., 2021; Rivera et al., 2020; Rajasekaran et al., 2020; Wang et al., 2020e).

Overall, the CFR was 25.4% (95% CI 22.9%–28.2%; Egger's test p = 0.001) (Fig. 1). A sensitivity analysis of the 66 studies (N = 31,184) including at least 100 patients showed a CFR of 21.9% (95% CI 19.1%–25.1%) (Fig. S1).

In total, 42 and 31 studies reported the mortality rate among COVID-

Table 1
Details of reported number of patients and deaths in the studies selected for the meta-analysis.

Author	Total patients with cancer and SARS-CoV-2 infection	Deaths in patients with cancer and SARS-CoV-2 infection	Total patients with lung cancer and SARS-CoV-2 infection	Deaths in patients with lung cancer and SARS-CoV-2 infection	Total patients with breast cancer and SARS-CoV-2 infection	Deaths in patients with breast cancer and SARS-CoV-2 infection
Ali et al.	201	16				
Alpert et al.	421	129				
Angelis et al.	113	29				
Antrim et al.	50	5				
Aries et al.	35	14				
Assaad et al.	55	8	7	3		
Ayhan et al.	46	0				
Barbui et al.	175	50				
Basse et al.	141	30	18	6		
Bhangu et al.	78	15				
Bhogal et al.	179	66				
Biernat et al.	10	7				
Bogani et al.	19	3				
Boilève et al.	16	2				
Booth et al.	66	34				
Borah et al.	130	26				
Brar et al.	117	29				
Breccia et al.	36	8				
Burn et al.	5595	670				
Caffo et al.	34	13				
Calles et al.	23	8	23	8		
Cattaneo et al.	102	40				
Cavanna et al.	51	25	12	7	4	2
Chari et al.	650	222				
Cherri et al.	53	16				
Ciceri et al.	22	11				
Cook et al.	75	41				
COVIDSurg Collaborative	189	43				
Cui et al.	32	9	26	7		
Dai et al.	31	8	31	8		
Dai et al.	105	12	22	4	11	0
De Azambuja et al.	832	283				
de Melo et al.	181	69	7	4	40	21
de Oliveira et al.	83	68	5	4	31	27
Deng et al.	107	6				
Docherty et al.	1743	617				
Duarte et al.	681	442	51	38	90	51
Elkrief et al.	249	71				
Engelhardt et al.	21	0				
Erdal et al.	77	17	7	1	11	1
Ferrari et al.	198	33	16	7	58	5
Fillmore et al.	1794	251	121			
Fox et al.	52	18				
Fuentes-Antras et al.	73	18	14	5	10	4
Ganatra et al.	195	48				
Garassino et al.	200	66				
García-Suárez et al.	697	230				
Glenthøj et al.	66	16				
Graselli et al.	331	202				
Guan et al.	18	3				
Gupta et al.	112	60				
Hanna et al	32	7				
He et al.	13	8				
Huang et al.	16	3	2			
Hultcrantz et al.	100	22				
Infante et al.	41	15				
Jee et al.	309	31				
Joharatnam-Hogan et al.	30	11	5	3	4	1
Kabarriti et al.	107	24				
Kalinsky et al.	27	1			27	1
Kathuria-Prakash et al.	21	2				
Kvåle et al.	372	36				
Lara Álvarez et al.	36	15				
Lara et al.	193	34				
Lattenist et al.	13	6				
Laurenge et al.	13	3				
Lee L et al.	1044	319	111	43	143	26

(*continued on next page*)

Table 1 (*continued*)

