Immune checkpoint inhibitor does not increase risks of poor outcomes in cancer patients with COVID-19 infection: A systematic review and meta-analysis

Gilbert Lazarus (✉ gilbert.lazarus@ui.ac.id)

Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia <https://orcid.org/0000-0002-3605-6167>

Refael Alfa Budiman

Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Ikhwan Rinaldi

Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Systematic Review

Keywords: Checkpoint inhibitor, COVID-19, Neoplasms, Prognosis, Programmed cell death 1 receptor

Posted Date: October 30th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-87038/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published at Cancer Immunology, Immunotherapy on October 30th, 2020. See the published version at <https://doi.org/10.1007/s00262-021-02990-9>.

Abstract

Background The association between prior exposure to immune checkpoint inhibitor (ICI) and outcomes of cancer patients with coronavirus disease 2019 (COVID-19) infection has yet to be systematically evaluated. As the current evidence remains equivocal, this meta-analysis aims to investigate the effects of ICI treatment on COVID-19 prognosis, including mortality, severity, and hospitalization.

Methods Eligible studies published up to 14 September 2020 were included and assessed for risk of bias using the Quality in Prognosis Studies tool. A random-effects meta-analysis was conducted to estimate the pooled effect size along with 95% confidence intervals (CIs). The quality of body evidence was evaluated using the modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.

Results Six studies involving a total of 1647 COVID-19-infected cancer patients were included in the systematic review. We discovered that prior ICI exposure was not associated with COVID-19 mortality (odds ratio [OR] 0.93 [95% CI: 0.37-2.36]; $I^2=30\%$), severity (OR 1.15 [95% CI: 0.40-3.28]; $I^2=0\%$), and hospitalization (OR 1.35 [95% CI: 0.64-2.87]; $I^2=51\%$). However, we discovered that prior exposure to chemoimmunotherapy predicted COVID-19 severity (OR 8.19 [95% CI: 2.67-25.08]; $I^2=0\%$), albeit with small sample size. GRADE assessments resulted in moderate-quality evidence for mortality, while the other outcomes yielded very low-to-low-quality evidence

Conclusion Our findings indicated that ICI treatment should not be adjourned nor terminated during the current pandemic. Rather, COVID-19 vigilance should be increased, especially in patients receiving chemoimmunotherapy. Further studies with larger ICI cohorts are required to confirm our findings

Trial registration number: This project has been prospectively registered at PROSPERO (registration ID: CRD42020202142) on 4 August 2020.

Introduction

The current coronavirus disease 2019 (COVID-19) pandemic has brought upon a significant burden in global economy and health, resulting in millions of cases and nearly one million of death.[1] Recent reports have suggested that cancer patients are more vulnerable to COVID-19-related death and complications[2–4]; thus, meticulous management to prevent further deterioration in such patients are essential. In light of this, the question remains whether to postpone or continue active cancer treatment, including immune checkpoint inhibitor (ICI), which exerts immunomodulatory functions[5]. To the best of our knowledge, the current evidence on the effect of prior ICI treatment on cancer patients infected with COVID-19 remains equivocal[6–8]. Therefore, this meta-analysis aims to explore the association between ICI and COVID-19 outcomes in cancer patients, thus providing the best available evidence to guide real-time treatment decisions in such cases.

Methods

This systematic review adhered to the guideline of systematic review of prognostic factor studies by Riley et al[9] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[10]. A detailed protocol has been registered prospectively at PROSPERO (CRD42020202142[11]).

Search strategy and selection criteria

We conducted a comprehensive search on PubMed, Scopus, MEDLINE (via EBSCO), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Controlled Register of Trials (CENTRAL), and the World Health Organization (WHO) COVID-19 research databases, searching for relevant studies published from inception up to 14 September 2020 with keywords listed in Supplementary Table S1. Furthermore, we also searched grey literature (i.e. Google Scholar, ProQuest, MedRxiv, BioRxiv, and Social Science Research Network) databases, in addition to manually searching reference lists from the included studies and similar reviews. Lastly, we retrieved similar records of the included studies with the PubMed's 'similar articles' algorithm and subsequently deduplicated and screened them against the pre-specified eligibility criteria. No language restrictions were applied during the search.

Literature searches were performed by two independent investigators, with any discrepancies resolved by the blind assessment of a third investigator. The retrieved records were screened against the following inclusion criteria: (1) study design, primary studies including case series or letter to editors with at least 10 patients; (2) population and exposure, studies enrolling COVID-19-infected cancer patients with and without prior exposure to ICIs; and (3) outcomes, including mortality, severity, and any other prognosis-related outcomes. In the case of studies only mentioning immunotherapy as an exposure to COVID-19 patients, the corresponding authors were contacted to confirm their study settings, and the studies were subsequently excluded when no response was provided (see Additional methods in Supplementary Material for more details). Contrarywise, records were excluded if the full-text articles were non-English or irretrievable.

