Case-control study assessing the impact of COVID19 in advanced kidney cancer patients treated with antiangiogenics or immunotherapy. The COVID-REN study

Jesús García-Donas[1], Guillermo de Velasco[2], Rodrigo Madurga[3], Jesús Chamorro[4], Diana Rosero[4], Olatz Etxaniz[5], Jose Luis Pérez-Gracia[6], Álvaro Pinto[7], Diego Cacho[8], María Barba[1], Pablo Borrega[9], Martín Lázaro[10], Laura Rodriguez[11], Laura Villalobos[12], Lourdes García[13], Andrés Cuellar[14], María del Pilar Solís Hernández[15], Amalia González[16], Cristina Pernaut[17], Juan Francisco Rodríguez-Moreno[1].

1-HM Hospitales-Centro Integral Oncológico Clara Campal, Madrid, Spain;

2-Hospital Universitario 12 de Octubre, Madrid, Spain;

3-Faculty of Experimental Sciences, Universidad Francisco de Vitoria, Madrid, Spain

4-Hospital Universitario Ramón y Cajal; Madrid, Spain;

5-Hospital Germá Trials I Pujol, Barcelona, Spain;

6-Clínica Universidad de Navarra, Pamplona, Spain;

7-Hospital Universitario La Paz, Madrid, Spain;

8-Hospital Universitario Marqués de Valdecilla, Santander, Spain;

9-Hospital Universitario de Cáceres, Cáceres, Spain;

10-Hospital Álvaro Cunqueiro, Vigo, Spain;

11-Hospital Universitario de Fuenlabrada, Madrid, Spain;

12-Hospital Universitario Príncipe de Asturias, Madrid, Spain;

13-Hospital de Segovia, Segovia, Spain;

14-Institut Català d'Oncologia, Badalona, Spain;

15-Hospital Central de Asturias, Asturias, Spain;

16-Hospital Virgen de la Salud, Toledo, Spain;

17-Hospital Severo Ochoa, Madrid, Spain.

ABSTRACT (261/300)

Background: Cancer is a risk factor for developing severe COVID19. Additionally, SARS-CoV2 has a special tropism for renal cells and complications like thrombosis or cytokine storm could be enhanced by standard treatments in kidney cancer (i.e: antiangiogenics or immunotherapy). Thus, understanding the impact of COVID19 in patients with this tumor is key for their correct management.

Methods: We designed a retrospective case-control study comparing the outcome of three groups of advanced kidney cancer patients on systemic treatment: cohort A (developed COVID19 while on antiangiogenics), cohort B (developed COVID19 while on immunotherapy) and cohort C (non-infected). Matching factors were age, gender and treatment.

Results: 95 patients were recruited in 16 centers in Spain from September 2020 to May 2021. Finally, 85 were deemed as eligible (23 cohort A, 21 cohort B, 41 cohort C)

Patients with COVID required more dose interruptions (25 vs six) and hospitalizations (10 vs none) than those without COVID (both p = 0.001). No difference between cohorts A and B was observed regarding hospitalization or length of stay. No ICU admission was registered and one patient in cohort B died due to COVID19. Regarding cancer evolution, three patients in cohort A presented progressive disease after COVID19 compared to two in cohort B. One case in cohort B, initially deemed as stable disease, achieved a partial response after COVID19.

Conclusions: Kidney cancer patients that developed COVID19 while on systemic therapy required more treatment interruptions and hospitalizations than those non-infected. However, no significant impact on cancer outcome was observed. Also, no difference was seen between cases on antiangiogenics or immunotherapy.

Main text (1796/4000)

Introduction

Cancer has been described as a risk factor for severe COVID19 and 20% of people who died from this disease presented an active neoplasia (1, 2).

Importantly, most of the pathogenic factors for renal carcinoma (age, hypertension, obesity, diabetes and smoking) have been associated with a severe infection (3).

