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REVIEW

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Comprehensive adjusted outcome data are needed to assess the impact of immune checkpoint inhibitors in cancer patients with COVID-19: Results of a systematic review and meta-analysis

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Abstract

Background: Determining how prior immune checkpoint inhibitor (ICI) therapy influences outcomes in cancer patients presenting with COVID-19 is essential for patient management but must account for confounding variables.

Methods: We performed a systematic review and meta-analysis of studies reporting adjusted effects of ICIs on survival, severe events, or hospitalisation in cancer patients with COVID-19 based on variables including age, gender, diabetes mellitus, hypertension (HTN), chronic obstructive pulmonary disease, and other comorbidities. When adjusted effects were unavailable, unadjusted data were analysed.

Results: Of 42 observational studies (38 retrospective), 7 reported adjusted outcomes for ICIs and 2 provided sufficient individual patient data to calculate adjusted outcomes. In eight studies, adjusted outcomes were based on ≤7 variables. Over all studies, only one included >100 ICI patients while 26 included <10. ICIs did not alter the odds ratio (95%CI) (OR) of death significantly (random effects model), across adjusted ($n = 8$) [1.31 (0.58–2.95) $p = 0.46$; $I^2 = 42\%$, $p = 0.10$], unadjusted ($n = 30$) [1.06 (0.85–1.32) $p = 0.58$; $I^2 = 0\%$, $p = 0.76$] or combined [1.09 (0.88;1.36) $p = 0.41$; $I^2 = 0\%$, $p = 0.5$)] studies. Similarly, ICIs did not alter severe events significantly across adjusted ($n = 5$) [1.20 (0.30–4.74) $p = 0.73$; $I^2 = 52\%$, $p = 0.08$], unadjusted ($n = 19$) [(1.23 (0.87–1.75) $p = 0.23$; $I^2 = 16\%$, $p = 0.26$] or combined [1.26 (0.90–1.77) $p = 0.16$; $I^2 = 25\%$, $p = 0.14$] studies. Two studies provided adjusted hospitalisation data and when combined with 13 unadjusted studies, ICIs did not alter hospitalisation significantly [1.19 (0.85–1.68) $p = 029$; $I^2 = 5\%$, $p = 0.40$]. Results of sensitivity analyses examining ICI effects based on 5 variables were inconclusive. Certainty of evidence was very low.

Abbreviations: COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; DM, diabetes; HR, Hazard ratio; HTN, hypertension; ICI, immune checkpoint inhibitor; ICI patients, patients that had previously received ICI therapy; IT, immunotherapies; non-ICI patients, patients that had not previously received ICI therapy; OR, odds ratio.

Conclusions: Across studies with adjusted and unadjusted results, ICIs did not alter outcomes significantly. But studies with comprehensive adjusted outcome data controlling for confounding variables are necessary to determine whether ICIs impact COVID-19 outcomes in cancer patients.

KEYWORDS
cancer, COVID-19, immune checkpoint inhibitors, immunotherapy, SARS-COV2d

1 | BACKGROUND

The incidence of severe disease and mortality with COVID-19 is higher in patients with cancer.[1-3] An unanswered question is whether prior immune checkpoint inhibitor (ICI) therapy, while highly effective for certain cancers, contributes to these worsened outcomes.[4-8] ICIs counter the immunosuppressive effects their targeted checkpoint molecules exert on innate and adaptive immune responses resulting in enhanced anti-tumour responses.[9,10] ICIs may also affect anti-viral responses.[11-14] However, the immune-related adverse events, including pneumonitis, that ICIs can produce and that occur days to months after treatment ends, could be precipitated by or complicate the intense inflammatory response COVID-19 produces in some patients.[6,15]

Determining whether prior ICI therapy has beneficial host defence or harmful inflammatory effects in cancer patients presenting with COVID-19 is critical for patient management.[4-8] There is an increasing number of published reports examining the impact of anti-cancer therapies, including ICIs, on outcomes for cancer patients with COVID-19. However, both cancer and non-cancer factors influence COVID-19 outcomes and confound assessment of ICI effects.[16-19] While an ideal study examining the impact of ICIs on COVID-19 outcomes would adjust for these variables and a systematic review addressing this question would focus on such adjusted studies, this has generally not been the case.[20-27] Among eight published systematic reviews of studies investigating cancer patients presenting with COVID-19 that previously received immunotherapies (IT) including ICIs, only 3 provided analyses of adjusted outcomes with IT, and each of these was based on five or fewer published studies.[20-27] Furthermore, only two of these systematic reviews specifically differentiated between ICIs and non-ICI ITs.[26,27] This distinction is essential since ICIs have different mechanisms of action and biologic effects than non-ICI ITs and in two recent studies, <10% of patients reportedly receiving ITs had received ICIs.[28,29] Of note, despite the rapidly increasing number of reports providing data on prior ICI treatment in cancer patients presenting with COVID-19, the two systematic reviews available so far examining this question included only 10 and 13 published reports respectively.[26,27] Therefore, the primary purpose of our systematic review was to analyse studies presenting the adjusted effects specifically of ICI therapy on either survival, a severe event, or need for hospitalisation in cancer patients presenting with COVID-19.

2 | METHODS

This systematic review was prepared using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement on guidance for literature review and data extraction (Supplementary-File A) and registered with the International Prospective Register of Systematic Reviews on 01/20/2021 (CRD42021222708). Additional methodologic details can be found in the Supplementary-Methods.

2.1 | Literature search and study inclusion

Published studies were retrieved and analysed that provided data on patients with cancer presenting with COVID-19 and that allowed a within study comparison of patients that had previously received ICI therapy (ICI patients) versus those who had not (non-ICI patients) regarding survival, severe events, or need for hospitalisation related to COVID-19. Severe events included either a composite severe event (i.e., any one of several outcomes such as respiratory failure, sepsis, or intensive care unit (ICU) admission defined and reported together as a severe event), development of respiratory failure (including Acute Respiratory Distress Syndrome or need for intubation/mechanical ventilation or non-mechanical ventilatory support), non-pulmonary organ failure or sepsis, or need for ICU admission. Using search terms and strategies listed in Supplementary-File B published studies were identified in the following databases from inception through 5/1/21 without language restrictions: PubMed, EMBASE, Scopus, and Web of Science. Title and abstract followed by full text reviews were conducted by two authors (S.J.M. and P.Q.E.) and disagreements resolved by a third author (P.T.P.). Recovered reports were hand searched for additional studies. Studies were included only when it could be confirmed from the publication or by correspondence with study authors, what the number and outcomes were of patients that had received ICI therapy as opposed to other ITs. Abstracts were not included.

