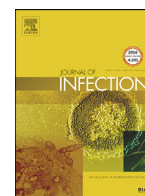




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Letter to the Editor

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


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 malignancies reported as 13.5%. To have a better estimation of fatality rate, in this letter, we aimed 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. There are limited evidences about the relationship between COVID-19 severity and cancer. However, few available publications indicated more fatality rate and poorer prognosis of this novel virus in cancer patients compared to general population. Also, it has been observed that patients with cancer are more likely to be admitted to the intensive care unit (ICU), to require invasive ventilation, and even more likely to die.²

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 used the search MeSH terms and relevant text-words including (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, Z MA), 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). Two studies didn't report the type of the malignancies. Seven studies reported the mean age of the patients. Among

them, the Mean \pm SD age of the all patients was 53.9 \pm 15.7 years. Only four 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 sever patients, the proportion of severe cases was more than 38%, with an exception of the one study (11%) (Table 1)

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 ($I^2 = 0.87\%$, $P < 0.001$). (Fig. 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. So, there was no significant publication bias. ($P = 0.55$).

The proportion of severe cases in cancer patients infected by COVID-19 is higher than patients without cancer. We collected only available data from published articles. So, unpublished papers are not included.

The pooled fatality rate should be interpreted with caution. Not only for limited information in some primary studies, but for some methodological issues in calculation of the fatality rate. So an accurate estimate of fatality rate may not be obtained in primary studies. As studies didn't report any data about the duration of the patient's hospitalization, we couldn't define case fatality rate during a certain time for example over one month. In addition, we didn't know if the cause of all deaths 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. Some of the primary studies had a poor quality to enter in the meta-analysis.

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 reason for this outcome might be the cytotoxic chemotherapies or radiations that these population underwent for curative or palliative care (4), which resulted 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 in patients with malignancies is high. It will be needed to calculate the time trends

Table 1
Study Characteristics

Number of study	autor	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	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: n= 1 (3.6); Endometrial cancer: n= 1 (3.6); Ovarian cancer: n= 1 (3.6); Carcinoma of testis: n= 1 (3.6)	28	65	17 (60.7%)	8	28.6	15 (53.6%)
3	Nikpouraghdama	2020	Iran	NP	17	NP	NP	1	5.88%	NP
4	Mehta	2020	USA	Genitourinary: n= 46; Breast: n= 28; Colorectal: n= 21; Gynecologic: n= 13; Lung: n= 11; Head & Neck: n= 8; Neuro: n= 8; upper GI: n= 8; Hepatobiliary: n= 7; Bone / Soft tissue: n= 5; Neuroendocrine: n= 3; Pancreas: n= 3; Skin: n= 3) hematologic malignancies: n= 54	218	69 years (range 10-92 years)	127 (58%)	61	25% solid tumors (lung (55%), gastrointestinal {Colorectal (38%), Pancreas (67%), Upper GI (38%)}, Gynecologic (38%), Genitourinary (15%), Breast (14%); Hematologic (37%).	84 (38%)
5	Liang	2020	China	Lung: 5(18%)	18	63.1	NP	7	39	7 (39%)
6	Miyashita	2020	USA	Breast: n=57; Prostate: n= 56; Lung: n=23; Urothelial: n= 18; and colon: n= 16; other: n=164	334	27.52	NP	37	11.07	37 (11%)
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 %

NP: Not provided.

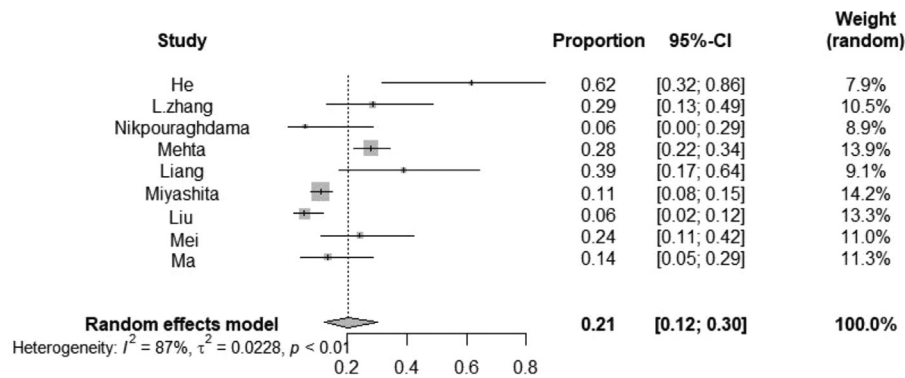


Fig. 1. Forest plot of the fatality rate of the covid-19 in patients with malignancies.

of case fatality rate in age and sex subgroups with the adequate sample size after emerging more data.

Declaration of Competing Interest

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

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References

- Jia Ma, Jing Yin, Yu Qian, Yuan Wu. Clinical characteristics and prognosis in cancer patients with COVID-19: A single center's retrospective study. *J Infect* 2020.
- Wenhua Liang, Weijie Guan, Ruchong Chen, Wei Wang, Jianfu Li, Ke Xu, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020;21(3):335–7.
- Mohamad Nikpouraghdam, Jalali Farahani Alireza, GholamHossein Alishiri, Soleyman Heydari, Mehdi Ebrahimi, Hossein Samadinia, et al. Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: A single center study. *J Clin Virol* 2020.
- Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. *Ann Oncol* 2020.
- Novel Coronavirus Pneumonia Emergency Response Epidemiology. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi= Zhonghua Liuxingbingxue Zazhi* 2020;41(2):145.
- Hirota Miyashita, Takahisa Mikami, Nitin Chopra, Takayuki Yamada, Svetlana Chernyavsky, Dahlia Rizk, et al. Do Patients with Cancer Have a Poorer Prognosis of COVID-19? An Experience in New York City. *Ann Oncol* 2020.
- Heng Mei, Xiaorong Dong, Yadan Wang, Liang Tang, Yu Hu. Managing patients with cancer during the COVID-19 pandemic: frontline experience from Wuhan. *Lancet Oncol* 2020;21(5):634–6.
- Wenjuan He, Lei Chen, Li Chen, Guolin Yuan, Yun Fang, Wenlan Chen, et al. COVID-19 in persons with haematological cancers. *Leukemia* 2020:1–9.
- Vikas Mehta, Sanjay Goel, Rafi Kabarriti, Daniel Cole, Mendel Goldfinger, Ana Acuna-Villaorduna, et al. Case Fatality Rate of Cancer Patients with COVID-19 in a New York Hospital System. *Cancer Discov* 2020.
- Dawei Wang, Bo Hu, Chang Hu, Fangfang Zhu, Xing Liu, Jing Zhang, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *Jama* 2020;323(11):1061–9.

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