Additionally, angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine-type 2 (TMPRSS2) receptors play a relevant role in the entry of SARS-CoV2 into the cell and are expressed in the kidneys (4). Thus, renal cells are one of the primary targets of the virus (5).

Finally, some of the secondary effects of the standard treatments in kidney cancer (antiangiogenics and immunotherapy), could enhance complications associated with SARS-Cov2 like thrombosis or cytokine storm. (6, 7)

As a consequence, health authorities and medical associations recommended to modify treatment schedules and patient management during the pandemic (8, 9, 10).

However, little experience has been communicated regarding the real impact of COVID19 in the evolution of kidney cancer patients.

We aimed to compare the outcomes of these cases while on treatment with antiangiogenics or immunotherapy among them and with paired patients that did not get infected.

Methods

Study design

A retrospective, observational, case-control study was designed in a multicentric setting.

Study population

Advanced kidney cancer patients on systemic therapy during the pandemic were eligible.

Patients were allocated into three different cohorts: Cohort A, kidney cancer cases who were receiving antiangiogenics when got infected by SARS-CoV2; cohort B, cases who developed COVID19 while on immunotherapy (alone or in combination with antiangiogenics); cohort C, matched controls (did not suffered the infection while on cancer treatment).

Matching factors were age, gender, and type of therapy.

SARS-Cov2 infection had to be confirmed by a positive PCR or serological test.

The study protocol was reviewed and approved by the ethics committee of the Hospital HM Sanchinarro (Madrid [Spain]). Consent for participating in this study was obtained from every patient.

Evaluation of response

To assess the potential effect of SARS-Cov2 on treatment efficacy, best tumor response was annotated for all cohorts.

Evaluations of response before and after the COVID episode were also recorded in cohorts A and B, to determine the evolution of tumors along SARSCoV-2 infection,.

Statistical analysis

Categorical variables are presented as absolute frequency (%) while quantitative variables are presented as median (IQR). Inference for categorical variables has been performed by Chi-squared test or Fisher test if needed. For quantitative variables, Mann-Whitney U test was used for two groups comparison while Kruskal Wallis test was used for multiple groups comparisons. All the statistical analyses were performed with R (version 4.1.1). A statistical threshold of 0.05 was used for this study.

Results

From September 2020 to May 2021, up to 95 patients in 16 institutions in Spain were included.

Five cases with COVID19 that were not on active treatment at the moment of the infection and five controls that did not match any case were deemed as ineligible. Thus, 85 patients were considered as the study population and were distributed among the study cohorts as follows: 23 (27%) in cohort A, 21 (25%) in cohort B, 41 (48%) in cohort C.

Median age was 63 (range: 25-88, IQR: 57-72) and 22 (26%) were female. Regarding their smoking history 15 (18%) were smokers, 29 (34%) former smokers and 40 (47%) had never smoked. The histology of tumors was clear cell in 78 (92%), papillary in four (5%), chromophobe in one (1%), rhabdoid associated with MIT translocation in one (1%) and unknown in one (1%). According to Heng´s classification 29 (34%) were favorable, 34 (40%) intermediate and four (5%) poor risk patients (18 [21%] unknown). Finally, 38 (45%) were on first line treatment, 29 (34%) on second, seven (8%) on third and 11 (13%) on fourth line or beyond. No statistically significant difference was observed among groups regarding baseline characteristics. (Table 1).

The antiangiogenic drugs administered in cohort A were: cabozantinib (six patients [26%]), pazopanib (five [22%]), sunitinib (ten [43%]) and tivozanib (two [9%]).

The Check Point Inhibitors (CPI) administered on cohort B, as single agents or in combination, were: pembrolizumab (two patients [9%]), nivolumab (17 [81%]), and atezolizumab (one [5%]). One patient (5%) was in a clinical trial with the drug MEDI5752, plus an anti-PD1 and an anti-CTLA-4.

In cohort C, the distribution of drugs among patients receiving antiangiogenic alone was: cabozantinib (35%), sunitinib (27%), pazopanib (23%), tivozanib (12%) and axitinib (3%). All cases on CPI (alone or in combination) received nivolumab.