2.2 | Data extraction

Two investigators (S.J.M. and P.Q.E.) independently extracted data from reports using a standardised extraction form (Supplementary-File C). These data, detailed fully in the Supplemental-Methods, included among others: numbers of patients that had or had not

previously received an ICI agent; whether ICIs had been administered alone or with another anti-cancer therapy; time from last ICI treatment to COVID-19 diagnosis; patient outcomes comparing ICI versus non-ICI patients including mortality, severe events and need for hospitalisation; duration and completeness of follow-up (i.e., proportion of patients follow-up was available for); whether a study's patient enrolment potentially overlapped with another study; and the methods (model and effect type and variables adjusted for) and results of adjusted analyses performed for the effects of ICI on the outcomes of interest. If more than one type of severe event type was reported in a study, only one was selected for analysis in the following hierarchical order; a composite severe event, development of respiratory failure, non-pulmonary organ failure or sepsis, or need for ICU admission. When sufficient individual patient data were available in reports for adjusted analysis, these were recorded.

2.3 | Quality of evidence and GRADE assessment

Two authors (S.J.M and P.Q.E) independently assessed included studies for quality of evidence using the nine-point Newcastle-Ottawa Scale tool (Supplementary-File D).[30] Disagreements were resolved by a third author (P.T.P.). GRADE analysis was performed to assess certainty of data.[31] Publication bias was assessed by funnel plot and Egger's regression.

2.4 | Statistical methods

Results from multivariable analyses were used when presented. Hazard ratio (HR) and relative risk (RR) were converted to odds ratio (95% CIs) (OR) (proportional hazard was assumed for HR). If multivariable analysis was not reported but individual patient data were provided, we performed multivariable logistic regression with these data if they included at least 10 subjects with the less frequent outcome and allowed adjustment for all of the following: age, gender and the presence or absence of hypertension (HTN), diabetes (DM), heart disease and chronic obstructive pulmonary disease (COPD). In one study that reported results from multivariable analyses for both ICI alone and ICI plus another anti-cancer agent, the results were combined for a single analysis.[32] If neither multivariable analysis or sufficient individual patient data for analysis were provided, unadjusted analysis was performed, and the ORs are presented and analysed. Heterogeneity among studies was assessed using the Q statistic and I^2 value. A random effects model was used to estimate the overall effects of ICI therapy in all analyses. Conventional forest plots were prepared, with the size of point estimates proportional to the inverse variance of each estimate. Five subgroup analyses were done using random-effects meta-analysis and adjusted and unadjusted results combined that compared studies with: <10 versus ≥10 ICI patients; patients receiving ICI therapy alone versus studies with patients receiving ICIs and another anti-cancer therapy; either only patients that had received an ICI <60 days before COVID-19 diagnosis or provided a mean or median time from last treatment to diagnosis of <60 days versus studies that included some or all patients who had received their last ICI within ≥60 days before the COVID-19 diagnosis; possible overlapping patient enrolments versus without overlap; and Newcastle-Ottawa scores ≥7 versus <7.[30] These subgroup analyses were based on the following rationales: small studies are inherently at risk for imprecision and prior systematic reviews have excluded studies with <10 patients receiving IT; patients requiring ICIs with other anti-cancer therapies might have advanced cancer and worsened outcomes; more recent versus more remote exposure to ICIs might affect the risk of immune-related adverse events; patients included repetitively in more than one study might influence analysed outcomes; risk of bias and study quality might impact study results. Studies not reporting data for these subgroups were not included in the respective sensitivity analysis. We used SAS version 9.4 for the multivariable analysis of individual patient data. Meta-analyses were conducted using *R* (version 4.0.3)[33] and packages *meta* (version 4.16–2)[34] and *metaphor* (version 2.4–0).[35]

3 | RESULTS

3.1 | Summary of retrieved studies

Of 20,980 retrieved reports, 42 met study inclusion criteria[28,29,32,36-74] (Supplementary-Figure 1). Study authors responded to requests to clarify the numbers and outcomes of IT patients receiving ICI therapy for 13 included reports[28,29,42,43,45,48-50,57,61,62,66,67] but not for 13 other reports which were excluded. Published data allowed determination of ICI patient numbers and outcomes in all other included studies.

Table 1 summarises study characteristics including country, centre number, cancer type, COVID-19 diagnosis-method, patient location, data source and enrolment dates. Total length of follow-up ranged from 12 to 218d in studies, but follow-up duration and completeness were unclear in 18 studies. All studies were observational, 34 were solely retrospective, and 4 included retrospective and prospective patients. Seven studies provided adjusted results for one or more outcome and two studies provided sufficient individual patient data for adjusted analyses. Only four studies specifically focussed on prior ICI therapy alone and two of these reported adjusted outcomes.

3.2 | Quality of evidence

Of the 42 studies analysed, 19 had Newcastle-Ottawa scale scores of ≥7 and 23 had scores of <7 (Supplementary-Table 1). Among the 19 studies with higher scores, only two received a score of 9, while 14 did not appear to provide a 30d follow-up or were not clear whether follow-up of all patients was complete, and 4 studies did not control for cancer type or other factors potentially influencing comparisons