Author	Total patients with cancer and SARS-CoV-2 infection	Deaths in patients with cancer and SARS-CoV-2 infection	Total patients with lung cancer and SARS-CoV-2 infection	Deaths in patients with lung cancer and SARS-CoV-2 infection	Total patients with breast cancer and SARS-CoV-2 infection	Deaths in patients with breast cancer and SARS-CoV-2 infection
Lee RJ et al.	302	104				
Li et al.	65	18	5	2	8	1
Lièvre et al.	1289	370			173	26
Liu et al.	216	37	49	14	34	1
Lundon et al.	149	35				
Lunski et al.	312	66	26	8	70	8
Luo et al.	102	25	102	25		
Martinez-Lopez et al.	167	56				
Martín-Moro et al.	34	11				
Mato et al.	198	66				
Mehta A et al.	218	61	11	6	28	4
Mehta V et al.	186	27	17	0	19	1
Miyashita et al.	334	37				
Montopoli et al.	430	75				
Morjaria et al.	304	53				
Nakamura et al.	32	11	2	1	2	0
Nichetti et al.	11	6	1	1	4	3
Nie et al	45	11	45	11		
Ozdemir et al.	1523	77	157	18	302	2
Passamonti et al.	536	198				
Pinato et al.	204	59				
Pinto et al.	138	47				
Piper-Valillo et al.	24	7	24	7		
Rajasekeran et al.	12	4				
Ramachandran et al.	53	32				
Ramaswamy et al.	198	23			30	3
Ramtohul et al.	70	17	11			
Reale et al.	18	8	10	4		
Rivera et al.	2186	357				
Robilotti et al.	423	51				
Rogado et al.	25	5	25	5		
Rogado et al.	45	19	17	9		
Rogiers et al.	110	18	17	4		
Rubio et al.	28	9				
Russell et al.	156	34				
Rutrich et al.	435	114				
Sadeghi et al.	41	26				
Sanchez-Pina et al.	39	14				
Scarfò et al.	190	56				
Shoumariyeh et al.	39	8				
Singh et al.	85	32				
Sng et al.	94	41	15	5	8	4
Song et al.	248	40	61	16	37	2
Sorouri et al.	53	27	5	0	4	2
Stroppa et al.	25	9	8	2	2	2
Sun et al.	67	9				
Tagliamento et al.	17	4				
Thompson et al.	87	47				
Tian et al.	232	46	23	9	31	5
Tsimafeyeu et al.	37	1				
Wang QQ et al.	670	100				
Wang J et al.	12	3	3	1	1	0
Wang L et al.	15	3				
Wang J et al.	283	50	51	13	38	2
Wang B et al.	58	14				
Westblade et al.	100	30				
Wang Q et al.	420	40				
Wood et al.	250	70				
Wu Y et al.	14	6				
Wu Q et al.	11	4				
Yang B et al.	37	7	37	7		
Yang K et al.	205	40	24	6	40	3
Yarza et al.	63	16	17	6		
Yigenoglu et al.	740	102				
Yu et al.	12	3	7	2	1	0
Zhang B et al	35	0			35	0
Zhang H et al.	107	23	21	5		
Zhang L et al.	28	8				

