Effect of cancer on outcome of COVID-19 patients: A systematic review and meta-analysis of studies of unvaccinated patients

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19 **Abstract**

20 Background. Since the beginning of the SARS-Cov2 pandemic, cancer patients affected by COVID-19
21 have been reported to experience poor prognosis; however, a detailed quantification of the effect of
22 cancer on outcome of unvaccinated COVID-19 patients has not been performed.

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24 Methods. To carry out a systematic review of the studies comparing the outcome of unvaccinated
25 COVID-19 patients with and without cancer, a search string was devised which was used to identify
26 relevant publications in PubMed up to December 31, 2020. We selected three outcomes: mortality,
27 access to ICU, and COVID-19 severity or hospitalization. We considered results for all cancers combined
28 as well as for specific cancers. We conducted random-effects meta-analyses of the results, overall and
29 after stratification by region. We also performed sensitivity analyses according to quality score and
30 assessed publication bias.

31 Results. For all cancer combined, the pooled odds ratio (OR) for mortality was 2.32 (95% confidence
32 interval [CI] 1.82-2.94, I^2 for heterogeneity 90.1%, 24 studies), that for ICU admission was 2.39 (95% CI
33 1.90-3.02, I^2 0.0%, 5 studies), that for disease severity or hospitalization was 2.08 (95% CI 1.60-2.72, I^2
34 92.1%, 15 studies). The pooled mortality OR for hematologic neoplasms was 2.14 (95% CI 1.87-2.44, I^2
35 20.8%, 8 studies). Data were insufficient to perform a meta-analysis for other cancers. In the mortality
36 meta-analysis for all cancers, the pooled OR was higher for studies conducted in Asia than studies
37 conducted in Europe or North America. There was no evidence of publication bias.

38 Conclusions. Our meta-analysis indicates a two-fold increased risk of adverse outcomes (mortality, ICU
39 admission and severity of COVID-19) in unvaccinated COVID-19 patients with cancer compared to
40 COVID-19 patients without cancer. These results should be compared with studies conducted in
41 vaccinated patients; nonetheless, they argue for special effort to prevent SARS-Cov2 infection in
42 patients with cancer.

43 Funding. No external funding was obtained.

44
45 Keywords

46 SARS-CoV-2; COVID-19; Cancer; Mortality; ICU; Disease severity; Meta-analysis

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49 **Introduction**

50 Since the emergence of SARS-CoV2, many studies have been conducted on the outcomes of COVID-19,
51 in order to identify factors associated with a higher death rate and a more severe infection course. Some
52 groups of patients at increased risk of severe COVID-19, morbidity and mortality have been identified,
53 including elderly patients, and those with comorbidities, as hypertension, diabetes, chronic kidney
54 disease or COPD [1]. Cancer patients are also a high-risk group due to their compromised immune
55 systems and vulnerability to infection resulting from their disease and the treatments [2].

56 It is generally assumed that cancer patients are at higher risk for severe COVID-19 and death attributed
57 to COVID-19 [3]. However, cancer encompasses a very heterogeneous group of diseases with a diverse
58 range of subtypes and stages. In addition, not all cancers are equal in terms of incidence, prognosis, and
59 treatment. This must be taken into account when the type of cancer is not specified [4]. For this reason,
60 although descriptions and analyses of risk factors, clinical courses, and mortality in cancer patients
61 infected with SARS-CoV-2 have been reported, a quantitative assessment of the effect of cancer in
62 patients with COVID-19 would be important to guide clinical decision-making.

63 We aimed at conducting a systematic review of the epidemiological features of the studies of COVID-19
64 in cancer patients conducted before the implementation of vaccination campaigns, and to provide a
65 quantitative estimate of the risk of severe infection course and mortality in COVID-19 patients with
66 cancer compared to COVID-19 patients without cancer. We decided to restrict our review to studies of
67 unvaccinated patients because (i) they provide the clearest picture of the effect of cancer on outcome of
68 COVID-19 patients, and (ii) the full effect of vaccination might not have been yet captured by available
69 studies.