TABLE 1 Study characteristics

Study [Author(y)[ref]]	Country	Number of centres	Patient location	Study design[data source]	Cancer types studied	COVID-19 diagnosis criteria	Dates of enrolment	Reported length of follow-up period (d)	Stated purpose of the study is to examine the effect of ICIs on outcomes	Study provided adjusted or patient level data
Albiges ('20)[36]	France	1	In/Out	Retro[a]	Mixed	PCR+/Clin	3/24/20–4/29/20	23 (13, 33)[b]	No	NR
Angelis ('20)[37]	UK	4	In/Out	Pro[a]	Mixed	PCR+	3/1/20–4/30/20	UC	No	NR
Assad ('20)[38]	France	1	In/Out	Retro[a]	Mixed	PCR+	3/1/20–4/15/20	25[c]	No	NR
Calles ('20)[39]	Spain	1	In/Out	Retro[a]	Lung	PCR+	2/24/20–5/12/20	30	No	NR
Crolley ('20)[40]	UK	2	In/Out	Retro[a]	Mixed	PCR+/Clin	3/2/20–5/31/20	UC	No	NR
Dai ('20)[41]	China	14	In	Retro[a]	Mixed	PCR+/Clin	1/1/20–2/24/20	0[d]	No	Pt level
de Joode ('20)[42]	Netherlands	45	In	Retro	Mixed	PCR+/Clin	3/2/20–5/4/20	UC	No	NR
Di Cosimo ('21)[43]	Italy	26	In/Out	Retro[a]	Mixed	PCR+	3/1/20–9/30/20	138 (12–218)[e]	No	NR
Fillmore ('21)[44]	US	US VAs	In/Out	Retro	Mixed	PCR+	1/1/20–5/4/20	UC	No	NR
Fuentes-Antras ('20)[45]	Spain	1	In	Pro[a]	Solid	PCR+	2/21/20–5/8/20	UC	No	NR
Garassino ('20)[32]	Internat	87	In/Out	Pro	Thoracic	PCR+/Clin	3-26-20–4/12/20	15 (8–24)[f]	No	NR
Gonzalez-Cao ('21)[46]	Spain	26	In/Out	Retro	Melanoma	PCR+/Clin	4/1/20–5/17/20	UC	Yes	NR
Goudsmit ('21)[47]	Belgium	1	In/Out	Retro[a]	Mixed	PCR+/Clin	3/10/20–5/18/20	UC	No	NR
Grivas ('21)[48]	US, Canada	79	In/Out	Retro	Mixed	PCR+	3/17/20–11/18/20	42 (22, 90)[b]	No	NR
Hanna ('21)[49]	US	2	In/Out	Retro[a]	Head/neck	PCR+	3/11/20–6/1/20	UC	No	NR
Jee ('21)[50]	US	1	In/Out	Retro[a]	Mixed	PCR+	3/8/20–6/2/20	28[g]	No	NR
Kalinsky ('20)[51]	US	1	In/Out	Retro[a]	Breast	PCR+/Clin	3/10/20–4/29/20	26 (1, 38)[e]	No	NR
Klebanov ('21)[52]	US	1	In/Out	Retro	Mixed	PCR+	3/1/20–6/19/20	UC	Yes	Adj
Lara ('20)[53]	US	6	In/Out	Retro[a]	Gyn	PCR+/Clin	3/1/20–4/22/20	UC	No	Adj
Lee ('20)[54]	UK	55	In/Out	Pro	Mixed	PCR+	3/18/20–4/26/20	5 (0–38)[h]	Anti-cancer Rxs	Adj
Luo ('20)[54]	US	1	In/Out	Retro[a]	Lung	PCR+/Clin	3/12/20–4/13/20	14 (7, 23)[b]	Yes	Adj
Mandala ('21)[56]	Italy	1	In/Out	Pro/Retro[a]	Mixed	PCR+	3/5/20–5/18/20	UC	Yes	NR
Mehta A. ('21)[28]	India	1	In	Retro[a]	Mixed	PCR+	6/8/20–8/20/20	63	No	NR
Mehta V. ('20)[57]	US	1	In	Retro[a]	Mixed	PCR+	3/18/20–4/8/20	UC	No	NR
Nakamura ('20)[58]	Japan	1	In	Retro[a]	Mixed	PCR+	1/31/20–5/25/20	UC	No	NR
Nichetti ('20)[59]	Italy	1	In/Out	Pro[a]	Solid	PCR+/Clin	2/16/20–4/10/20	UC	Anti-cancer Rxs	NR
Nie ('20)[60]	China	12	In	Retro[a]	Lung	PCR+	1/3/20–5/6/20	UC	No	NR

TABLE 1 (Continued)

Study [Author(y)[ref]]	Country	Number of centres	Patient location	Study design[data source]	Cancer types studied	COVID-19 diagnosis criteria	Dates of enrolment	Reported length of follow-up period (d)	Stated purpose of the study is to examine the effect of ICIs on outcomes	Study provided adjusted or patient level data
Pinato ('20)[61]	Germany, Italy, Spain, UK	19	In/Out	Retro[i]	Mixed	PCR+	2/26/20–4/1/20	19 ± 16[j]	No	NR
Pinto ('20)[62]	Italy	4	In	Retro	Mixed	PCR+	2/1/20–4/3/20	87[k]	No	NR
Robilotti ('20)[63]	US	1	In/Out	Retro[a]	Mixed	PCR+	3/10/20–5/7/20	≥30	No	Adj
Rogado ('20)[64]	Spain	1	In/Out	Retro[a]	Mixed	PCR+/Clin	2/1/20–4/7/20	UC	No	NR
Russell ('20)[65]	UK	1	In/Out	Pro/Retro[a]	Mixed	PCR+	2/29/20–5/12/20	37 (18, 49)[b]	No	NR
Singh ('20)[66]	US	1	In	Retro[a]	Mixed	PCR+	3/10/20–4/17/20	16[k]	No	NR
Sng ('20)[67]	UK	1	In	Retro[a]	Solid	PCR+	3/1/20–5/31/20	18 (8–44)[e]	Anti-cancer Rxs	Adj
Stroppa ('20)[68]	Italy	1	In	Retro[a]	Mixed	PCR+	2/21/20–3/18/20	15d after DC	No	NR
Trapani ('20)[69]	Italy	1	In/Out	Retro[a]	Mixed	PCR+	2/1/20–4/2/20	UC	No	NR
Wang ('20)[70]	China	1	In	Retro[a]	Mixed	PCR+	12/30/19–3/10/20	UC	No	NR
Wood ('20)[29]	Internat	Multi	In/Out	Retro	Heme	PCR+/Clin	4/1/20–7/8/20	UC	No	NR
Yarza ('20)[71]	Spain	1	In	Pro/Retro[a]	Solid	PCR+/Clin	3/9/20–4/19/20	UC	Anti-cancer Rxs	Adj
Yu ('20)[72]	China	1	In	Retro[a]	Solid	PCR+/Clin	12/30/19-2/17/20	UC	No	NR
Zhang, H ('20)[73]	China	5	In	Retro[a]	Mixed	PCR+/Clin	1/5/20–3/18/20	UC	No	Pt level
Zhang, L ('20)[74]	China	3	In	Retro[a]	Solid	PCR+	1/13/20–2/26/20	UC	No	NR