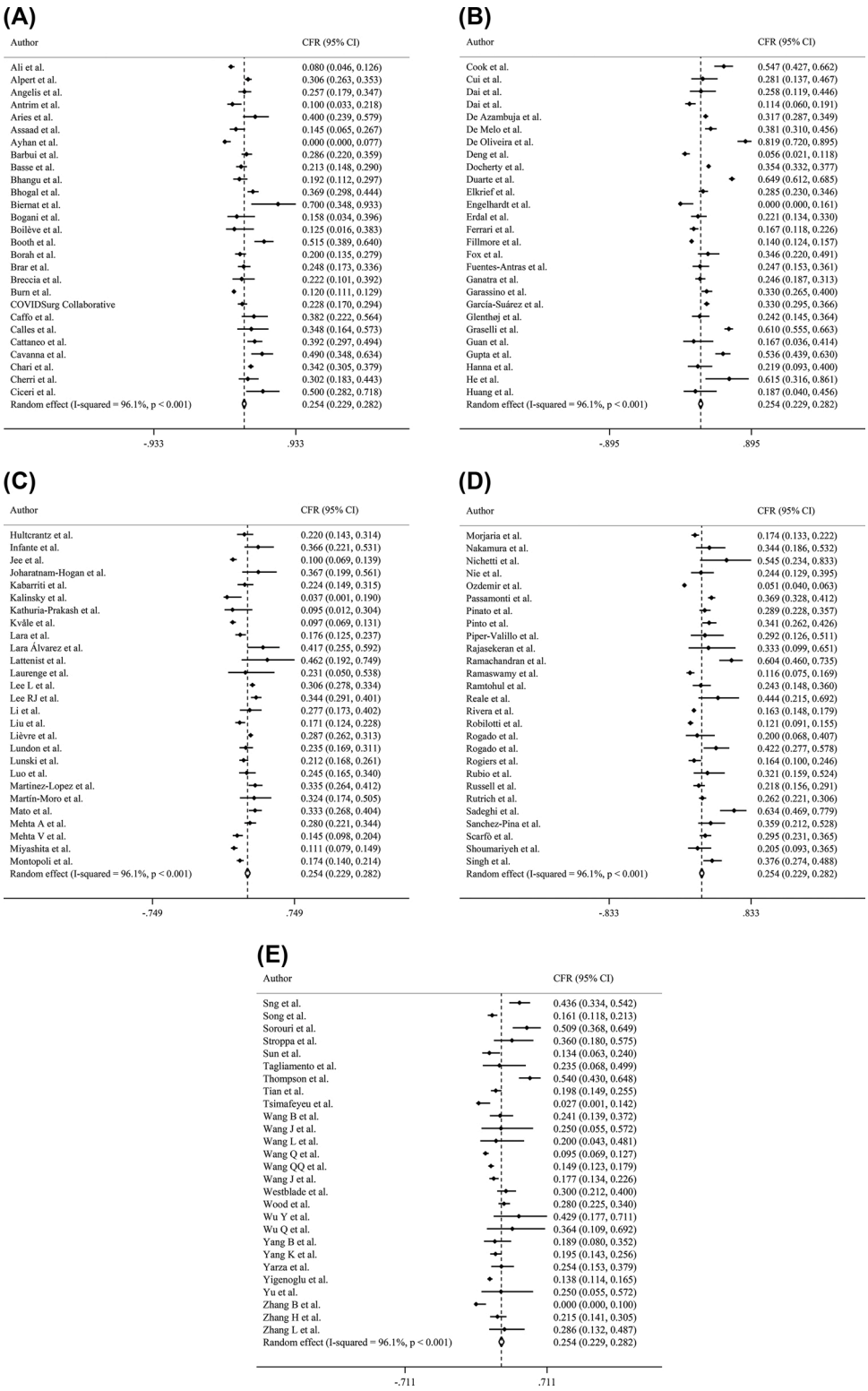

Fig. 1. (A, B, C, D, E). Forest plot of studies reporting the CFR among patients with solid or hematological malignancies and SARS-CoV-2 infection. (A) Authors from A to C. (B) Authors from C to H. (C) Authors from H to M. (D) Authors from M to S. (E) Authors from S to Z.
Abbreviations. CFR: case-fatality rate; 95% CI: 95% confidence interval.

19 patients with lung (N = 1,135) and breast (N = 1,296) cancers, respectively (Table 1). The CFR among patients with lung cancer and SARS-CoV2 infection was 32.4% (95% CI 26.5%–39.6%) when including all studies (Fig. 2) and 22.7% (95% CI 11.8%–43.8%) at the sensitivity analysis after excluding studies with less than 100 patients (Fig. S2). The CFR among patients with breast cancer and SARS-CoV2 infection was 14.2% (95% CI 9.3%–21.8%) when including all studies (Fig. 3) and 9.4% (95% CI 4.0%–22.4%) at the sensitivity analysis after excluding studies with less than 100 patients (Fig. S3).