Treatment interruptions, dose reductions and hospitalization

In the overall study population 31 (36%) cases required treatment interruption, 6 (7%) dose reductions and 10 (12%) hospitalization. (Table 2). No patient was admitted to the ICU and one died due to COVID19 (cohort B).

Comparisons between COVID arms showed a non-significant trend towards a lower frequency of treatment interruptions in patients on antiangiogenics vs CPI (48% vs 67%, p = 0.34). Patients who got infected by SARS-CoV2 (cohorts A+B) required treatment interruptions more frequently than those who did not (cohort C) (57 vs 15% [p = 0.001]).

Dose reductions were required only in 2 (9%) patients in cohort A and none in cohort B (p = 0.49). Four cases (10%) in cohort C, lowered the dose along the study period (p = 0.41).

Regarding hospitalizations, no difference was observed between cohort A (4 [17%]) vs B (6 [29%]) (p = 0.48). No patient was admitted to the participating institutions in cohort C (p = 0.001).

Median days of hospital stay was 7 (range 4-14, IQR 4-11) in cohort A and 10 (range 5-42, IQR 6-15.5) in cohort B (p = 0.28). (Figure 1A)

Median duration of dose interruptions was 34 days (range 6-239, IQR 23-42) in the study population, 30 (range 8-84, IQR 12.5-34) in cohort A and 36 (range 12-68, IQR 30-42) in cohort B (p = 0.27). (Figure 1B)

Overall, patients with COVID19 (cohort A+B) interrupted treatment during 30 days (range 8-84, IQR 19-40) and those non-infected (cohort C) during 40 days (range 6-239, IQR 37-43 [p = 0.27]). (Figure 1B)

In order to directly compare patients to their matching controls, cohort C was subdivided among those who had received antiangiogenics (C_A) and (C_B). (Figure 1C).

Median days of treatment interruption in the C_A cohort was 38 (range 6-42, IQR 22-40 days) and 43 (range 36-239, IQR 40-141 days) in the cohort C_B. No difference was observed when compared to cohorts A or B respectively.

Treatment response

Tumor response evaluation was available in 63 patients. As a whole, eight (42%) cases in cohort A, 10 (63%) in cohort B and 18 (64%) in cohort C achieved an objective response. Regarding clinical benefit numbers were 16 (84%), 12 (75%) and 25 (89%) respectively. Finally, 3 (16%) patients progressed in cohort A, 4 in cohort B (25%) and 3 (11%) in cohort C. No comparison between cohorts A vs B or infected (A+B) vs non infected (C) reached statistical significance. (Table 3)

Regarding the evolution of the tumor after the infection, three cases in cohort A and two in cohort B progressed. One case in cohort B, initially deemed as stable disease, achieved a partial response after COVID19 (Figure 2).

Discussion

SARS-CoV2 presents a tropism for renal cells and therapies usually administered in kidney cancer, antiangiogenics and immunotherapy, may enhance complications of COVID19 like thrombosis or hyperinflammation. Thus, we designed a case-control study to compare the outcome of advanced renal cancer patients who got infected while on systemic treatment with cases who did not. The analysis of 85 eligible patients showed that SARS-CoV2 significantly led to more treatment interruptions and hospital admissions. However, no impact on mortality or response to therapy was observed.

Early in the SARS-CoV2 outbreak, cancer was identified as a risk factor for severe disease. Additionally, some oncological therapies demonstrated to conditionate a worse outcome (11). Intriguingly, the description of some tumor responses in patients who got COVID19, led to the notion that immune activation by SARS-CoV2 could play a role in terms of efficacy (12, 13)

Some particularities of kidney cancer regarding COVID19 (like the expression of receptors that the virus requires to access eukaryotic cells and the overlap between secondary effects due to therapy and complications of SARS-CoV2) represent a major concern. Though several authors have analyzed the patterns of treatment of renal tumors along the pandemic, no direct comparison between patients infected and non-infected has been presented (14).