Data extraction and risk of bias assessment

The following information were extracted from each included studies: (1) author and year of publication; (2) study characteristics, including recruitment period, study design, settings, location and sample size; (3) patient characteristics, including mean/median age, proportion of male patients, comorbidities, cancer types, adjuvant therapies, and characteristics of ICI (i.e. last exposure to treatment, drug class); and (4) outcomes. The primary outcomes in this review were the risk of poor prognosis (i.e. mortality and severity) among COVID-19-infected cancer patients. Whenever possible, outcomes were further investigated per criterion according to the WHO interim guidance, viz. rate of hospitalization, intensive care unit (ICU) admission, invasive ventilation, acute respiratory distress syndrome (ARDS), and shock.[12] Data extraction were performed by one review author (GL) using a pre-specified form in MS Excel® for Office 365 MSO ver. 2002 (Microsoft Corporation, Redmond, WA, 2018). A second investigator (RAB) checked the accuracy of these data extractions, and any disagreements resolved by the consensus between the authors.

Any reported effect size types (i.e. hazard ratio [HR], odds ratio [OR], relative risk [RR]) were incorporated in this study. When only binary data were provided, unadjusted odds ratio were calculated from the frequency of events and sample sizes.[13] In the case of studies reporting multiple adjustment models, we extracted the adjusted model incorporating the greatest number of covariates.

The included studies were further assessed for risk of bias by using the Quality in Prognosis Studies (QUIPS) tool[14], where the overall bias risk was judged to be low, moderate, and high risk. Risk of bias assessments were conducted by two independent reviewers, and any discrepancies were resolved by a third adjudicator in a blinded fashion. Details on the QUIPS checklist can be found on Supplementary Table S2.

Data analysis and synthesis

Data analyses were performed by using the Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen) [15] and MetaXL software version 5.3. (EpiGear International, Queensland, Australia)[16]. In the case of studies involving overlapping populations, analyses were prioritized to the largest-sized study. Outcomes were pooled as ORs, RRs, or HRs separately along with their 95% confidence intervals (CIs) by using the generic inverse variance methods. Both unadjusted and adjusted outcomes were extracted and synthesized in this study; however, adjusted estimates were prioritized for reporting and interpretation whenever available. Due to the likeliness of unexplained heterogeneity[9], a DerSimonian-Laird random-effects model was used[17]. Heterogeneity between studies was investigated with Cochran's Q test and I^2 statistics. According to I^2 values, heterogeneity was classified as negligible (0-25%), low (25-50%), moderate (50-75%), or high (>75%), while the significance level for Q statistics were set at 10%.

Subgroup analyses were performed only for outcomes with at least two studies in each subset. A priori, we defined subgroups according to study design, location, sample size, and risk of bias; while additional subsets based on the presence of adjuvant therapy (i.e. ICI monotherapy vs ICI plus chemotherapy), cancer type (i.e. lung vs non-lung cancer), and comparator group (i.e. no treatment, chemotherapy, targeted therapy, radiotherapy, and surgery) were determined posteriori. On the other hand, sensitivity analysis was conducted by leave-one-out analysis and simultaneous exclusion of studies with high-bias risk. A P-value of <0.05 indicated statistical significance. When the number of studies was adequate (n10)[18], potential publication bias was investigated visually by contour-enhanced funnel plot[19] and quantitatively with Egger's[20] and Begg's test[21].

Lastly, the overall quality of evidence was assessed with the modified version of Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for prognostic reviews[22], where the certainty of evidence was rated as high, moderate, low, or very low according to the judgements of these following domains: phase of investigation, study limitation, inconsistency, indirectness, imprecision, publication bias, moderate/large effect sizes, and exposure-response gradients.

Results

Search results and study characteristics

The initial search yielded 898 records, of which 406 were deduplicated and 470 were excluded after title and abstract screening. The remaining 22 studies were retrieved for full-text assessments, where 14 studies were excluded due to inappropriate design (i.e. case series/reports with <10 patients) and an additional two due to inappropriate or unidentifiable settings (see Additional methods in Supplementary Materials for further details). Consequently, six studies cumulating a total of 1647 patients were included in this review—among which 919 (55.8%) were male, and hypertension were the most reported comorbidities (37.8%; Table 1). Lastly, we expanded our search by using a non-human skill-dependent search method based on PubMed's 'similar articles' algorithm, in addition to manually hand-searching reference lists of included studies. No new studies were identified from these expanded searches. Details on the literature search strategy are illustrated on Figure 1. Among the included studies, two each were conducted in America[23, 24] and Europe[25, 26], one in Asia[27], and one[28] in multiple regions (i.e. Asia, Europe, and USA). All studies were conducted retrospectively, and all but one[23] was multicentered.

Most patients suffered from solid tumor (1183 [71.8%]), and nearly half of the cases were metastatic (785 [47.7%]). Among them, the most frequent type was lung cancer (407 [24.7%]), followed by gastrointestinal (200 [12.1%]) and breast tumors (199 [12.1%]). With regards to ICI type, most patients received anti-PD-1 (94 [5.7%]), followed by anti-PD-L1 (49 [3.0%]) and anti-CTLA-4 (46 [2.8%]; Table 1).