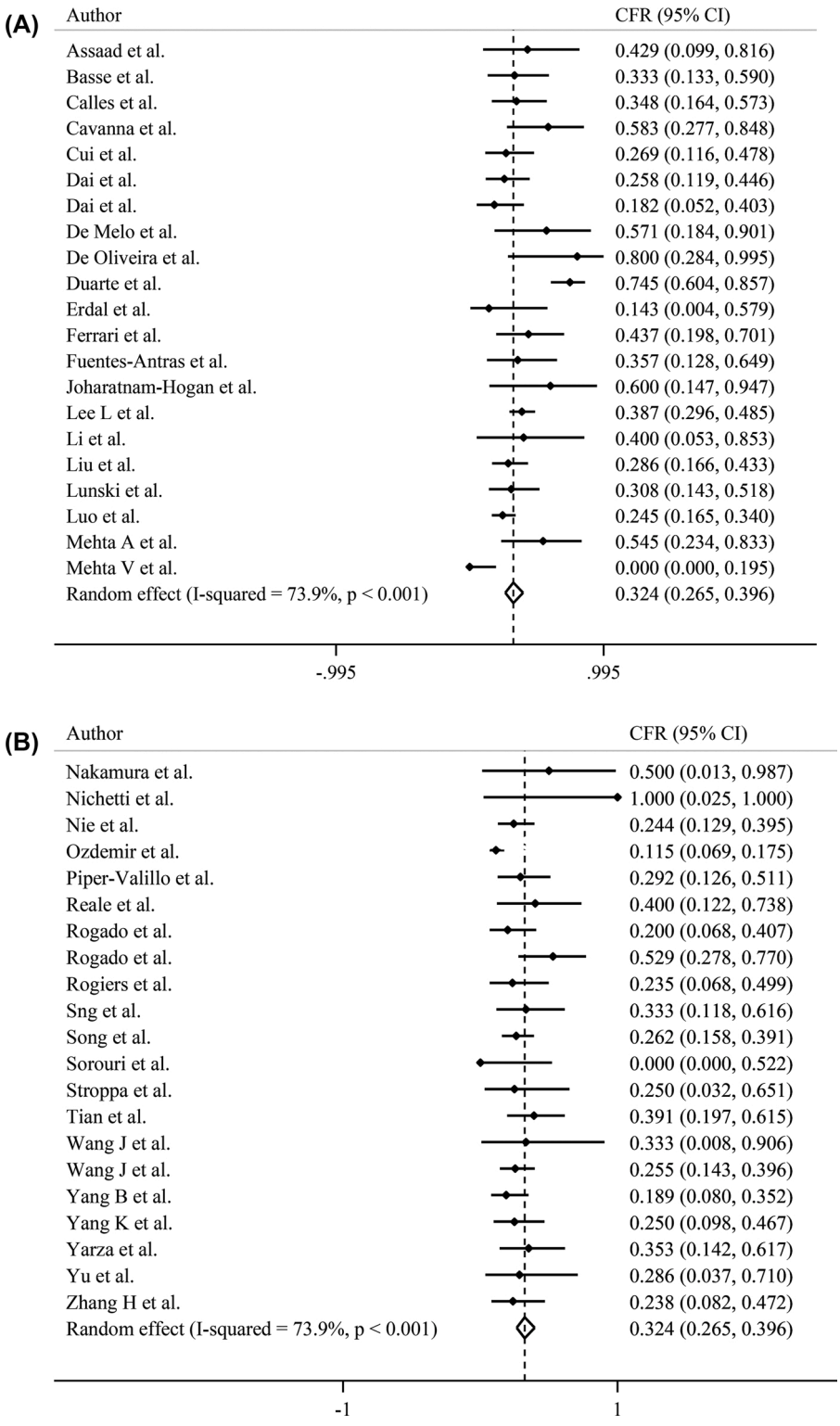

Fig. 2. (A, B). Forest plot of studies reporting the CFR among patients with lung cancer and SARS-CoV-2 infection. (A) Authors from A to M. (B) Authors from N to Z. *Abbreviations*. CFR: case-fatality rate; 95% CI: 95% confidence interval.

4. Discussion

Over a year after the outbreak of the pandemic, this large meta-analysis reports the impact of COVID-19 in patients with solid or hematological malignancies. Overall, these patients were found to have a high probability of mortality (CFR = 25.4%); the absolute rate was particularly high among patients with lung cancer (32.4%), while it was lower in those with breast cancer (14.2%). These findings strongly highlight the need to dedicate special attention to patients with cancer during the ongoing pandemic.

Overall, there is a growing evidence that patients with a history of cancer have a higher mortality rate due to COVID-19 as compared with the general population. Several international registries, such as the International Severe Acute Respiratory and Emerging Infections

