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Fatality rate of COVID-19 in patients with malignancies: a sytematic review and meta-analysis

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Dear Editor

With great interest, we read the recently published letter by Ma et. al.(2020)¹ who describe the demographics, clinical features, and prognosis of cancer patients with COVID-19 infection. In this study fatality rate of the COVID-19 in patients with malignancy reported as 13.5%. To have a better estimation of fatality rate, in this letter, we aim to summarize the fatality rate among cancer patients with COVID-19 infection using meta-analysis.

It is currently well known that one of the most important risk factors for COVID-19 morbidity and mortality is comorbid conditions, of which, immunosuppression might be the most challenging one. Evidences about the relationship between COVID-19 severity and cancer are limited; however, the available few publications are indicative of more fatality rate and poorer prognosis of this novel virus in cancer patients compared with general population. It has been observed that patients with cancer patients are more likely to be admitted to the intensive care unit and require invasive ventilation, and ultimately death².

Case fatality rate (CFR) is the likelihood of an infection to result in death. We conducted a systematic search on published studies limited to ones between December 30, 2019 and May 7, 2020 in PubMed, EMBASE, and Scopus. EndNote X8.000 software was used to manage the records and exclude duplicates. We use the search term (2019 novel coronavirus OR COVID-19 OR SARS-CoV-2 OR nCoV-2019) AND (cancer OR neoplasms OR malignancy OR tumor OR carcinoma) AND (mortality OR fatality OR death). Eligible articles were those that described the case fatality rate (CFR) of COVID-19 in cancer patients.

The two investigators (MN, FGh), independently extracted data from the literature. We extracted the following variables: author, date, age, sex, number of total patients with malignancy, the proportion of death among them in each study. Case fatality was calculated as percentage of patients with cancer and infected by COVID-19 who died within hospitalization period.

The meta-analysis was performed using R version 3.2.3. Pooled case fatality rates and their 95% confidence intervals (95% CIs) were used to summarize the weighted effect size for each study grouping variable using the random-effects model. Publication bias was assessed by funnel plot and Egger's test of asymmetry.

From all 122 papers, 9 studies reported fatality rate of cancer patients with COVID-19 in hospital. A total of 805 patients from three countries including Iran (n=1)³, China (n=7)^{1,2,4-8}, and USA (n=1)⁹ were studied. The most frequent malignancies was breast cancer (n=95) followed by solid tumors (n=74) and hematologic cancer (n=67). Two studies didn't report the type of the malignancies. Seven studies reported the mean age of the patients. So, the Mean \pm SD age of the all patients in our study was 53.9 \pm 15.7 years. Only 4 studies presented the number of patients according to the sex, with a male percentage ranged from 53% to 60%. From all, 141 cancer patients died and fatality rate ranged from 5.5% to 60%. In the six studies that reported, the proportion of severe cases was more than 38%, with a exception of the one study (11%) (Table1)

The pooled case fatality rate of cancer patients who infected by COVID-19 was 0.21 (95% CI: 0.12-0.30). A significant heterogeneity was detected ($I^2 = 0.87\%$, $P < 0.001$). (Figure 1) Patients and number of the included studies were relatively small. Therefore, subgroup analysis was not performed to identify the possible source of study heterogeneity. However, the heterogeneity may be related to type of the cancer and cancer progression, different stage of the malignancies, sample size of the study, and sociodemographic characteristics. All the P values of Egger's tests were more than 0.05. The funnel plot's shape is symmetrical. There was no significant publication bias. ($P = 0.55$).

The proportion of severe cases in cancer patients affected by COVID-19 is higher than patients without cancer. We collected only available data from published articles. So, unpublished papers are not included. For the reason that COVID-19 is a new pandemic disease, the preprint platforms may have in some cases authors misuse fundamental terms.

The pooled fatality rate should be interpreted with caution. Not only for limit information in some primary studies, but for some methodological issues in calculation of the fatality rate, an accurate estimate of fatality rate may not be obtained. As studies didn't report any data about the duration of the patient's hospitalization, we couldn't define fatality rate during a certain time for example over one month. In addition, we didn't know if the cause of all death were actually due to COVID-19 or cancer. Some primary studies have suffered from small sample size, comprising a small cohort of hospitalized cancer patients. In addition, cancer patients who died from COVID-19 out of the hospital were possibly missed and some of them with mild symptoms or who were misdiagnosed are removed from the denominator, resulting in overestimation or underestimation of the fatality rate. Another issue is the variation of the study design.

However, a meta-analysis recently conducted by Cao et. al. (2020) showed that the pooled case fatality rate of COVID-19 was 6.8% (CI: 0.04-0.09) in general population. However, this is very lower than we obtained. The leading reasons for this outcome might be the cytotoxic chemotherapies or radiations these populations undergo for curative or palliative care (4), which result in a systemic immunosuppression. The proportion of severe COVID-19 patients, ranged from 11% to 69%, was also significantly higher than that of the general population.¹⁰

In conclusion, the estimated case fatality rate is high. The leading reasons for this outcome might be the cytotoxic chemotherapies or radiations these populations undergo for curative or palliative care, which

result in a systemic immunosuppression. Time trends of case fatality in age and sex subgroups with the adequate sample size will be needed after emerging more data.