Thus, we conducted a case-control study to better characterize the evolution of kidney cancer patients who suffered COVID19 and to explore the differences between cases on antiangiogenics and immunotherapy.

Regarding the selection of controls, we established age, gender and type of therapy as the matching factors.

As expected, the cohorts with COVID19 significantly required treatment interruption and hospital admission more frequently than non-COVID patients. However, length of

stay was similar among those receiving antiangiogenics or immunotherapy, none required ICU support and only one patient died from the disease.

These results are in line with prior communications in lung cancer and other tumors where CPI did not increase the mortality of COVID19 (15, 16).

Interestingly, duration of treatment interruptions was similar among all cohorts. This points to a relatively low incidence of severe COVID19, generally not requiring definitive withdrawal of therapy and reintroducing treatments shortly.

Accordingly, Grivas et al in a retrospective analysis of around 5000 cancer patients, identified chemotherapy and DNA methyltransferase inhibitors as the only therapies related with a worse outcome (11).

Regarding treatment modifications, cases on immunotherapy did not require dose reductions. This is likely due to the flat dose schedules widely adopted nowadays rather than to a clinical or biological difference with antiangiogenics.

Importantly, all results remained consistent when the control cohort was subdivided in patients on antiangiogenics and immunotherapy (cohorts C_A and C_B) and compared to the matched cases.

Finally, overall response rate was similar among study cohorts. Only one case who had achieved stable disease before COVID, improved the tumor response evaluation after the disease. Thus, SARS-CoV2 infection does not seem to have neither a detrimental nor a beneficial effect.

Some limitations of our work must be highlighted. Frist, retrospective studies usually imply a selection bias that could lead to underrepresentation of cases with poor outcome. Second, since matching factors are limited, some additional characteristics like comorbidities, chronic medications, or heterogenic management of COVID19 in different institutions could be disbalanced among cohorts.

Finally, our study did not address the long term evolution of patients included. Also, many therapeutic options, currently used in COVID19, were not available by the time of the work.

Conclusions

COVID19 led to more dose interruptions and hospitalizations in advanced kidney cancer patients who were on systemic therapy compared to non-infected cases. However, no impact in tumor response or mortality was observed. Also, no significant difference was seen between those receiving antiangiogenics or immunotherapy.

Tables & figures

Table 1. Demographics of study population. * Kruskal-Wallis test, ᵀ Chi-squared test, ‡ Fisher test.

	Total (n=85)	Cohort A (n=23)	Cohort B (n=21)	Cohort C (n=41)	P value
AGE (years)	63 (57-72)	63 (57-73)	63 (54-71)	63 (57-72)	0.80*
GENDER					
Male	63 (74%)	17 (74%)	17 (81%)	29 (71%)	0.69ᵀ
Female	22 (26%)	6 (26%)	4 (19%)	12 (29%)	
SMOKER STATUS					
Smoker	15 (18%)	4 (17%)	4 (19%)	7 (17%)	0.95‡
Former smoker	29 (34%)	7 (31%)	8 (38%)	14 (34%)	
Never smoked	40 (47%)	12 (52%)	8 (38%)	20 (49%)	
Unknown	1 (1%)	0	1 (5%)	0	
HISTOLOGY					
Clear cell	78 (92%)	19 (83%)	20 (95%)	39 (95%)	
Papillary	4 (5%)	2 (9%)	1 (5%)	1 (2%)	0.28‡
Chromophobe	1 (1%)	1 (4%)	0	0	
Rhabdoid	1 (1%)	1 (4%)	0	0	
Unknown	1 (1%)	0	0	1 (2%)	
NEPHRECTOMY					
Yes	72 (85%)	20 (87%)	17 (81%)	35 (85%)	0.86‡
No	13 (15%)	3 (13%)	4 (19%)	6 (15%)	
HENG PROGNOSTIC					
Favorable	29 (34%)	7 (30%)	6 (28%)	16 (39%)	
Intermediate	34 (40%)	8 (35%)	9 (43%)	17 (41%)	0.77‡
Poor	4 (5%)	2 (9%)	1 (5%)	1 (2%)	
Unknown	18 (21%)	6 (26%)	5 (24%)	7 (17%)	
LINES OF TREATMENT					
1	38 (45%)	11 (48%)	8 (38%)	19 (46%)	
2	29 (34%)	5 (22%)	9 (42%)	15 (37%)	0.70‡
3	7 (8%)	2 (8%)	2 (10%)	3 (7%)	
>4	11 (13%)	5 (22%)	2 (10%)	4 (10%)	