Risk of bias assessment resulted in low risk for three studies[24, 26, 28], moderate risk for two studies[23, 27], and high risk for one study[25]. Most of the studies yielded unclear risks in study attrition and confounding domains (Supplementary Figure S1), which may be explained by the fact that all studies were retrospective. Furthermore, two studies reported that their studies were underpowered due to small sample sizes[24, 25], while the other two acknowledged their relatively small sample size as a potential limitation[27, 28]. Details on the risk of bias assessment for each signaling question can be found on Supplementary Figure S2.

Outcomes

The summary of pooled unadjusted and adjusted effects can be found on Table 1, while the certainty of evidence according to GRADE assessment can be seen on Supplementary Table S3. GRADE assessment of the effects of prior ICI treatment on COVID-19 mortality resulted in moderate-quality evidence, while the remaining outcomes yielded very low-to-low-quality evidence. Publication bias assessments were not performed as no outcomes yielded more than 10 studies[29]. Furthermore, sensitivity analyses were only eligible for unadjusted and adjusted effects on mortality outcome.

We discovered that prior exposure to ICI was not associated with COVID-19 mortality (OR 0.94 [95% CI: 0.53-1.66]; Figure 3A), which was further ascertained by our findings from the adjusted effects (OR 0.93 [95% CI: 0.37-2.36]; Figure 4A). Although both models yielded low and non-significant heterogeneity (unadjusted estimates, $I^2=29\%$; adjusted estimates, $I^2=30\%$; both with $p>0.10$), we discovered that smaller-sized studies and studies with moderate-to-high risk of bias tend to yield excessively wide CIs. Nonetheless, we proved that these studies did not contribute much to the pooled effects as our estimates remained relatively robust following sensitivity analysis (Supplementary Figure S3A). Considering this, we judged the certainty of evidence for both qualitative and quantitative assessments to be moderate. Furthermore, subgroup analyses based on cancer type, presence of adjuvant therapy, and comparator group also revealed similar trends.

Similar to mortality, we also demonstrated a non-significant association between prior ICI treatment with severity and hospitalization (OR 1.99 [95% CI: 0.91-4.34] and OR 1.35 [95% CI: 0.64-2.87], respectively; Figure 3B-C). However, we were unable to establish a firm evidence as the observed low-to-moderate heterogeneity (severity, $I^2=28\%$; hospitalization, $I^2=51\%$) remained unexplained due to inability to perform subgroup and sensitivity analyses (see footnote of Table 1). Furthermore, study-specific findings showed equivocal trends, where Robilotti et al[23] revealed that prior ICI exposure was an independent risk factor of COVID-19 severity and hospitalization (Supplementary Table S4), while the other studies[24, 25, 27, 28] stated otherwise. Meta-analysis of adjusted estimates on hospitalization outcome was not possible due to overlapping populations[23, 24], while those of severity outcome revealed that ICI may increase risks of COVID-19 severity in cancer patients (OR 3.17 [95% CI: 1.44-6.94] in Figure 4B). Nonetheless, it is important to note that the observed effect was primarily driven by a single study[23], hence indicating that the independent model was unreliable. Considering this, we judged the quality of evidence on COVID-19 severity to be low for qualitative and very low for quantitative assessments, while those of COVID-19 hospitalization resulted in low-quality evidence for both assessments.

Subset analyses based on cancer type and presence of adjuvant therapy for hospitalization outcome revealed similar trends to those of mortality outcome. However, we discovered that concomitant use of ICI and chemotherapy was associated with COVID-19 severity (OR 8.19 [2.67-25.08]; $I^2=0\%$, $p=0.441$). Furthermore, we also found that the risk of severity was higher in patients with prior ICI treatment than patients without active cancer treatment (OR 2.39 [95% CI: 1.24-4.62], $I^2=0\%$), and that the risk of hospitalization was higher in patients receiving ICI than those receiving targeted therapy (OR 2.60 [95% CI: 1.35-5.01], $I^2=0\%$). Nonetheless, it is important to note that the observed effects may be primarily driven by a single study as most of the included studies yielded small sample sizes and wide CIs.

Discussion

This meta-analysis showed that prior exposure to ICI treatment was not associated with poor prognosis in COVID-19-infected cancer patients. We demonstrated that there was a moderate-quality evidence that ICI did not increase the risks of COVID-19 mortality, while the certainty of evidence for other outcomes yielded very low-to-low quality, which was primarily due to the observed equivocal trends where, unlike other studies, Robilotti et al[23] reported an independent association between ICI and COVID-19 severity and hospitalization—which may partly be explained by the fact that the included patients had worse conditions than general cancer populations, thus potentially overestimating the trends.[23]. Although we observed that ICI may independently increase the risk of COVID-19 severity, the interpretation of our findings were limited as study-specific estimates were imprecise and the model was primarily driven by a single study[23]. Furthermore, the observed risk may be elucidated by the relatively prevalent hematological cancer patients, which was a known risk factor of ICI-related immune adverse events[30]. This was further ascertained by Robilotti et al, stating that the risk may potentially be accentuated in patients with metastatic and hematologic cancers.[23] In addition, we also discovered that concomitant use of ICI and chemotherapy was associated with COVID-19 severity. Although further studies are

required to confirm these trends, the effects may potentially be elucidated by the fact that patients receiving chemoimmunotherapy are at higher risks of immune-mediated adverse events[30, 31], thus predisposing these patients to COVID-19 complications.