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72 **Materials and methods**

73 This systematic review was conducted according to the PRISMA statement [5]. We submitted the
74 protocol (available as Supplementary File 1) to the PROSPERO Registry. To carry out the systematic
75 review of the scientific literature, the following string was used for the PubMed database:

76 *(neoplas*[TIAB] OR tumor*[TIAB] OR cancer*[TIAB] OR malignancy [TIAB]) AND (2019 novel*
77 *coronavirus[TIAB] OR COVID-19[TIAB] OR COVID19[TIAB] OR SARS-CoV-2[TIAB] OR 2019-nCoV[TIAB]).*

78 In order restrict the review to studies populations on unvaccinated COVID-19 patients, we included
79 papers published in peer-reviewed journals up to December 31, 2020. We excluded abstracts and non-
80 peer-reviewed reports, articles in languages other than English, and studies including children. We also
81 excluded reviews, meta-analysis and case reports, and studies with less than 50 patients or less than 10
82 events. Finally, we excluded studies in which diagnosis of Sars-Cov2 infection was not made by PCR
83 testing.

84 The articles were independently reviewed and abstracted by 2 pairs of reviewers [GDF and MA; GV and
85 FT], on the basis of title, abstract and full text; the disagreement between the authors of the reviews
86 (6.1% of all studies) and was resolved through discussion with a fifth reviewer [PB].

87 We selected the following outcomes: mortality, ICU admission, severity of COVID-19 symptoms, and
88 hospitalization: we combined these latter two outcomes because the definition of severity was
89 heterogeneous across studies and the number of available studies was low. We excluded from the
90 review studies addressing the impact of SARS-Cov2 infection on prevention, diagnosis, and treatment of
91 cancer patients, e.g., studies comparing cancer patients with and without SARS-CoV-2 infection, as well
92 as studies on the oncogenic effect of the virus, e.g., analyses of cancer-related alterations. In addition,
93 we carried out a back-search by inspecting the lists of references of articles selected for the review.

94 Figure 1 shows the flowchart for selection of the studies. Details on the studies retained in each step of
95 the process are available from the authors.

96 We abstracted the following parameters from the articles retained for the review: country, sample size,
97 number of persons affected by cancer and by SARS-Cov2 infection, cancer type and comparison group
98 (patients without cancer or patients with a different type of cancer), outcome, and risk estimate
99 (relative risk or odds ratio [OR]) with 95% confidence interval (CI). If the risk estimate or the CI were not
100 reported in the publication, we calculated them from the raw data, if possible. We also performed a
101 quality assessment (QA) based on a modified version of CASP score [6], that included 10 criteria
102 (Supplementary file 2).

103

104 *Statistical analysis*

105 We conducted random-effects [7] meta-analyses of the risk estimates for the combinations of cancers
106 and outcomes with more than five independent results. We also conducted stratified meta-analyses

107 according to geographic region, to explore potential sources of heterogeneity, that we quantified using
108 the I^2 test [8].

109 To evaluated results stability, we performed sensitivity analyses by quality score and repeated the meta-
110 analysis after excluding one study at a time. We also conducted secondary analyses excluding studies
111 with results calculated on the basis of raw data. Furthermore, we considered the funnel plot and
112 performed the Egger's regression asymmetry test to assess publication bias [9].

113 Finally, we conducted a cumulative meta-analysis, based on date of publication of subsequent studies.

114 Analyses were performed by STATA16 program [10], using specific commands metan, metabias, and
115 metafunnel.

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119 Results

120 We identified a total of 3488 publications from the literature search, and excluded three because they
121 were duplicates. We screened the titles and abstracts of 3485 articles: we excluded 3145 of them
122 because not relevant (Figure 1), and retained 340 articles as potentially eligible.

123 After reviewing the full-texts, we excluded 303 articles because these did not meet the inclusion criteria,
124 and included the remaining 37 studies in the review: we finally included 35 of them in the quantitative
125 synthesis.