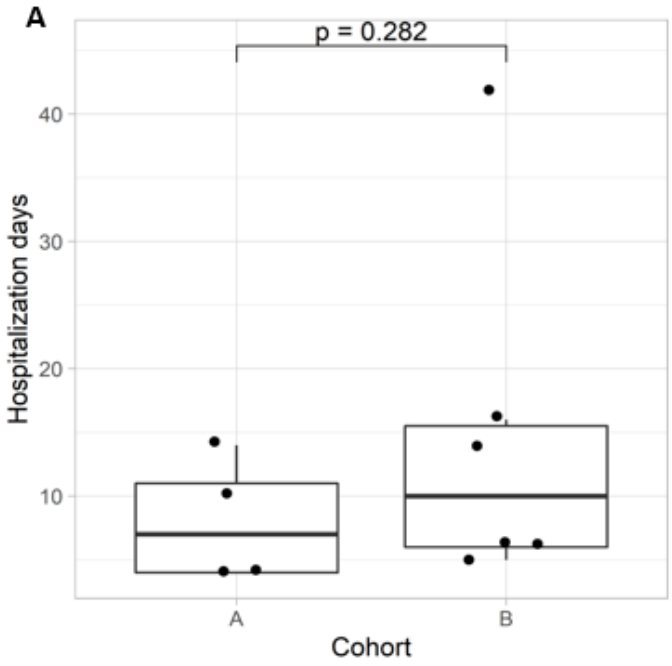
Table 2. Treatment modifications and hospitalization

	Total (n=85)	Cohort A (n=23)	Cohort B (n=21)	Cohort A+B (n=44)	Cohort C (n=41)	P value
TREATMENT INTERRUMPTION	31 (36%)	11 (48%)	14 (67%)	25 (57%)	6 (15%)	0.001
TREATMENT REDUCTION	6 (7%)	2 (9%)	0	2 (5%)	4 (10%)	0.41
HOSPITALIZATION	10 (12%)	4 (17%)	6 (29%)	10 (23%)	0	0.001

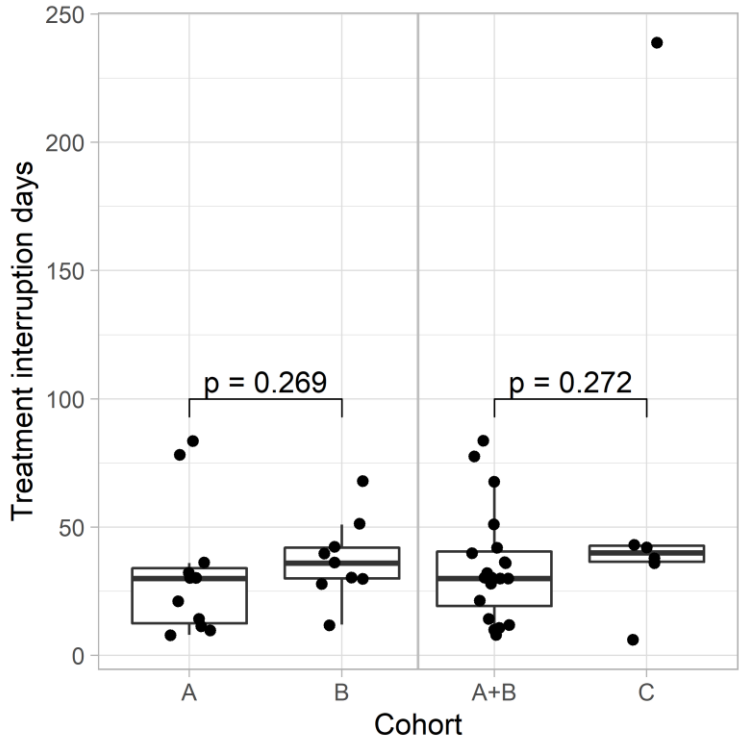
Table 3. Tumor response in the whole population and by study arm