The dilemma to whether continue, postpone, or even terminate active cancer treatment, including ICI, persisted during the current COVID-19 pandemic. While physicians are expected to prioritize patients' safety, it is also important to ensure that patients receive timely treatment. Several reports and guidelines have regarded ICI as unsafe during the pandemic, and have advised the postponement of such treatments due to safety concerns[32–34]. These are based on two hypothetical adverse interactions between ICI and COVID-19 infection. First, recent reports have suggested that COVID-19 infection may mask ICI-related pneumonitis symptoms, thus potentially delaying essential treatments.[7, 35] Although this might be detrimental considering that ICI-related pneumonitis accounts for about one-third of treatment-related deaths, their incidence is relatively rare. Furthermore, the risks of ICI pneumonitis tend to be augmented in early ICI recipients and super-responders[36], suggesting that a prompt and accurate risk stratification, in addition to increased COVID-19 vigilance, may be able to mitigate this issue.

In addition, early hypotheses postulated that ICI may worsen COVID-19 outcomes due to potential immune hyperactivation[36–38], where they may upregulate pro-inflammatory cytokines[36, 37] and over-activate CD8 T-cells[38]—resulting in the dysregulation and exhaustion of T-cells[36, 39]. This hypothesis was supported by the fact that severe COVID-19 cases were associated with lymphopenia and immune hyperactivity[6, 37]—thus suggesting that ICI may synergistically exacerbate cytokine storm in COVID-19 infection[38]. Nevertheless, a recent report by Di Cosimo et al stated that the occurrence of cytokine storm in COVID-19 patients was more likely to be driven by direct viral damage rather than immune-mediated inflammation[40]. Moreover, recent studies have argued the potential role of ICI on the prevention and management of COVID-19 infection. ICI has exhibited immunity protection against several infectious agents[37], while also restoring cellular-mediated immunocompetence resulting in increased viral control[6, 41]. In addition, ICI may enhance immune response to viral antigens without triggering adverse immune reactions[40], thus further suggesting the potential therapeutic utility of ICI.

Altogether, these findings indicated that ICI treatment should not be unnecessarily deferred during the current pandemic; but rather, COVID-19 vigilance in ICI-treated cancer patients, especially those receiving chemoimmunotherapy, should be increased. This is especially important to ensure prompt diagnosis and treatment of COVID-19 infection, thus preventing adverse outcomes in such patients. The decision to continue or suspend ICI treatment should be based on case-by-case approaches[36, 42], where treatment adjustments may be performed to mitigate risks of COVID-19 infection by reducing patients' contacts to medical system, rather than due to ICI-related safety concerns. Furthermore, alternative decisions to specific cohorts may be adopted, e.g. early treatment discontinuation in patients with complete or prolonged response[8], adjustments of treatment interval or modality[7, 43], or adjournments of ICI treatment in high risk patients (e.g. elderly, patients with history of immune-related adverse events and/or comorbidities)[43].

This study has several limitations. Although our findings rejected the early hypotheses stating that ICI may cause deleterious effects to COVID-19 cancer patients, study paucity and small-sized cohorts limited the interpretation of our results. Furthermore, some models (i.e. severity and hospitalization) were also limited by the predominant moderate-to-high-bias risk, which was further worsened by the observed heterogeneity in hospitalization outcome, thus resulting in the judgement of very low-to-low-quality evidence. Nonetheless, we demonstrated a relatively consistent and robust findings that ICI was not associated with COVID-19 mortality. Moreover, although all included studies were conducted retrospectively, the studies involved diverse populations, thus ascertaining the generalizability of our findings. Despite this, it is worth noting that none of the included studies directly compared the risks between different ICI classes, implying that further studies with larger ICI cohorts are required to confirm our findings and to explore the observed effects. In addition, we also advise future studies to specifically investigate the association between prior ICI exposure and COVID-19 severity in hematological cancer patients and in patients receiving chemoimmunotherapy, as the current evidence was still equivocal. Lastly, although our eligibility criteria may introduce language bias, we did not discover any non-English article during the literature search process, thereby suggesting that any potential bias was insignificant.

To the best of our knowledge, this is the first meta-analysis conducted to evaluate the association between prior ICI exposure and COVID-19 outcomes. Although our findings were limited due to study scarcity and small-sized cohorts, we were able to establish a moderate-quality evidence on the non-significant relationship between ICI and COVID-19 mortality. We hope that our findings may encourage physicians to increase COVID-19 vigilance and perform risk-benefit assessments on each ICI-treated cancer patients, rather than indifferently deferring ICI treatment throughout the pandemic, which may cause significant harms to cancer patients in the long run.