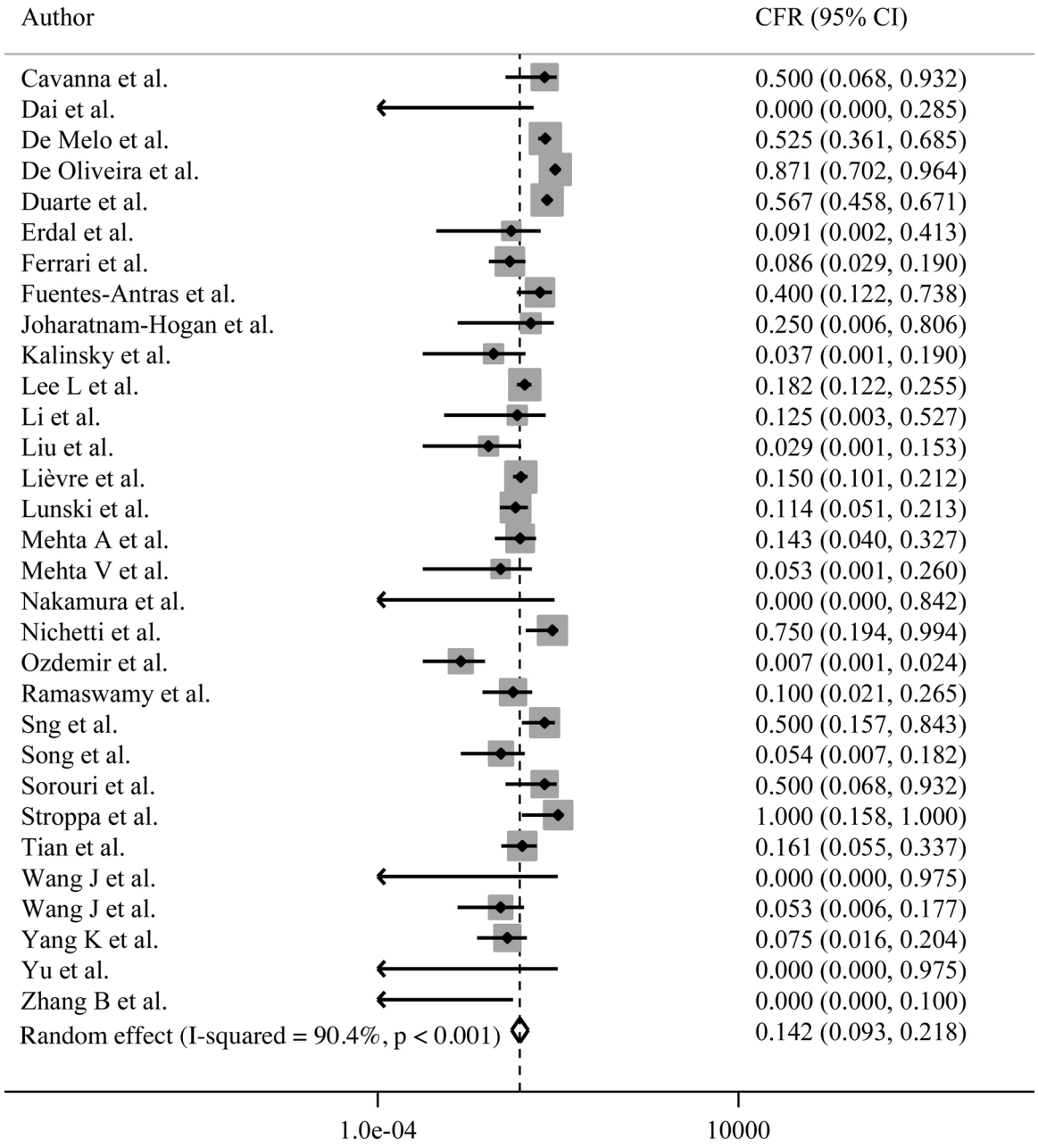

Fig. 3. Forest plot of studies reporting the CFR among patients with breast cancer and SARS-CoV-2 infection.
Abbreviations. CFR: case-fatality rate; 95% CI: 95% confidence interval.

Consortium (ISARIC) (Docherty et al., 2020), the OnCOVID (Pinato et al., 2020b), the Clinical impact of COVID-19 on patients with Cancer (CCC-19) (Kuderer et al., 2020), the GCO-002 CACOVID-19 (Lièvre et al., 2020), reported a mortality rate of oncological patients with SARS-CoV-2 infection up to 40% (Lee and Purshouse, 2021). The majority of these studies did not foresee a control group of patients with COVID-19 without cancer. Instead, a recent retrospective study, evaluating by a multivariate model the difference in mortality from COVID-19 between 312 patients with cancer and 4,833 patients without cancer in the U.S., found a higher death rate in the cancer group. Among patients with cancer, having an active or progressive disease was shown to increase the likelihood of mortality ($p < 0.001$) (Lunski et al., 2021). Our findings confirm a high mortality rate in patients with solid or hematological malignancies and SARS-CoV-2 infection.

Since the COVID-19 outbreak, major efforts have been implemented to protect most vulnerable patients from SARS-CoV-2 infection. Among them, the following measures have been suggested in cancer care: the rationalization of working practices, the adaptation of chemotherapy regimens as well as other systemic treatments, the deferral of procedures for diseases with favorable biology or not requiring urgent care, and additional measures related to specific subtypes of cancer (Poggio et al., 2020; Tagliamento et al., 2020b; Burki, 2020; Onesti et al., 2020, 2021). Aggressive preventive measures include preferential access to COVID-19 vaccination, which should be administered as early as possible (Garassino et al., 2021). Furthermore, ensuring cancer care continuity during the COVID-19 pandemic should represent a priority, considering treatment interruptions or discontinuations only on a case-by-case basis, taking into account patient and tumor characteristics (Lambertini et al.,

2020; Tagliamento et al., 2020a).