PATIENT RESPONSES	Total (n=85)	Cohort A (n=23)	Cohort B (n=21)	Cohort C (n=41)
Responses (PR+CR)	36 (42%)	8 (42%)	10 (63%)	18 (64%)
Clinical benefit (PR+CR+SD)	53 (62%)	16 (84%)	12 (75%)	25 (89%)
Progression (PD)	10 (12%)	3 (16%)	4 (25%)	3 (11%)
Unknown	22	4	5	13

Figure 1. Days of hospitalization and treatment interruption by study cohort. A) Hospitalization days Cohort A vs B. B) Treatment interruption days Cohort A vs B and A+B (infected) vs C (non-infected). C) Treatment interruption days Cohort A vs C_A and B vs C_B .



B



C

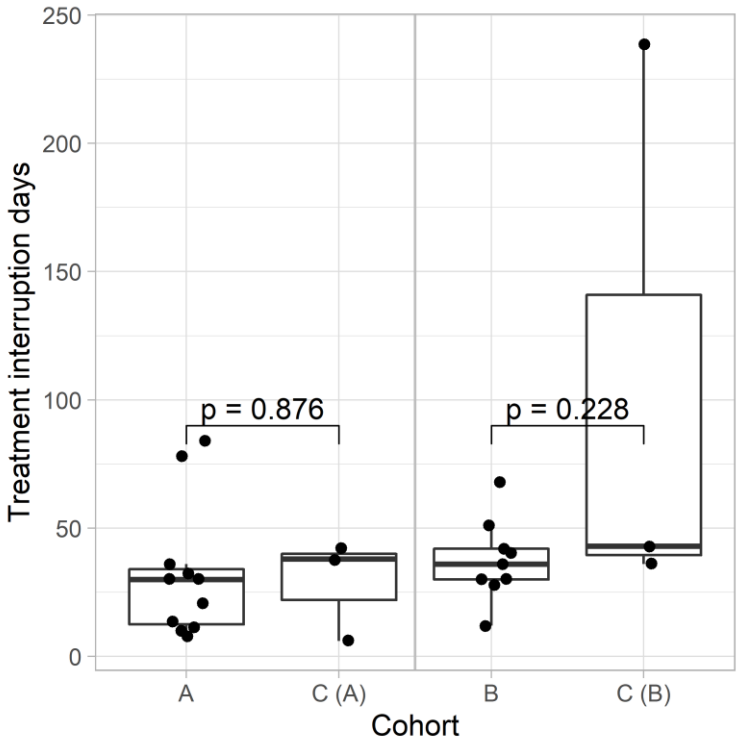
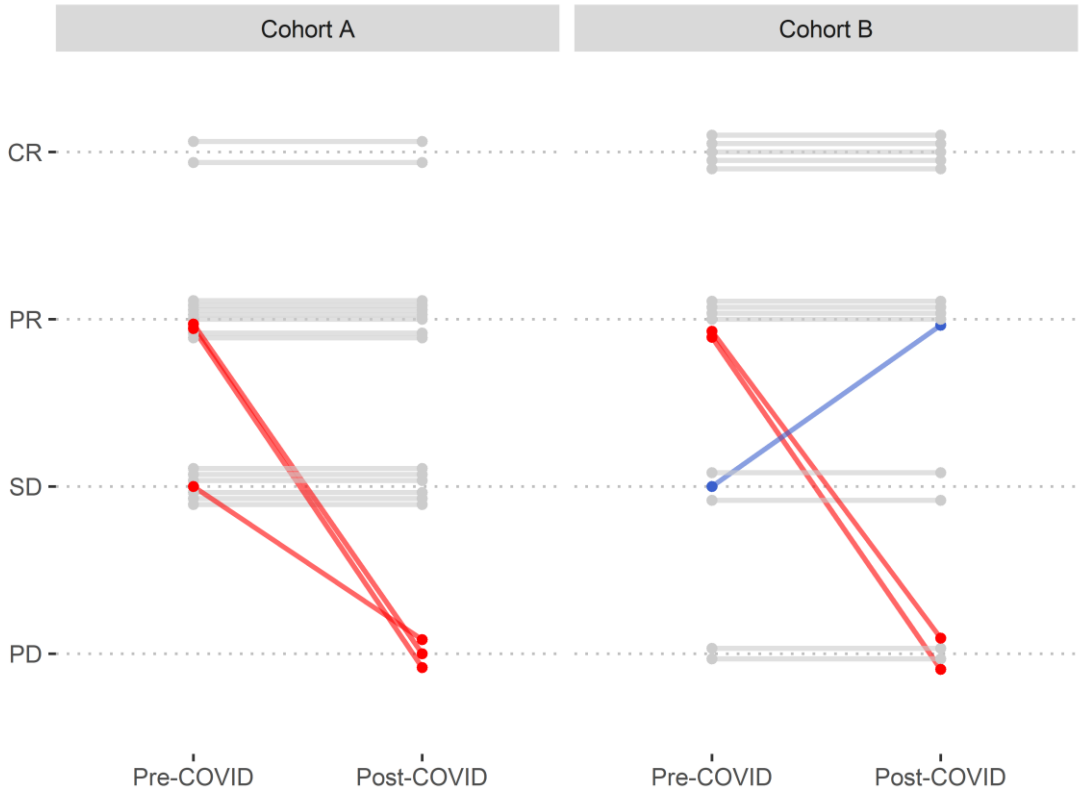