Abbreviations: Adj, Adjusted; ASH, American Society of Haematology; CCC19 Reg, COVID-19 and Cancer Consortium; Clin, patient met clinical criteria for COVID-19; d, days; DC, discharge; DOCC, Dutch Oncology COVID-19 Consortium; GEM, Spanish melanoma registry; Heme, haematological malignancies; In, in patient; Internat, international; MGH, Massachusetts General Hospital registry; Mixed, solid and haematological cancers; Multi, multiple centres; Out, out patient; PCR+, patients included based on positive SARS-CoV-2 PCR test; PCR+/Clin, patients included based on PCR + test and/or clinical criteria; Pro, prospective; Pt, patient; Ref, reference number; RET, Reggio Emilia Tumour; Retro, retrospective; Rx, therapy; Solid, solid tumours; TERAVOLT Reg, Thoracic Cancers International COVID-19 Collaboration registry; UC, Unclear; UKCCMP, UK Coronavirus Cancer Monitoring Project; VA CDW, Veterans Administration Corporate Data Warehouse; VA, Veterans Administration.

[a]Chart review.

[b]median and interquartile range.

[c]median.

[d]follow-up ended on the last day of enrolment.

[e]median and range.

[f]median (and interquartile range) follow-up since COVID-19 diagnosis.

[g]follow-up time period of all survivors.

[h]median time (range) from COVID-19 diagnosis to the time endpoints met.

[i]OnCOVID Reg.

[j]mean and standard deviation.

[k]follow-up past final enrolment.

of ICI versus non-ICI patients. All 9 studies that provided adjusted outcomes or individual patient data for adjusted analysis had scores ≥7. Scores <7 in studies were due to both inadequate comparability of study groups and unclear or insufficient follow up.

3.3 | Mortality

Thirty-eight studies provided data allowing comparison of mortality in ICI versus non-ICI patients (Figure 1, Supplementary-Table 2). Six