In our meta-analysis, patients with lung cancer had a comparatively higher CFR than the overall population, consistent with the data reported in the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry (not included in our separate analysis of the CFR in lung cancer, since patients with non-lung thoracic malignancies were included as well, like in the study by Lièvre et al.) (Garassino et al., 2020; Lièvre et al., 2020), and with previous reports in patients from China (Yu et al., 2020; Liang et al., 2020; Zhang et al., 2020b). Whether this high mortality rate may be reduced with special management of such patients in intensive care is an open question (Garassino et al., 2020).

On the contrary, a comparatively lower CFR was observed in patients with breast cancer, suggesting that breast cancer *per se* does not seem to be a major determinant of COVID-19 mortality. One potential explanation might be that patients with lung cancer tend to be older than those with breast cancer. Furthermore, co-existing pulmonary conditions might further raise the risk for an unfavorable outcome in patients with lung cancer diagnosed with COVID-19, as well as the different spectrum of anticancer treatments received compared to breast cancer. Conversely, the delays in cancer diagnosis and treatment due to the COVID-19 pandemic may have an impact on outcomes, considering that a significant proportion of the important gain in disease-specific overall survival observed in the last 20–30 years are attributable to early detection and improved treatments (Gathani et al., 2021). The long-term effect on cancer-specific survival outcomes of the temporary suspension of routine screening during the peak of the pandemic will be only and fully revealed in the future (Gathani et al., 2021).

Our meta-analysis has some limitations that should be acknowledged. It included heterogeneous cohorts, involving hospitalized and non-hospitalized patients, with both solid or hematological malignancies currently receiving or not active anticancer treatments (and different types) at the time of SARS-CoV-2 infection. Some studies only reported on in-hospital mortality, and sometimes exclusively on 30-day rate. Moreover, we evaluated the mortality rate considering death from any cause, instead of focusing specifically on death due to COVID-19 or due to cancer progression (this specific information was frequently unavailable in the studies included in the meta-analysis). As expected, the heterogeneity in the analyses was significant ($p < 0.001$) probably due to the high number of evaluated studies characterized by different study design, population, sample size, and the geographical variability in the spread of the pandemic. Nevertheless, notably, more than 75% of CFRs reported in the individual studies ranged between 10% and 39%, so our pooled estimate (CFR = 25.4%) reflects this trend.

Our study has also several strengths. The present meta-analysis included a large number of studies (n = 135) and patients (n = 33,879). All studies published in the first year since the start of the pandemic were evaluated. The CFR computed among the overall population is consistent with a previous analysis (Saini et al., 2020). In addition, we also separately focused on patients with lung and breast cancers, in order to evaluate the CFRs associated with these two common malignancies.

5. Conclusions

Our systematic review and meta-analysis showed that patients with solid or hematological malignancies and SARS-CoV-2 infection have a high probability of mortality, with a comparatively higher CFR in patients with lung cancer, and a comparatively lower CFR in patients with breast cancer. Based on these results, patients with underlying cancer deserve special attention with aggressive preventive measures that should also include early access to COVID-19 vaccination.

Authors' contribution

Conceptualization: Marco Tagliamento, Matteo Lambertini.

Data curation: Marco Tagliamento, Elisa Agostinetto, Marco Bruzzone, Marcello Ceppi, Francesca Poggio, Matteo Lambertini.

Formal analysis: Marco Bruzzone, Marcello Ceppi.

Methodology: Marco Tagliamento, Elisa Agostinetto, Marco Bruzzone, Marcello Ceppi, Francesca Poggio, Matteo Lambertini.

Project administration: Marco Tagliamento, Matteo Lambertini.

Validation: all authors.

Writing - original draft: Marco Tagliamento, Elisa Agostinetto, Matteo Lambertini

Writing - review & editing: all authors.

Disclosures

Dr. Tagliamento reported travel grants from Roche, Bristol-Myers Squibb, AstraZeneca, Takeda and Honoraria as medical writer from Novartis, Amgen outside the submitted work.

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Appendix A. Supplementary data

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