126 Among the 35 studies, 30 reported results for all cancers combined, and 8 for hematologic neoplasms
127 (three of these reported both sets of results). Results for other specific cancers were sparse, and we
128 could not conduct meta-analyses of them. Out of the 35 studies, 13 were from Europe, 11 from North
129 America (all from USA), and 11 from Asia (9 from China and two from Iran). Fifteen studies were
130 considered good quality (CASP score >9.5), nineteen studies were of moderate quality ($9.5 \geq$ CASP score
131 > 6), whereas one was considered inadequate (CASP score ≤ 6).

132 Tables 1 and 2 show the details of the studies included in the analysis.

133 Figures 2, 3 and 4 report the results of the meta-analyses of studies of COVID-19 patients with all
134 cancers combined compared to patients without cancer, for mortality, admission to ICU and
135 hospitalization or severity of COVID-19, respectively. The pooled OR for mortality was 2.32 (95% CI 1.82-
136 2.94, I^2 90.1%), that for ICU admission was 2.39 (95% CI 1.90-3.02, I^2 0.0%), and that for
137 hospitalization/severity of disease was 2.08 (95% CI 1.60-2.72, I^2 92.1%).
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139 In the analysis by geographic region (Figure 2), the association between SARS-Cov2 infection and
140 mortality in cancer patients was stronger, and less heterogeneous, in studies from Asia (OR 2.92; 95% CI
141 2.13-4.01, I^2 37.8%) than in studies from either Europe (OR 2.37; 95% CI 1.65-3.40; I^2 67.9%) or North
142 America (OR 1.97; 95% CI 1.31-2.97; I^2 95.9%), respectively). Too few studies were available on the other
143 outcomes to justify a meta-analysis stratified by region of origin.

144 The cumulative meta-analysis, based on date of publication of subsequent studies of mortality (all type
145 of cancer), showed a stronger association in the studies published before July 2020 than in studies
146 published later (results not shown in detail).

147 As shown in Figure 5, we found no evidence of publication bias in the meta-analysis concerning
148 mortality (p-value of Egger's test 0.67). The number of studies included in the other meta-analyses was
149 too low to yield meaningful results on publication bias.
150

151 In the sensitivity analysis based on QA, the pooled OR of mortality results of studies with acceptable
152 quality was not different from that of results of good-quality studies: OR 2.25 (95% CI 1.73-2.94) vs. OR
153 2.50 (95% CI 1.47-4.26). When we repeated the analysis after excluding one study at a time, we did not
154 identify a major effect of any single study; in particular, the exclusion of the only study that suggested a
155 negative association between cancer and mortality [18] yielded a pooled OR of 2.41 (95% CI 1.95-2.99, I^2
156 85.5%). The association with mortality was less pronounced in studies whose results were reported by

157 the authors (OR 2.11; 95% CI 1.55-2.87) compared to studies whose results were calculated by us (OR
158 2.66; 95% CI 1.97-3.60%), although the difference was not statistically significant. [Figure 6]

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160 Figure 7 presents the results of the meta-analysis of eight studies on mortality in patients with
161 hematologic neoplasms. The pooled RR was 2.14 (95% CI 1.87-2.44, I^2 20.8%). Results for other
162 outcomes (admission to ICU, hospitalization, severity of symptoms) were too sparse to conduct a meta-
163 analysis.

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170 Discussion

171 Since the beginning of the SARS-Cov2 pandemic, cancer patients affected by COVID-19 have been
172 identified to be at increased risk of poor prognosis, together with other vulnerable categories of patients
173 as those affected by cardiovascular disease, diabetes, kidney injury, obesity, or stroke [46].
174 However, how much SARS-CoV2 infection resulted in more severe outcomes in cancer patients
175 compared to patients without cancer and what caused their worse clinical course has not been fully
176 clarified. In a previous editorial, some of us addressed the issue of the different interactions that COVID-
177 19 and cancer may have [47]. On one hand, it is interesting to study how COVID-19 evolves in patients
178 with cancer, by assessing whether the infection in these patients has a more severe course than in a
179 control group affected by the infection but without cancer. On the other hand, it is important to identify
180 the effects that the pandemic itself has determined in patients with cancer, including reduced access to
181 treatment, delay in diagnosis for postponed screening, increased time between follow-up visits, and
182 change in treatment organization. Acquiring more severe infection could be due to both components.