Conclusion

In the end, this meta-analysis adds to the growing body of evidence suggesting that ICI was not associated with poor COVID-19 outcomes in cancer patients. Our findings indicated that the adjournment of ICI treatments during the pandemic is unwarranted, but rather COVID-19 vigilance should be performed more rigorously, especially in patients receiving chemoimmunotherapy. Further studies with larger cohorts and higher quality of evidence are required to confirm our findings on COVID-19 severity and hospitalization.

Abbreviations

ARDS	Acute respiratory distress syndrome
CENTRAL	Cochrane Controlled Register of Trials
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COVID-19	Coronavirus disease 2019
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
CVD	Cardiovascular disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICI	Immune checkpoint inhibitor
ICU	Intensive care unit
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
QUIPS	Quality in Prognosis Studies tool
WHO	World Health Organization

Declarations

Funding

This project received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare no conflict of interest

Ethics approval

Not applicable

Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

All data generated or analyzed during this study are included in this published article [and its supplementary information files]

Code availability

Not applicable

Authors' contribution

GL conceptualized the idea, designed the methodology, administered the study protocol, undertook the formal analysis, and visualized the findings. GL, RAB, and IR screened the literature and assessed the risk of bias. GL and RAB extracted the data and drafted the original manuscript,

while GL and IR reviewed and edited the manuscript for final submission. IR supervised the project. All authors have approved of the final manuscript for publication.

Acknowledgement

The authors would like to express their gratitude to Dr. Ying Taur and Dr. Mini Kamboj (Infectious Diseases, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA) for the provision of additional data for analyses. The authors would also like to thank Dr. Lennard YW Lee (Institute of Cancer and Genomic Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK) and Prof. Jeremy L. Warner (Vanderbilt-Ingram Cancer Center at Vanderbilt University Medical Center, Nashville, TN, USA) for the confirmation of study settings.

References

1. (2020) Coronavirus disease (COVID-19) weekly epidemiological update: 14 September 2020. Geneva
2. Ofori-Asenso R, Ogunidipe O, Agyeman AA, et al (2020) Cancer is associated with severe disease in COVID-19 patients: a systematic review and meta-analysis. *Ecantermedicalscience* 14:1047. <https://doi.org/10.3332/ecancer.2020.1047>
3. Giannakoulis VG, Papoutsis E, Siempos II (2020) Effect of Cancer on Clinical Outcomes of Patients With COVID-19: A Meta-Analysis of Patient Data. *JCO Glob Oncol* 6:799–808. <https://doi.org/10.1200/GO.20.00225>
4. ElGohary GM, Hashmi S, Styczynski J, et al (2020) The risk and prognosis of COVID-19 infection in cancer patients: A systematic review and meta-analysis. *Hematol Oncol Stem Cell Ther* S1658-3876(20)30122–9. <https://doi.org/10.1016/j.hemonc.2020.07.005>
5. Zappasodi R, Merghoub T, Wolchok JD (2018) Emerging Concepts for Immune Checkpoint Blockade-Based Combination Therapies. *Cancer Cell* 33:581–598. <https://doi.org/10.1016/j.ccell.2018.03.005>
6. Vivarelli S, Falzone L, Grillo CM, et al (2020) Cancer Management during COVID-19 Pandemic: Is Immune Checkpoint Inhibitors-Based Immunotherapy Harmful or Beneficial? *Cancers (Basel)* 12:2237. <https://doi.org/10.3390/cancers12082237>
7. Sullivan RJ, Johnson DB, Rini BI, et al (2020) COVID-19 and immune checkpoint inhibitors: initial considerations. *J Immunother Cancer* 8:e000933. <https://doi.org/10.1136/jitc-2020-000933>
8. Davis AP, Boyer M, Lee JH, Kao SC (2020) COVID-19: the use of immunotherapy in metastatic lung cancer. *Immunotherapy* 12:545–548. <https://doi.org/10.2217/imt-2020-0096>
9. Riley RD, Moons KGM, Snell KIE, et al (2019) A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ* 364:. <https://doi.org/10.1136/bmj.k4597>
10. Moher D, Liberati A, Tetzlaff J, et al (2009) Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* 6:e1000097. <https://doi.org/10.1371/journal.pmed.1000097>
11. Lazarus G, Rinaldi I Immune checkpoint inhibitors in the treatment of cancer patients with COVID-19 infection: a systematic review protocol. PROSPERO 2020. CRD42020202142
12. (2020) Clinical management of COVID-19: interim guidance - 27 May 2020
13. Szumilas M (2010) Explaining odds ratios. *J Can Acad Child Adolesc Psychiatry* 19:227–229
14. Hayden JA, Côté P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 144:427–437. <https://doi.org/10.7326/0003-4819-144-6-200603210-00010>
15. (2014) Review Manager (RevMan) [Computer program], Version 5.3
16. Barendregt JJ, Doi S a (2015) MetaXL user guide, version 5.3. 1–52
17. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. *Control Clin Trials* 7:177–188. [https://doi.org/10.1016/0197-2456\(86\)90046-2](https://doi.org/10.1016/0197-2456(86)90046-2)
18. Higgins J, Thomas J, Chandler J, et al (2019) Cochrane handbook for systematic reviews of interventions version 6.0 (updated July 2019), 6th ed. Cochrane
19. Peters JL, Sutton AJ, Jones DR, et al (2008) Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 61:991–996. <https://doi.org/10.1016/j.jclinepi.2007.11.010>
20. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315:629 LP – 634. <https://doi.org/10.1136/bmj.315.7109.629>
21. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlationTest for publication bias. *Biometrics* 50:1088–1101
22. Hugué A, Hayden JA, Stinson J, et al (2013) Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. *Syst Rev* 2:71. <https://doi.org/10.1186/2046-4053-2-71>
23. Robilotti E V, Babady NE, Mead PA, et al (2020) Determinants of COVID-19 disease severity in patients with cancer. *Nat Med* 26:1218–1223. <https://doi.org/10.1038/s41591-020-0979-0>
24. Luo J, Rizvi H, Egger J V, et al (2020) Impact of PD-1 blockade on severity of COVID-19 in patients with lung cancers. *Cancer Discov* 10:1121 LP – 1128. <https://doi.org/10.1158/2159-8290.CD-20-0596>