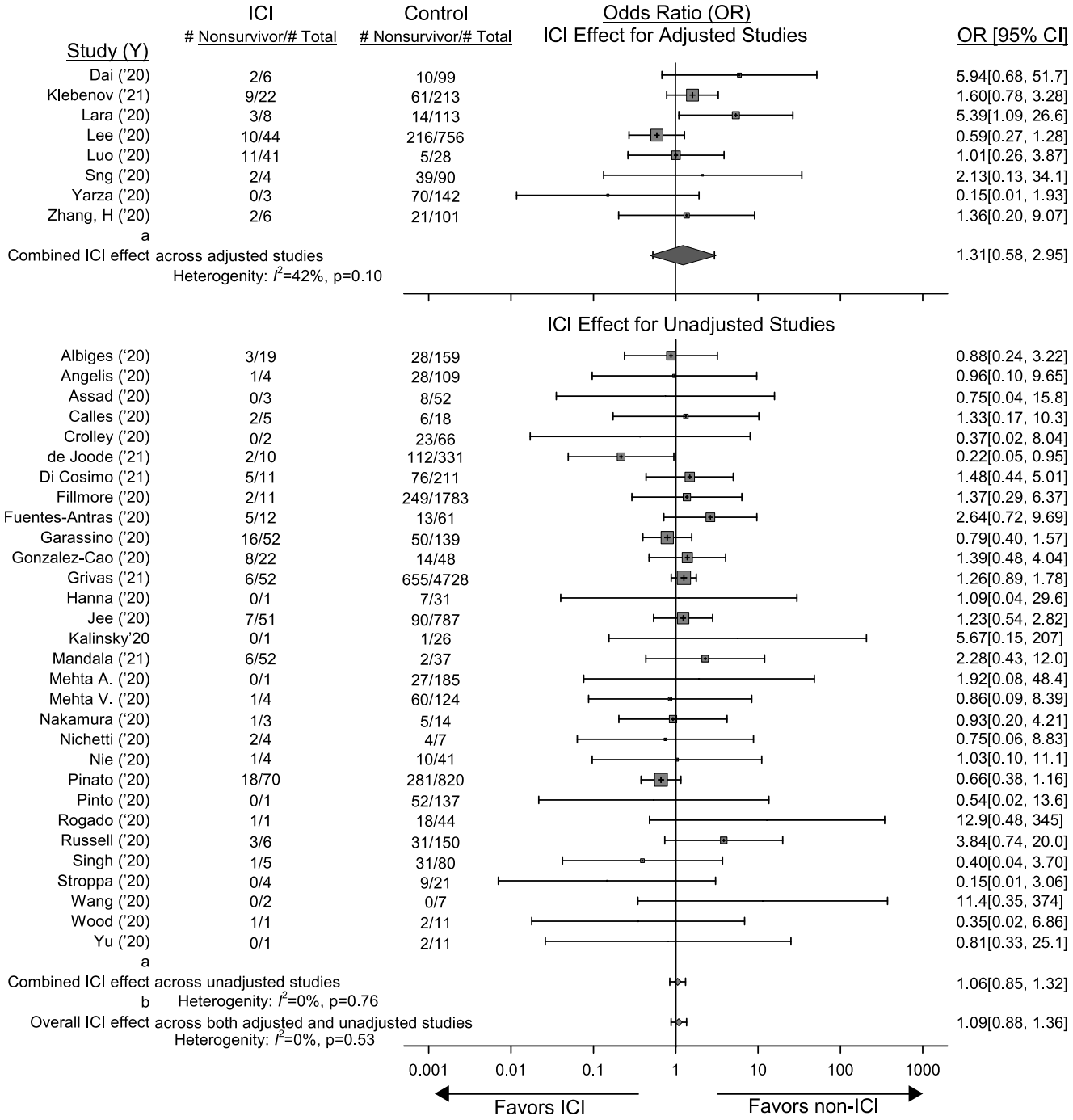

FIGURE 1 Forrest plot showing the effect of prior immune checkpoint inhibitor (ICI) therapy on the odds ratio [OR (95% CI)] of death in studies providing data on cancer patients presenting with COVID-19 that had or had not previously received ICIs. Also shown are the total numbers of patients (Total) and the number of non-survivors (NS) in patients that had or not previously received ICI. Shown at the top are the adjusted effects of ICIs on the OR of death in the eight studies reporting these data and the combined OR and I^2 value (random effects model). See Table 2 for the models, variables and effect types reported in these studies. Effects were converted to the OR of death for all studies as described in the methods. Shown at the bottom are the unadjusted effects of ICIs on the OR of death from 30 studies that provided data allowing this calculation and the combined OR and I^2 value. The effects of ICIs did not differ significantly ($p = 0.56$) comparing studies with adjusted and unadjusted results and the overall OR of death and I^2 value for all 38 studies is shown at the very bottom of the figure

of these included adjusted outcomes, and two reported sufficient individual patient data to perform adjusted analyses (Tables 1 and 2). Three of these eight studies included >10 ICI patients. Studies adjusted for seven or fewer variables (Table 2). The most common variables included age, gender, HTN, COPD, DM, and heart disease.

The effects of ICI therapy on the odds ratios (95% CI) (OR) of death across the eight studies with adjusted results were not significant [combined OR 1.31 (0.58; 2.95), $p = 0.46$] although there was moderate but non-significant heterogeneity ($I^2 = 42\%$, $p = 0.10$) (Figure 1). ICI's effects on the OR of death across the 30 studies with unadjusted outcome data were also not significant [1.06 (0.85; 1.32), $p = 0.58$] but were consistent ($I^2 = 0\%$; $p = 0.76$)]. Adjusted versus unadjusted effects did not differ ($p = 0.56$) and over the 38 studies were not significant [1.09 (0.88;1.36) $p = 0.41$; $I^2 = 0\%$, $p = 0.53$)].

Characteristics from individual studies employed in four of the five sensitivity analyses are shown in Supplementary-Table 3. Data on the Newcastle Ottawa score is noted above. As shown in Table 3, the OR of death was increased in studies where some or all patients received ICI therapy within ≥60d before COVID-19 diagnosis versus patients only receiving ICI therapy <60d or a mean or median time to treatment <60d before COVID-19 diagnosis ($p = 0.04$). Study

TABLE 2 Summary of effect type, model, ICI patient numbers and variables included in studies presenting adjusted outcome analysis data or used in analysis of individual patient data from studies for either survival, severe events, or need for hospitalisation

Author(y)[Ref]	Effect type	Model	ICI patient number	Variables included in multivariate analysis
Survival				
Studies providing adjusted outcome data				
Klebanov ('21)[52]	OR	Logistic regression	22	Age, gender, race, cancer category, CCI severity grade, median income, local infection
Lara ('20)[53]	RR	Poisson regression	8	Age, race, number of comorbidities, performance status, smoking history
Lee ('20)[54]	OR	Logistic regression	44	Age, gender, DM, HTN, COPD, other comorbidities
Luo ('20)[55]	OR	Logistic regression	40	Gender, smoking history
Sng ('20)[67]	HR	Cox proportional hazards	4	Age, HTN, CVD
Yarza ('20)[71]	OR	Logistic regression	8	Age, HTN, CVD
Studies providing individual patient data				
Dai ('20)[41]	OR	Logistic regression	6	Age, gender, DM, HTN, COPD, other comorbidities
Zhang, H ('20)[73]	OR	Logistic regression	6	Age, gender, DM, HTN, COPD, other comorbidities
Severe events				
Studies providing adjusted outcome data				
Luo ('20)[55,a]	OR	Logistic regression	40	Gender, smoking history
Robilotti ('20)[63,b]	HR	Logistic regression	31	Age, sex, race, DM, HTN, CVD, COPD/asthma, and 9 others[c]
Yarza ('20)[71,b]	OR	Logistic regression	8	Age, HTN, CVD
Studies providing individual patient data				
Dai ('20)[41,a]	OR	Logistic regression	6	Age, gender, DM, HTN, COPD, other comorbidities
Zhang, H ('20)[73,a]	OR	Logistic regression	6	Age, gender, DM, HTN, COPD, other comorbidities
Need for hospitalisation				
Studies providing adjusted outcome data				
Luo ('20)[55]	OR	Logistic regression	40	Gender, smoking history
Robilotti ('20)[63]	OR	Logistic regression	31	Age, sex, race, DM, HTN, CVD, COPD/asthma, and 9 others[c]

Abbreviations: CCI, Charlson Comorbidity Index; CVD, cardiovascular disease; HR, hazards ratio; OR, odds ratio; RR, relative risk.

[a]Composite severe event.

[b]Respiratory failure severe event.

[c]Chronic kidney disease, BMI, smoking status, cancer type and metastases, major surgery ≤30d, systemic chemo ≤30d, chronic lymphopenia, chronic steroids, ICI ≤ 90d.