183
184 In this systematic review and meta-analysis we focused on the effect that cancer had in patients with
185 COVID-19 compared with those without cancer in terms of mortality, ICU access, and severity of COVID-
186 19 (hospitalization or severity of symptoms). We found that patients with cancer and SARS-Cov2
187 infection have a two-fold higher risk of experiencing these adverse outcomes compared to non-cancer
188 patients. Our results are in agreement with those of the meta-analysis by Venkatesulu et al. [48], who
189 included a smaller number of studies, mainly from China, and reported an OR of 2.54 (95% CI 1.47-4.42)
190 for mortality in cancer patients with concurrent COVID-19, compared to non-cancer patients. Similar to
191 our results, these authors also reported a stronger association in studies from China than in those from
192 other regions. Our results are also similar to those by Zhang et al. [49], who reported a meta-analysis of
193 five studies from China, yielding a meta-OR of 2.63, with limited heterogeneity. Compared to these early
194 reports, we included more studies, which should lead to a more robust and precise risk estimate.

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196 The higher risk of mortality in studies from China compared to those from other countries could be
197 explained by the fact that some of the studies from China were conducted during the very early phase of
198 the infection, when diagnosis and treatment for SARS-CoV2 might have been delayed, resulting in higher
199 death rate. This interpretation is reinforced by the results of the cumulative meta-analysis, that showed
200 a stronger effect detected in the early studies compared to later studies.

201
202 Our summary results on risk of ICU admission and severity of COVID-19 indicated a somehow weaker
203 association than that reported by other authors. An early meta-analysis reported a 3-fold increase for
204 ICU admission, an almost 4-fold increase for a SARS-Cov2 infection classified as severe, and a 5-fold
205 increase in being intubated [51]. The fact that our values are lower might be explained by the inclusion
206 of studies conducted when management of cancer patients with SARS-Cov2 infection was more
207 effective.

208
209 Immunosuppression and impaired T-cell response due to therapies may underlie the worse outcome in
210 hematologic cancer diseases, even if some authors suggested that the attenuated inflammatory
211 response in hematological patients can protect from severe COVID-19 morbidity [52]. The results of our

212 meta-analysis confirm a higher mortality from COVID in patients with hematological neoplasms
213 compared to non-neoplastic patients, with limited heterogeneity, with a pooled risk estimate similar to
214 that for all cancers combined.

215
216 We were not able to derive pooled results for other specific cancers. Results for patients with
217 hematologic and solid neoplasms were compared in some individual studies. In particular, Desai et al.
218 [53] reported a higher mortality in the former group, but the comparison was not adjusted for age and
219 type of therapy.

220
221 Although our study provides the most precise measure to date of the effect of cancer in COVID-19
222 patients, it suffers from some limitations. Many studies included in our analysis did not provide results
223 adjusted for important determinants such as sex, age, comorbidities, and therapy. As mentioned above,
224 we were not able to analyse specific cancers other than hematologic neoplasms, because results were
225 too sparse.

226
227 In conclusion our meta-analysis confirms, by giving a more precise and accurate estimation, evidence to
228 the hypothesis of an association in COVID-19 patients between cancer (and more specific hematologic
229 neoplasm) and a worst outcome on mortality, ICU admission and severity of COVID-19.

230 Future studies will be able to better analyse this association for different subtypes of cancer, and to
231 evaluate whether the effects identified before vaccination are attenuated vaccinated patients.