250
200
150
100
50
0
Treatment interruption days
p = 0.876
p = 0.228
A
C (A)
B
C (B)
Cohort

Figure 2. Evolution of tumor response before and after COVID19 in Cohorts A (A) and B (B). CR (complete response), PR (partial response), SD (stable disease), PD (progressive disease). “PRE-COVID” means tumor evaluation before and “POST-COVID” after the COVID episode. Lines represent tumor evolution: grey (no change), red (tumor growth) and blue (tumor shrinkage).



References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054-1062. doi: 10.1016/S0140-6736(20)30566-3. Epub 2020 Mar 11. Erratum in: Lancet. 2020 Mar 28;395(10229):1038. Erratum in: Lancet. 2020 Mar 28;395(10229):1038. PMID: 32171076; PMCID: PMC7270627.

2. Zhang H, Han H, He T, Labbe KE, Hernandez AV, Chen H, Velcheti V, Stebbing J, Wong KK. Clinical Characteristics and Outcomes of COVID-19-Infected Cancer Patients: A Systematic Review and Meta-Analysis. J Natl Cancer Inst. 2021 Apr 6;113(4):371-380. doi: 10.1093/jnci/djaa168. Erratum in: J Natl Cancer Inst. 2022 Feb 7;114(2):328-330. PMID: 33136163; PMCID: PMC7665647.

3. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020;323(20):2052–2059. doi:10.1001/jama.2020.6775

4. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med. 2020 Apr 23;382(17):1653-1659. doi: 10.1056/NEJMsr2005760. Epub 2020 Mar 30. PMID: 32227760; PMCID: PMC7121452.

5. Ahmadian E, Hosseiniyan Khatibi SM, Razi Soofiyani S, Abediazar S, Shoja MM, Ardalan M, Zununi Vahed S. Covid-19 and kidney injury: Pathophysiology and molecular mechanisms. Rev Med Virol. 2021 May;31(3):e2176. doi: 10.1002/rmv.2176. Epub 2020 Oct 6. PMID: 33022818; PMCID: PMC7646060.

6. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, Merdji H, Clere-Jehl R, Schenck M, Fagot Gandet F, Fafi-Kremer S, Castelain V, Schneider F, Grunebaum L, Anglés-Cano E, Sattler L, Mertes PM, Meziani F; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020 Jun;46(6):1089-1098. doi: 10.1007/s00134-020-06062-x. Epub 2020 May 4. PMID: 32367170; PMCID: PMC7197634.

7. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020 May 1;368(6490):473-474. doi: 10.1126/science.abb8925. Epub 2020 Apr 17. PMID: 32303591.

8. Labaki C, Peters S, Choueiri TK. Treatment Decisions for Patients with Cancer during the COVID-19 Pandemic. Cancer Discov. 2021 Jun;11(6):1330-1335. doi: 10.1158/2159-8290.CD-21-0210. Epub 2021 Apr 2. PMID: 33811043.

9. Rubinstein SM, Steinharter JA, Warner J, et al. The COVID-19 and Cancer Consortium: A Collaborative Effort to Understand the Effects of COVID-19 on Patients with Cancer. Cancer Cell. 2020 Jun;37(6):738-741. DOI: 10.1016/j.ccell.2020.04.018. PMID: 32454025; PMCID: PMC7188629.

10. Ürün Y, Hussain SA, Bakouny Z , Castellano D, Kılıçkap S, Morgan G, Mckay RR, Pels K, Schmidt A, Doroshow DB, Schütz F, Albiges L, Lopes G, Catto JWF, Peters S, Choueiri TK. Survey

of the Impact of COVID-19 on Oncologists' Decision Making in Cancer. JCO Glob Oncol. 2020 Aug;6:1248-1257. doi: 10.1200/GO.20.00300. PMID: 32755479; PMCID: PMC7456315.

11. Grivas P, Khaki AR, Wise-Draper TM, French B, Hennessy C, Hsu CY, Shyr Y, Li X, Choueiri TK, et al. Association of clinical factors and recent anticancer therapy with COVID-19 severity among patients with cancer: a report from the COVID-19 and Cancer Consortium. Ann Oncol. 2021 Jun;32(6):787-800. doi: 10.1016/j.annonc.2021.02.024. Epub 2021 Mar 19. PMID: 33746047; PMCID: PMC7972830.

12. Challenor S, Tucker D. SARS-CoV-2-induced remission of Hodgkin lymphoma. Br J Haematol. 2021 Feb;192(3):415. doi: 10.1111/bjh.17116. Epub 2021 Jan 2. PMID: 33386647.

13. M., Gelardi F., Carlo-Stella C., Chiti A. Complete remission of follicular lymphoma after SARS-CoV-2 infection: From the “flare phenomenon” to the “abscopal effect” Eur. J. Nucl. Med. Mol. Imaging. 2021;48:2652–2654. doi: 10.1007/s00259-021-05275-6.

14. Aeppli S, Eboulet EI, Eisen T, Escudier B, Fischer S, Larkin J, et al. Impact of COVID-19 pandemic on treatment patterns in metastatic clear cell renal cell carcinoma. ESMO Open. 2020;5.

15. Luo J, Rizvi H, Egger JV, Preeshagul IR, Wolchok JD, Hellmann MD. Impact of PD-1 Blockade on Severity of COVID-19 in Patients with Lung Cancers. Cancer Discov. 2020 Aug;10(8):1121-1128. doi: 10.1158/2159-8290.CD-20-0596. Epub 2020 May 12. Erratum in: Cancer Discov. 2021 Feb;11(2):520. PMID: 32398243; PMCID: PMC7416461.

16. Rogiers A, Pires da Silva I, Tentori C et al. Clinical impact of COVID-19 on patients with cancer treated with immune checkpoint inhibition. J. Immunother. Cancer 9(1), e001931 (2021).