TABLE 3 Results of sensitivity analyses

Mortality		
Studies (n) with <10 patients versus ≥10 patients		
<10 patients (n = 24)	≥10 patients (n = 14)	p = 0.29
1.36 (0.85, 2.18) (I^2 = 0%)	1.03 (0.78, 1.36) (I^2 = 18%)	
Studies (n) with ICI given within <60d versus ≥60d[a]		
<60d (n = 18)[b]	≥60d (n = 12)[b]	p = 0.04
0.86 (0.60, 1.23) (I^2 = 18%)	1.26 (1.05, 1.53) (I^2 = 0%)	
Studies (n) with ICI alone versus ICI + other[a]		
ICI alone (n = 9)[c]	ICI + other (n = 17)[c]	p = 0.39
1.58 (0.82, 3.04) (I^2 = 0%)	1.18 (0.80, 1.76) (I^2 = 7%)	
Studies (n) with potential overlap versus no potential overlap		
No overlap (n = 27)	Overlap (n = 11)	p = 0.42
1.23 (0.98, 1.53) (I^2 = 0%)	1.01 (0.62, 1.64) (I^2 = 29%)	
Studies (n) with NOS ≥ 7 versus < 7		
≥7 (n = 15)	<7 (n = 23)	p = 0.46
1.25 (0.78, 1.99) (I^2 = 11%)	1.04 (0.81, 1.33) (I^2 = 0%)	
Severe events		
Studies (n) with <10 patients versus ≥10 patients		
<10 patients (n = 14)	≥10 patients (n = 10)	p = 0.83
OR 1.35 (0.72, 2.55) (I^2 = 0%)	OR 1.25 (0.77, 2.03) (I^2 = 53%)	
Studies (n) with ICI given within <60d versus ≥60d[a]		
<60d (n = 15)[d]	≥60d (n = 8)[d]	p = 0.61
1.19 (0.81, 1.75) (I^2 = 0%)	1.42 (0.72, 2.82) (I^2 = 62%)	
Studies (n) with ICI alone versus ICI + other[a]		
ICI alone (n = 7)[e]	ICI + other (n = 12)[e]	p = 0.83
1.89 (0.95, 3.76) (I^2 = 0%)	1.76 (1.18, 2.63) (I^2 = 0%)	
Studies (n) with potential overlap versus no potential overlap		
No overlap (n = 16)	Overlap (n = 8)	p = 0.02
0.88 (0.55, 1.41) (I^2 = 2%)	1.66 (1.11, 2.47) (I^2 = 0%)	
Studies (n) with NOS ≥ 7 versus < 7		
≥7 (n = 13)	<7 (n = 11)	p = 0.33
1.54 (0.80, 2.96) (I^2 = 19%)	1.10 (0.75, 1.62) (I^2 = 22%)	
Need for hospitalisation		
Studies (n) with < 10 patients versus ≥10 patients		
<10 patients (n = 8)	≥10 patients (n = 7)	p = 0.91
1.17 (0.54, 2.53) (I^2 = 0%)	1.23 (0.71, 2.11) (I^2 = 47%)	
Studies (n) with ICI given within <60d versus ≥60d[a]		
<60d (n = 5)[d]	≥60d (n = 9)[d]	p = 0.22
1.67 (0.64, 4.38) (I^2 = 60%)	1.05 (0.74, 1.50) (I^2 = 0%)	
Studies (n) with ICI alone versus ICI + other[a]		
ICI alone (n = 7)[f]	ICI + other (n = 6)[f]	p = 0.02
2.22 (1.08, 4.55) (I^2 = 0%)	1.06 (0.77, 1.45) (I^2 = 0%)	

Studies (n) with potential overlap versus no potential overlap		
No overlap (n = 10)	Overlap (n = 5)	p = 0.03
0.88 (0.68, 1.14) (I^2 = 58%)	1.50 (0.82, 2.75) (I^2 = 0%)	
Studies (n) with NOS ≥ 7 versus < 7		
≥7 (n = 8)	7 (n = 7)	p = 0.85
1.20 (0.62, 2.31) (I^2 = 4%)	1.12 (0.70, 1.81) (I^2 = 0%)	

Abbreviations: NA, not applicable; NOS, Newcastle Ottawa score; NR, not reported.
[a]See text for criteria subgroups were based on.
[b]data not reported in 8 studies with this outcome.
[c]data not reported in 12 studies with this outcome.
[d]data not reported in 1 study with this outcome.
[e]data not reported 5 studies with this outcome.
[f]data not reported in 2 studies with this outcome.

subgroups did not differ significantly in the other four sensitivity analyses (p = 0.29–0.46).

3.4 | Severe events

Twenty-four studies provided data comparing severe events in ICI versus non-ICI patients including a composite severe event (see methods) in 17 studies, respiratory failure in 4 studies, and ICU admission for 3 studies (Figure 2, Supplementary-Table 2). Three studies reported adjusted outcomes, and two included sufficient individual patient data to perform adjusted analyses. Two of these studies had ≥10 ICI patients. While one study adjusted for up to 16 variables, the other 4 studies included the number and types of variables as in the survival analysis (Table 2).

The effects of ICI therapy on OR of severe events across the five studies with adjusted outcome results were not significant but had moderate heterogeneity that did not reach significance [1.20 (0.30; 4.74), p = 0.73; I^2 = 52%; p = 0.08)]. Across the 19 studies with unadjusted outcome data, ICI effects on the OR of severe events were also not significant [(OR 1.23 (0.87; 1.75), p = 0.23; I^2 = 16%, p = 0.26). ICI effects did not differ comparing adjusted versus unadjusted studies (p = 0.96) and, when combined across all 24 studies, the OR of severe events with ICIs was still not significant although there was moderate heterogeneity [(1.26 (0.90, 1.77), p = 0.16; I^2 = 25%, p = 0.14]. Sensitivity analyses were performed on the same subgroups as for mortality (Table 3, Supplementary-Table 3). In studies with possible overlapping patent enrolments, the OR of severe events was increased (p = 0.02) in ICI patients. Study subgroups did not differ significantly in the remaining four sensitivity analyses (p = 0.33–0.83).

3.5 | Hospitalisation

Fifteen studies provided data comparing need for hospitalisation in ICI versus non-ICI patients (Figure 2, Supplementary-Table 2). Only two studies included adjusted outcome results, and none provided individual patient data for adjusted analysis. Therefore, adjusted and unadjusted results were analysed together. Across the 15 studies, ICI therapy was not associated with a significant effect on the OR of hospitalisation [1.19 (0.85; 1.68), p = 0.29; I^2 = 5%, p = 0.40]. In sensitivity analyses, ICI therapy had an increased effect on the OR of hospitalisation in studies with ICI therapy alone versus studies with ICI therapy with another anti-cancer treatment (p = 0.02) and studies with versus without possible overlapping patient enrolment (p = 0.03) but not the other 3 analyses (p = 0.22–0.91) (Table 3, Supplementary-Table 3).