232

233 **Declarations**

234

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236

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448

449 **Figure Caption**
450
451 1. Flowchart for the identification of articles for the meta-analyses (PRISMA).
452
453 2. Forest plot - All type of cancer - Outcome 1
454
455 3. Forest plot - All type of cancer - Outcome 2
456
457 4. Forest plot - All type of cancer - Outcome 3 or 4

458 5. Funnel plot of Egger's test to assess publication bias - All type of cancer - Outcome 1

459 6. Forest plot - All type of cancer - Outcome 1 - Reported vs Calculated OR

460 7. Forest plot - Hematological neoplasms - Outcome 1
461 7. S1. Forest plot - Hematological neoplasms – Outcome 2, 3 or 4
462 8. Meta-analysis of studies of mortality (all type of cancer) by month of publication
463 9. Quality Assessment - All type of cancer - Outcome 1
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Reference	Country	N patients	N outcomes	Quality score	Comparison	Outcome	RR/OR*	95% CI
Dai et al.-2020 [11]	China	641	105	9.25	Internal	Mortality	2.34	1.15-4.77
						ICU	2.84	1.59-5.08
						Severity	2.79	1.75-4.44
Haase et al.-2020 [12]	Denmark	323	15	11.5	Internal	Mortality	3.18	1.66-6.09
Meng et al.-2020 [13]	China	436	109	9.5	Internal	Mortality	2.98°	1.76-5.05
Sun et al.-2020 [14]	USA	323	67	10.5	Internal	Mortality	5.67°	1.49-21.58
						ICU	1.91°	0.90-4.06
						Hospitalization	2.16°	1.12-4.17
Nogueira et al.-2020 [15]	Portugal	20293	611	9.25	Internal	Mortality	1.48	1.07-2.05
Zandkarimi et al.-2020 [16]	Iran	1831	32	6.5	Internal	Mortality	3.57	1.82-7.02
Zhao et al.-2020 [17]	China	539	23	6.5	Internal	Mortality	3.23	1.39-7.51
Harrison et al.-2020 [18]	USA	31461	1966	9.75	Internal	Mortality	0.87°	0.72-1.09
Gupta et al.-2020 [19]	USA	2215	112	7.5	Internal	Mortality	2.20	1.50-3.22
Ganatra et al.-2020 [20]	USA	2476	195	9.25	Internal	Mortality	3.53	2.95-4.23
						Severity	3.75	3.17-4.44

						Hospitalization	2.78	2.37-3.26
Westblade et al.-2020 [21]	USA	2294	100	8.5	Internal	Mortality	1.29	1.04-1.61
						Severity	0.76	0.57-1.01
Wang et al.-2020 [22]	USA	16570	1200	11	Internal	Mortality	3.20	2.89-3.55
						Hospitalization	2.85	2.63-3.09
Cherri et al.-2020 [23]	Italy	2039	53	11	Internal	Mortality	2.22°	1.25-3.94
Gorgulu et al.-2020 [24]	Turkey	483	75	11	Internal	Mortality	1.81°	0.88-3.72
						ICU	2.14	1.26-3.63
Jimenez et al.-2020 [25]	Spain	1549	103	9.75	Internal	Mortality	4.29°	2.40-7.67
Thompson et al.-2020 [26]	UK	470	87	10	Internal	Mortality	2.20°	1.27-3.81
Li et al.-2020 [27]	China	1859	65	9	External	Mortality	1.59°	0.94-2.68
Shoumariyeh et al.-2020 [28]	Germany	78	39	8.5	External	Mortality	1.01	0.41-2.49
						Severity	1.15	0.61-2.17
Mehta et al.-2020 [29]	USA	1308	218	8.5	External	Mortality	2.38	1.69-3.35
Rogado et al.-2020 [30]	Spain	42495	45	8	External	Mortality	4.82	2.67-8.71
Brar et al.-2020 [31]	USA	585	117	9.5	External	Mortality	0.98	0.58-1.66
						Severity	0.80	0.57-1.13