Declaration of Competing Interest

All the authors declare that there are no conflicts of interest.

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Table 1. Study Characteristics

Number of study	author	year	country	Cancer type n (%)	Number of cancer COVID	Age (median)	Sex male n (%)	Number of death	Case fatality rate	Severe cases N(%)
1	He	2020	china	Hematologic n= 13 (100)	13	37	7(53)	8	62	9(69%)
2	Zhang	2020	china	Lung cancer: n= 7 (25.0); Oesophagus cancer: n= 4 (14.3); Breast cancer: n= 3 (10.7); Laryngocarcinoma: n= 2 (7.1); Liver cancer: n= 2 (7.1); Prostate cancer: n= 2 (7.1); Cervical cancer: n= 1 (3.6); Gastric cancer: n= 1 (3.6); Colon cancer: n= 1 (3.6); Rectum cancer: n= 1 (3.6); Nasopharynx cancer:	28	65	17 (60.7%)	8	28.6	15 (53.6%)

				n= 1 (3.6); Endometria l cancer: n= 1 (3.6); Ovarian cancer: n= 1 (3.6); Carcinoma of testis: n= 1 (3.6)						
3	Nikpourag hdama	2020	Iran	NP	17	NP	NP	1	5.88%	NP
4	Mehta	2020	USA	164 (75%) solid tumors(; 54 (25%): (GU: n= 46; breast: n= 28; colorectal: n= 21; gyn: .. n= 13; lung: n= 11; H & N: n= 8; neuro: n= 8; upper GI: n= 8; hepato: n= 7; B& S: n= 5; neuroendoc rine: n= 3; pancreas: n= 3; skin: n= 3) hematologi c malignancie s: n= 54	218	69 years (range 10-92 years)	127 (58%)	61	25% solid tumors(lung cancers: (55%), gastrointestinal cancers {colorectal (38%), pancreas (67%), upper GI (38%)} , gynecologic malignancies (38%). Genitourinary (15%), breast cancers (14%); Hematologic malignancies (37%).	84 (38%)
5	Liang	2020	Chin a	Lung: 5(18%)	18	63.1	NP	7	39	7 (39%)
6	Miyashita	2020	USA	Breast: n=57; Prostate: n=	334	27.52	NP	37	11.07	37 (11%)

				56; Lung: n=23; Urothelial: n= 18; and colon: n= 16 ; other: n=164						
7	Liu	2020	China	NP	107	NP	NP	6	5.6	NP
8	Mei	2020	China	Hematologic: n=13; Solid tumors: n=20	33			8	24 % (hemato: 46.2%; Solid: 10.0%)	
9	Ma	2020	china	Colorectal cancer 11 (29.7); Lung cancer 8 (21.6); Breast cancer 7 (18.9); Gynecological cancer 5 (13.5); Other cancers 6 (16.2)	37	62	20 (54.1 %)	5	13.5	54.1 %

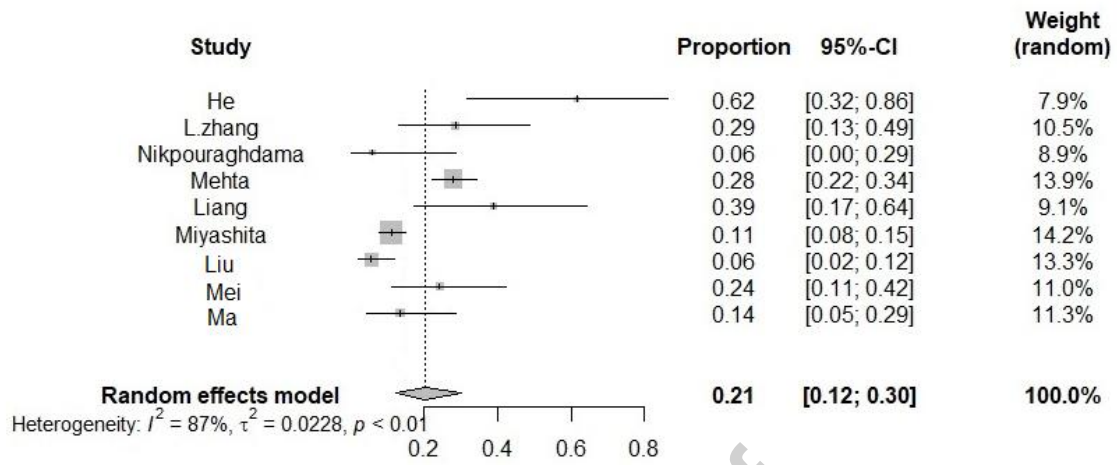


Figure 1: Forest plot of the fatality rate of the covid-19 in patients with malignancies