3.6 | Certainty of evidence (GRADE) and publication bias

Because all studies analysed here were observational and most were retrospective, the overall certainty of evidence presented starts at a low level.[75] Certainty of evidence was further downgraded to *very low*, based on risk of bias, inconsistency, indirectness, and/or imprecision, for four of the five GRADE criteria for each of the three outcomes assessed (Supplementary-Table 4). Overall, a high proportion of studies (23 of 42%, 55%) had Newcastle-Ottawa scale scores <7 and a potential for risk of bias (Supplementary-Table 1). There was moderate or greater heterogeneity (I^2 ≥ 42%) among adjusted studies for survival and severe events. Overall, results were indirect since only 4 studies (10%) specifically examined the impact of ICI therapy on outcomes,[46,52,55,56] and 13 studies required clarification from authors regarding the number and outcomes of patients receiving ICIs among all IT patients.[28,29,42,43,45,48-50,57,61,62,66,67] Finally, these findings are imprecise since only 1 study included >100 ICI patients while 37 had <50 and 26 had <10 ICI patients. Based on funnel plots and Egger's regression analysis (p = 0.66, 0.31 and 0.19 for mortality, severe events and hospitalisation respectively) the outcome results did not appear subject to publication bias (Supplementary-Figure 2).

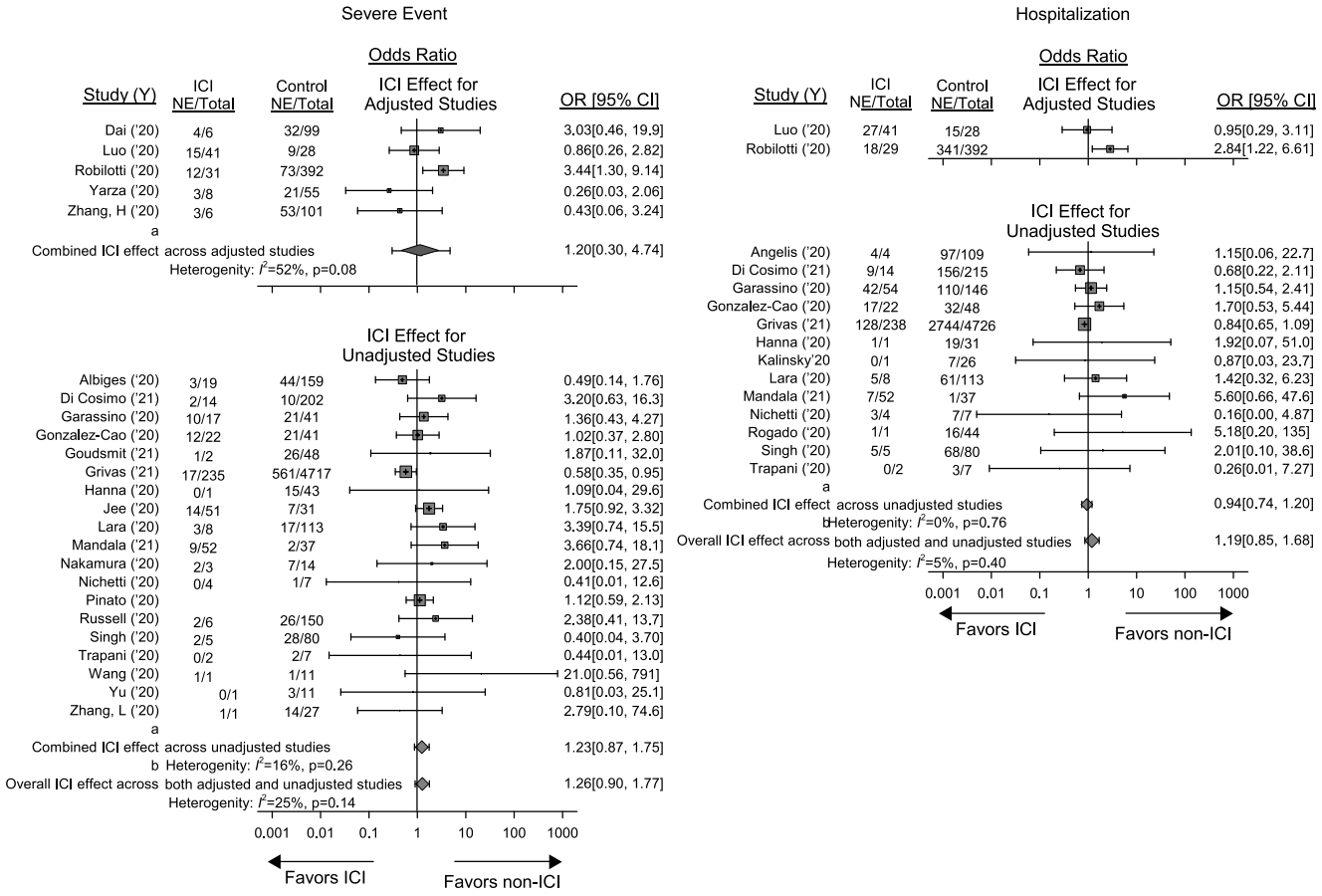

FIGURE 2 Forrest plots showing the effect of prior immune checkpoint inhibitor (ICI) therapy on the odds ratio [OR (95% CI)] of severe events and need for hospitalisation in studies providing data on cancer patients presenting with COVID-19 that had or had not previously received ICIs. Also shown for each outcome are the total numbers of patients (Total) and the number of patients with either event (NE) that had or not previously received ICI. For severe events, shown at the top are the adjusted effects of ICIs on the OR of a severe event in five the studies reporting these data and the combined adjusted OR and I^2 value (random effects model). See Table 2 for the models, variables and effect types reported in these studies. Effects were converted to the OR of a severe event for all studies as described in the methods. Shown at the bottom are the unadjusted effects of ICIs on the OR of a severe event from 19 studies that provided data allowing this calculation and the combined OR and I^2 value. The effects of ICIs did not differ significantly ($p = 0.96$) comparing studies with adjusted and unadjusted results and the overall OR and I^2 value of a severe event for all 24 studies is shown at the very bottom of the panel. For hospitalisation, only 2 studies reported the adjusted effects of ICIs on the need for this and no combined OR was calculated for these two. Thirteen studies provided unadjusted OR for hospitalisation and the combined OR and I^2 value for these studies are shown. The adjusted effects of ICs in the two studies did not differ significantly ($p = 0.25$) from the unadjusted effects from the 13 studies that allowed this calculation and the overall effect of ICIs on the OR (95%CI) and I^2 value of hospitalisation for all 15 studies is shown at the very bottom of the panel