Zhang et al.- 2020 [32]	China	217	112	9.5	External	Mortality	<i>4.83</i>	<i>2.87-8.12</i>
						ICU	<i>2.60</i>	<i>1.87-3.62</i>
						Severity	<i>1.43</i>	<i>1.09-1.87</i>
Sorouri et al.- 2020[33]	Iran	159	53	10	External	Mortality	3.27°	0.93-11.55
						ICU	1.52°	0.56-4.12
Lunski et al.- 2020 [34]	USA	5145	312	9.5	External	Mortality	2.03°	1.44-2.87
Atalla et al.- 2020 [35]	USA	339	27	10.5	Internal	Hospitalization	<i>3.34</i>	<i>1.81-6.16</i>
Cheng et al.- 2020 [36]	China	1476	29	6	Internal	Severity	<i>2.14</i>	<i>0.97-4.73</i>
Song et al.-2020 [37]	China	961	21	7	Internal	Severity	<i>2.77</i>	<i>1.16-6.62</i>
Liang et al.- 2020[38]	China	1590	18	8.75	Internal	Severity	4.07°	1.23-13.45
Bauer et al.- 2020 [39]	USA	1449	108	8.5	Internal	Severity	1.72°	1.11-2.67
Tian et al.-2020 [40]	China	751	232	9	External	Severity	<i>3.75</i>	<i>2.71-5.19</i>

471 RR: Relative Risk
472 OR: Odds Ratio
473 CI: Confidence interval

474 ICU: Intensive Care Unit

475 * Results derived from data reported in the publication are in italics

476 °Risk estimates derived from multivariate analysis

477

AUTHOR – YEAR	COUNTRY	SAMPLE SIZE (n)	CANCER (n) O number of	QUALITY ASSESSMENT	COMPARISON	OUTCOME	RR/OR*	IC
Dai et al.-2020[11]	China	641	9	9.25	Internal	Mortality	9.07	2.16-38.13
Haase et al.-2020[12]	Denmark	323	13	11.5	Internal	Mortality	1.83	0.85-3.93
Meng et al.-2020[13]	China	327	16	9.5	Internal	Mortality	2.83°	0.96-8.32
Ygenoglou et al.- 2020[41]	Turkey	1480	740	10.5	External	Mortality	2.20	1.93-2.50
Shah et al.-2020[42]	UK	1183	68	9.75	External	Mortality	1.74°	1.12-2.71
Sanchez-pina et al.- 2020 [43]	Spain	92	39	10.25	External	Mortality	6.65°	1.87-23.67
Passamonti et al.- 2020 [44]	Italy		536	11	External	Mortality	2.04°	1.77-2.35
Cattaneo et al.- 2020[45]	Italy	204	102	9	External	Mortality	2.10	1.14-3.85

479 CASP: Critical Appraisal Skills Programme
480 RR: Relative Risk
481 OR: Odds Ratio
482 IC: Interval Confidence

483 ICU: Intensive Care Unit

484 *italics characters when calculated manually

485 °Risk estimates derived from multivariate analysis

Figure 1 PRISMA

2009 Flow Diagram

Figure 2 All type of cancer: Outcome 1 (Mortality) by Continental of publication

Figure 3 All type of cancer: Outcome 2 (access to ICU)

Figure 4 All type of cancer: Outcome 3 or 4 (Hospitalization or Severity of symptoms)

Figure 5 Funnel Plot: All type of cancer Outcome1 (Mortality)

p-value of Egger's test: P= 0.665 for Mortality studies

Figure 6 All type of cancer: Outcome 1 (Mortality) Reported vs Calculated OR

Figure 7 Hematological tumors: Outcome 1 (Mortality)

Figure 7 – Figure Supplement 1 Hematological tumors: Outcome 2 (access to ICU), 3 (Hospitalization), 4 (Severity of Symptoms)

Figure 8 Meta-analysis of studies of mortality (all type of cancer) by month of publication

Figure 9 Quality Assessment by CASP_all type of cancer Outcome 1 (Mortality):

Acceptable studies (CASP>6-9.5) vs Good studies (CASP>9.5-12)