25. Gonzalez-Cao M, Antonazas-Basa M, Puertolas T, et al (2020) Cancer immunotherapy does not increase the risk of death by COVID-19 in melanoma patients. medRxiv 2020.05.19.20106971. <https://doi.org/10.1101/2020.05.19.20106971>
26. Lee LYW, Cazier J-B, Angelis V, et al (2020) COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet* 395:1919–1926. [https://doi.org/10.1016/S0140-6736\(20\)31173-9](https://doi.org/10.1016/S0140-6736(20)31173-9)
27. Dai M, Liu D, Liu M, et al (2020) Patients with cancer appear more vulnerable to SARS-CoV-2: A multicenter study during the COVID-19 outbreak. *Cancer Discov* 10:783 LP – 791. <https://doi.org/10.1158/2159-8290.CD-20-0422>
28. Garassino MC, Whisenant JG, Huang L-C, et al (2020) COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. *Lancet Oncol* 21:914–922. [https://doi.org/10.1016/S1470-2045\(20\)30314-4](https://doi.org/10.1016/S1470-2045(20)30314-4)
29. Sterne JAC, Sutton AJ, Ioannidis JPA, et al (2011) Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. <https://doi.org/10.1136/bmj.d4002>
30. Zhou Y, Chen C, Zhang X, et al (2018) Immune-checkpoint inhibitor plus chemotherapy versus conventional chemotherapy for first-line treatment in advanced non-small cell lung carcinoma: a systematic review and meta-analysis. *J Immunother Cancer* 6:155. <https://doi.org/10.1186/s40425-018-0477-9>
31. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al (2018) Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. *N Engl J Med* 378:2078–2092. <https://doi.org/10.1056/NEJMoa1801005>
32. Ürün Y, Hussain SA, Bakouny Z, et al (2020) Survey of the Impact of COVID-19 on Oncologists' Decision Making in Cancer. *JCO Glob Oncol* 6:1248–1257. <https://doi.org/10.1200/GO.20.00300>
33. Tagliamento M, Spagnolo F, Poggio F, et al (2020) Italian survey on managing immune checkpoint inhibitors in oncology during COVID-19 outbreak. *Eur J Clin Invest* 50:e13315. <https://doi.org/10.1111/eci.13315>
34. (2020) Clinical guide for the management of non-coronavirus patients requiring acute treatment: Cancer - 23 March 2020 version 2
35. Russano M, Citarella F, Napolitano A, et al (2020) COVID-19 pneumonia and immune-related pneumonitis: critical issues on differential diagnosis, potential interactions, and management. *Expert Opin Biol Ther* 20:959–964. <https://doi.org/10.1080/14712598.2020.1789097>
36. Bersanelli M (2020) Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors. *Immunotherapy* 12:269–273
37. Gatto L, Franceschi E, Nunno V Di, Brandes AA (2020) Potential protective and therapeutic role of immune checkpoint inhibitors against viral infections and COVID-19. *Immunotherapy*
38. Citarella F, Russano M, Pantano F, et al (2020) Facing SARS-CoV-2 outbreak in immunotherapy era. *Future Oncol* 16:1475–1485. <https://doi.org/10.2217/fon-2020-0340>
39. Gambichler T, Reuther J, Scheel CH, Becker JC (2020) On the use of immune checkpoint inhibitors in patients with viral infections including COVID-19. *J Immunother cancer* 8:. <https://doi.org/10.1136/jitc-2020-001145>
40. Di Cosimo S, Malfettone A, Pérez-García JM, et al (2020) Immune checkpoint inhibitors: a physiology-driven approach to the treatment of coronavirus disease 2019. *Eur J Cancer* 135:62–65. <https://doi.org/10.1016/j.ejca.2020.05.026>
41. Finelli C (2020) Obesity, COVID-19 and immunotherapy: the complex relationship! *Immunotherapy*
42. Sehgal K, Costa DB, Rangachari D (2020) Extended-Interval Dosing Strategy of Immune Checkpoint Inhibitors in Lung Cancer: Will it Outlast the COVID-19 Pandemic? *Front Oncol* 10:1193. <https://doi.org/10.3389/fonc.2020.01193>
43. Quaglino P, Fava P, Brizio M, et al (2020) Metastatic melanoma treatment with checkpoint inhibitors in the COVID-19 era: experience from an Italian Skin Cancer Unit. *J Eur Acad Dermatol Venereol* 34:1395–1396. <https://doi.org/10.1111/jdv.16586>