4 | DISCUSSION

In this systematic review and meta-analysis, across 9 studies presenting adjusted outcome data and 33 studies with unadjusted results, there was no clear evidence that prior ICI therapy altered survival, the incidence of severe events or need for hospitalisation in cancer patients presenting with COVID-19. Sensitivity analyses examining ICI effects based on 5 variables were inconclusive. While eight other published systematic reviews have examined IT in this patient group, the present one has notable strengths: it is the most recent study; it included three to four times the number of reports in the final analysis of mortality and severe events; it examined two times the number of published studies with adjusted outcome data and almost five times the number of studies with ICI patients alone (Supplementary-Table 5).[20-27] Unfortunately, GRADE analysis demonstrated that even with this increasing body of data the certainty of evidence regarding the effects of ICIs in cancer patients with COVID-19 is very low.

The literature has repeatedly emphasised the need to determine whether prior ICI therapy impacts outcomes in cancer patients with COVID-19.[4-8] When treating patients with COVID-19 pneumonia, any theoretical anti-viral effect that ICIs exert must be weighed against the well documented immune-related adverse events, including pneumonitis, that ICIs can produce.[6,11-15] There is growing concern of probable synergy, or an inability to distinguish between COVID-19 pneumonitis and pneumonitis as an adverse event ICI therapy.[76] Additionally, as a result of reinvigorated T-cells, patients on ICIs might have an increased risk of cytokine

release syndrome, an important cause of mortality in COVID-19.[77] If harmful, besides implications for discontinuation of ICI therapy, this determination would influence the management of worsening organ injury in infected patients, such as possibly supporting earlier corticosteroid use for pneumonitis.[78] Alternatively, if ICIs exert a beneficial host defence effect as proposed for other viral infections, continued or even initiation of ICIs might be considered.[11-14]

The present study highlights the weaknesses in currently available data to assess the impact of ICI therapy on COVID-19 outcomes. Thirty-eight of the studies analysed were solely or partially retrospective ones. Only four studies specifically examined the effects of ICIs on the outcomes of cancer patients with COVID-19. Only one study included more than 100 ICI patients and 26 (62%) had <10 patients. Despite the complexity of cancer patients with COVID-19, eight of the nine studies providing adjusted outcome data controlled for seven or fewer variables. There were not sufficient data to examine the effects of specific ICI regimens. While sensitivity analysis suggested some associations with timing of ICI treatment, treatment regimen, and studies with potential overlapping patient enrolment, these findings were not consistent across all three outcomes and are difficult to interpret.

Overall, the present analysis indicates that more comprehensive observational studies will be required to determine how ICIs impact COVID-19 outcomes in cancer patients. Such databases would need to contain detailed patient-level data and clearly differentiate ICI from non-ICI IT-treated patients. The databases would have to reliably assess the impact of a range of covariates confounding interpretation of the effects of ICIs including among others: type and stage of cancer, presence of other anti-cancer therapies, and patient performance status; the certainty, duration and severity of COVID-19 itself; the specific type, mechanism of action, and regimen of the ICIs being used; information on a range of non-cancer variables like those in the Charlson co-morbidity index[79]; and comprehensive assessment of outcomes and patient follow-up. Power analysis, possibly based on the known ICI adverse event rate in uninfected cancer patients, would be necessary.

There are growing databases and registries that could provide stronger estimates of the effects of prior ICI therapy in cancer patients with COVID-19. Both national and international registries focussed primarily on cancer patients such as The Thoracic Cancers International COVID-19 Collaboration might provide the most informative results.[80] More general registries like the US Veterans Administration's National Database could also be used.[81] Early data from several of these sources were included in the present analysis.[29,32,42,44,46,48,52,54,61]

On the one hand, the persistence of SARS-CoV-2 variants and continued high infection rates coupled with the widespread use of ICIs for cancer emphasises the importance of understanding how prior ICI treatment alters COVID-19 outcomes in cancer patients. But these circumstances may provide a unique opportunity to understand whether ICIs should be considered for the treatment of other types of acute or chronic infections. Therapy with ICIs has been proposed for infections as varied as malaria, HIV and HBV.[82] While several trials directly assessing the effects ICIs in COVID-19 have been planned (NCT04413838, NCT04356508, NCT04268537, NCT04268537, NCT04333914), results are not available. But a comprehensive assessment of the effects of ICI therapy in COVID-19 cancer patients might prove informative regarding their therapeutic value for this and other types of viral infection.

There are several limitations to this study. First, although our search criteria were broad and resulted in over 20,000 reports, in this rapidly evolving field it is possible that very recent studies were overlooked. Second, our search did not include pre-print literature which had not yet undergone peer-review. Third we restricted our review to English publications. Finally, despite attempts to contact authors to clarify patient numbers, outcomes and types of IT therapy investigated, 13 studies had to be excluded from analysis as there was no response to these communications.

In conclusion, while vaccination has reduced COVID-19 in some counties, the infection remains a pressing health problem in large parts of the world. Even with more widespread vaccination, SARS-CoV-2 and its variants will remain a health threat well into the future, especially for patients with cancer. Given the effectiveness and need for ICI therapy in many cancer patients, it is essential to understand with the most credible evidence how ICIs impact outcome when these patients develop COVID-19.

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CONFLICTS OF INTEREST

The authors declare no competing interests.

ETHICS STATEMENT

Not applicable.

AUTHOR CONTRIBUTIONS

Parizad Torabi-Parizi and Samuel J. Minkove conceived and designed the study with contributions from Junfeng Sun and Peter Q.

Eichacker. Diane Cooper conducted the initial search and contributed to the manuscript. Parizad Torabi-Parizi, Samuel J. Minkove and Peter Q. Eichacker reviewed search results and Samuel J. Minkove, Xizhong Cui, Yan Li and Peter Q. Eichacker extracted data. Parizad Torabi-Parizi, Junfeng Sun, Samuel J. Minkove, and Peter Q. Eichacker wrote and edited the manuscript. All authors reviewed and approved the final version of this manuscript for submission.

CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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