Tables

TABLES

Table 1. Characteristics of included studies and patients^a

Author; Year	Recruitment period	Study design; Settings	Country/ Region	Sample size	Median age (years)	Male; n (%)	Comorbidities; n (%)				
							Hypertension	Diabetes	CVD	CKD	COPD
Dai M; 2020	1 Jan - 24 Feb 2020	Retrospective; Multicenter	China	105	64 (IQR: 14)	57 (54.3)	30 (28.6)	7 (6.7)	12 (11.4)	6 (5.7)	NR
Garassino MC; 2020	26 Mar - 12 Apr 2020	Retrospective; Multicenter	Asia, Europe, USA	200	68 (IQR: 61.8- 75.0)	141 (70.5)	93 (47.0)	29 (15.0)	30 (15.0)	15 (8.0)	51 (26.0)
Gonzalez- Cao M; 2020	1 Apr - 17 May 2020	Retrospective; Multicenter	Spain	50	69 (Range: 6-94)	27 (54.0)	NR	NR	NR	NR	NR
Lee LYW; 2020	18 Mar - 26 Apr 2020	Prospective; Multicenter	UK	800	69 (59- 76)	449 (56.1)	247 (30.9)	131 (16.4)	109 (13.6)	NR	61 (7.6)
Luo J; 2020	12 Mar - 13 Apr 2020	Retrospective; Multicenter	USA	69	69 (Range: 31-91)	33 (47.8)	38 (55.1)	21 (30.4)	5 (7.2)	NR	12 (17.4)
Robilotti EV; 2020	10 Mar - 7 Apr 2020	Retrospective; Single center	USA	423	NR	212 (50.1)	214 (50.7)	84 (19.9)	84 (19.9)	36 (8.5)	29 (6.9)

Table 1. Characteristics of included studies and patients (cont.)

Author; Year	Cancer types; n (%)			Adjuvant therapy; n(%)	ICI				Outcomes
	Hematologic	Solid tumor	Metastatic		Last exposure to treatment (days)	Anti- PD- 1	Anti- CTLA- 4	Anti- PD- L1	
Dai M; 2020	9 (8.6)	96 (91.4)	17 (16.2)	Targeted therapy: 1 (1.0) Chemotherapy: 3 (2.9)	4040.5	6 (5.7)	0 (0.0)	0 (0.0)	ICU admission, Invasive ventilation, Mortality, Severity
Garassino MC; 2020	0 (0.0)	200 (100)	147 (74.0)	Chemotherapy: 24 (12) Radiotherapy: 3 (1.5) Cementoplasty: 1 (0.5) Targeted therapy: 2 (1.0)	NR	NR	NR	NR	Hospitalization, ICU admission, Mechanical ventilation, Mortality, Prolonged hospitalization (>8 days)
Gonzalez- Cao M; 2020	0 (0.0)	50 (100.0)	36 (72.0)	0 (0.0)	56	22 (44)	0 (0.0)	0 (0.0)	Hospitalization, ICU admission, Mortality, Severity
Lee LYW; 2020	169 (21.1)	584 (73.0)	347 (43.4)	NR	Max: 28	0 (0.0)	44 (5.5)	44 (5.5)	Mortality
Luo J; 2020	0 (0.0)	69 (100)	NR	Surgery/Radiotherapy: 32 (46.4)	Median: 45 (Range: 4-820)	41 (59)	0 (0.0)	0 (0.0)	Hospitalization, Mortality, Severity
Robilotti EV; 2020	102 (24.1)	184 (43.5)	238 (56.3)	NR	24.4 20.8	25 (5.9)	2 (0.5)	5 (1.2)	Hospitalization, Mortality, Severity (30 days)

^aUnless explicitly stated, data are presented in n (%), mean standard deviation, or median (interquartile range). CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CTLA-4, cytotoxic T-lymphocyte associated protein 4; CVD, cardiovascular disease; ICI, immune checkpoint

inhibitor; ICU, intensive care unit; IQR, interquartile range; PD-1, programmed cell death protein 1; PD-L1, PD-1 ligand 1; NR, not reported; UK, United Kingdom; USA, United States of America

Table 2. Pooled adjusted and unadjusted effects of prior ICI exposure on COVID-19 outcomes

Outcome	Studies	Events/N		OR (95% CI)	Heterogeneity	
		ICI	No ICI		Ꝁ²	P-value
Adjusted effects						
Mortality	3[24, 26, 27]	23/89	228/883	0.93 (0.37-2.36)	30%	0.239
Severity	2[24, 27]	16/37	111/491	3.17 (1.44-6.94)	0%	0.865
Unadjusted effects						
Mortality	5[24–28]	42/163	284/1050	0.94 (0.53-1.66)	29%	0.226
Subgroup analysis						
Sample size						
<100 patients	2[24, 25]	14/61	11/56	1.13 (0.38-3.40)	25%	0.247
100 patients	3[26–28]	28/102	273/994	0.91 (0.42-2.00)	48%	0.144
Risk of bias						
Low	3[24, 26, 28]	37/135	271/923	0.83 (0.50-1.40)	11%	0.324
Moderate/High	2[25, 27]	5/28	13/127	1.51 (0.21-11.06)	65%	0.091
Cancer type						
Lung cancer	3[24, 27, 28]	28/96	58/184	0.98 (0.55-1.74)	0%	0.495
Non-lung solid cancer	2[25, 27]	4/23	10/101	5.13 (0.07-375.71)	93%	<0.001
Adjuvant therapy						
ICI monotherapy	3[25, 27, 28]	15/57	66/266	1.00 (0.38-2.64)	29%	0.246
ICI + chemotherapy	2[27, 28]	6/22	60/238	0.77 (0.34-1.73)	0%	0.595
Comparator group ^a						
No treatment	4[25–28]	31/124	114/395	0.90 (0.40-2.04)	50%	0.110
Chemotherapy	4[25–28]	31/124	100/359	0.77 (0.40-1.46)	21%	0.283
Targeted therapy	3[26–28]	28/102	24/101	1.12 (0.58-2.16)	0%	0.753
Surgery	2[26, 27]	12/50	9/37	1.01 (0.37-2.74)	0%	0.713
Radiotherapy	2[26, 27]	12/50	19/89	1.53 (0.31-7.50)	40%	0.196
Severity ^{b,c,d}	3[23, 25, 27]	31/59	131/519	1.99 (0.91-4.34)	28%	0.247
Subgroup analysis						
Cancer type						
Lung cancer ^e	2[24, 27]	18/44	17/43	1.27 (0.51-3.19)	0%	0.758
Non-lung solid cancer	3[23, 25, 27]	21/42	78/331	1.66 (0.66-4.14)	23%	0.273
Adjuvant therapy						
ICI monotherapy	3[23, 25, 27]	20/41	113/519	1.21 (0.52-2.82)	0%	0.386
ICI + chemotherapy	2[23, 27]	9/14	3/491	8.19 (2.67-25.08)	0%	0.441
Comparator group ^a						
No treatment	3[23, 25, 27]	31/59	68/285	2.39 (1.24-4.62)	0%	0.490
Chemotherapy	3[23, 25, 27]	31/59	47/159	1.75 (0.84-3.67)	8%	0.335
Targeted therapy	2[23, 27]	16/37	18/70	2.38 (0.62-9.17)	18%	0.269
Hospitalization ^{b,c,d}	3[23, 25, 28]	76/105	282/555	1.35 (0.64-2.87)	51%	0.128
Subgroup analysis						

Cancer type						
Lung cancer ^e	2[24, 28]	69/94	172/193	1.32 (0.72-2.39)	0%	0.570
Non-lung solid cancer	2[23, 25]	24/39	105/244	1.03 (0.43-2.46)	14%	0.282
Adjuvant therapy						
ICI monotherapy	3[23, 25, 28]	49/71	282/555	1.03 (0.56-1.87)	0%	0.614
ICI + chemotherapy	2[23, 28]	25/31	259/527	2.03 (0.19-21.63)	81%	0.023
Comparator group ^a						
No treatment	3[23, 25, 28]	76/105	135/269	1.25 (0.46-3.40)	61%	0.075
Chemotherapy	3[23, 25, 28]	76/105	100/188	1.24 (0.44-3.49)	59%	0.088
Targeted therapy	2[23, 28]	60/83	47/111	2.60 (1.35-5.01)	0%	0.718

^aFor study-specific estimates, see Supplementary Table S5. ^bOverlapping populations were observed between Luo et al[24] and Robilotti et al[23], of which Robilotti[23] et al was prioritized due to larger sample size. ^cSensitivity analysis was not eligible as only two studies remained after the exclusion of studies with high-bias risk. ^dSubgroup analyses based on study location, design, sample size, and risk of bias were not eligible as none of the subgroups yielded a minimum of two studies. ^eOverlapping lung cancer patients were observed between Luo et al[24] and Robilotti et al[23], of which Luo et al[24] was prioritized due to larger sample size. CI, confidence interval; ICI, immune checkpoint inhibitor; OR, odds ratio

Figures

Figure 1

Diagram flow illustrating the literature search strategy. CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; SSRN, Social Science Research Network; WHO, World Health Organization.

(A) Mortality

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
-------------------	-----------------	----	--------	----------------------------------	----------------------------------

Figure 2

Pooled unadjusted estimates on the association between prior ICI exposure with risks of: (A) mortality, (B) severity, and (C) hospitalization. ICI, immune checkpoint inhibitor

(A) Mortality

(B) Severity

Figure 3

Pooled adjusted estimates on the association between prior ICI exposure with risks of: (A) mortality and (B) severity

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryMaterialResearchSquare.pdf](#)