World Journal of Clinical Cases

World J Clin Cases 2021 October 6; 9(28): 8280-8626





Contents

Thrice Monthly Volume 9 Number 28 October 6, 2021

REVIEW

8280 Transmission of severe acute respiratory syndrome coronavirus 2 via fecal-oral: Current knowledge

Silva FAFD, de Brito BB, Santos MLC, Marques HS, da Silva Júnior RT, de Carvalho LS, de Sousa Cruz S, Rocha GR, Correa Santos GL, de Souza KC, Maciel RGA, Lopes DS, Silva NOE, Oliveira MV, de Melo FF

8295 Nutrition, nutritional deficiencies, and schizophrenia: An association worthy of constant reassessment

Onaolapo OJ, Onaolapo AY

MINIREVIEWS

8312 Grounded theory qualitative approach from Foucault's ethical perspective: Deconstruction of patient selfdetermination in the clinical setting

Molina-Mula J

Diabetes mellitus and COVID-19: Understanding the association in light of current evidence 8327

Sen S, Chakraborty R, Kalita P, Pathak MP

ORIGINAL ARTICLE

Case Control Study

8340 Pregnancy complications effect on the nickel content in maternal blood, placenta blood and umbilical cord blood during pregnancy

Ding AL, Hu H, Xu FP, Liu LY, Peng J, Dong XD

Retrospective Study

8349 Clinical observation of Kuntai capsule combined with Fenmotong in treatment of decline of ovarian reserve function

Lin XM, Chen M, Wang QL, Ye XM, Chen HF

8358 Short-term effect and long-term prognosis of neuroendoscopic minimally invasive surgery for hypertensive int-racerebral hemorrhage

Wei JH, Tian YN, Zhang YZ, Wang XJ, Guo H, Mao JH

8366 Ultrasonographic assessment of cardiac function and disease severity in coronary heart disease

Zhang JF, Du YH, Hu HY, Han XQ

8374 COVID-19 among African Americans and Hispanics: Does gastrointestinal symptoms impact the outcome?

Ashktorab H, Folake A, Pizuorno A, Oskrochi G, Oppong-Twene P, Tamanna N, Mehdipour Dalivand M, Umeh LN, Moon ES, Kone AM, Banson A, Federman C, Ramos E, Awoyemi EO, Wonni BJ, Otto E, Maskalo G, Velez AO, Rankine S, Thrift C, Ekwunazu C, Scholes D, Chirumamilla LG, Ibrahim ME, Mitchell B, Ross J, Curtis J, Kim R, Gilliard C, Mathew J, Laiyemo A, Kibreab A, Lee E, Sherif Z, Shokrani B, Aduli F, Brim H

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 9 Number 28 October 6, 2021

Observational Study

8388 Validated tool for early prediction of intensive care unit admission in COVID-19 patients

Huang HF, Liu Y, Li JX, Dong H, Gao S, Huang ZY, Fu SZ, Yang LY, Lu HZ, Xia LY, Cao S, Gao Y, Yu XX

8404 Comparison of the impact of endoscopic retrograde cholangiopancreatography between pre-COVID-19 and current COVID-19 outbreaks in South Korea: Retrospective survey

Kim KH. Kim SB

Randomized Controlled Trial

8413 Effect of family caregiver nursing education on patients with rheumatoid arthritis and its impact factors: A randomized controlled trial

Li J, Zhang Y, Kang YJ, Ma N

SYSTEMATIC REVIEWS

8425 Dealing with hepatic artery traumas: A clinical literature review

Dilek ON, Atay A

8441 Clinical considerations for critically ill COVID-19 cancer patients: A systematic review

Ramasamy C, Mishra AK, John KJ, Lal A

CASE REPORT

8453 Atypical granular cell tumor of the urinary bladder: A case report

Wei MZ, Yan ZJ, Jiang JH, Jia XL

8461 Hepatocyte nuclear factor 1B mutation in a Chinese family with renal cysts and diabetes syndrome: A case report

Xiao TL, Zhang J, Liu L, Zhang B

8470 Ultrasound features of primary non-Hodgkin's lymphoma of the palatine tonsil: A case report

Jiang R, Zhang HM, Wang LY, Pian LP, Cui XW

8476 Percutaneous drainage in the treatment of intrahepatic pancreatic pseudocyst with Budd-Chiari syndrome:

A case report

Zhu G, Peng YS, Fang C, Yang XL, Li B

8482 Postmenopausal women with hyperandrogenemia: Three case reports

Zhu XD, Zhou LY, Jiang J, Jiang TA

8492 Extremely high titer of hepatitis B surface antigen antibodies in a primary hepatocellular carcinoma

II

patient: A case report

Han JJ, Chen Y, Nan YC, Yang YL

8498 Surgical treatment of liver metastasis with uveal melanoma: A case report

Kim YH, Choi NK

Contents

Thrice Monthly Volume 9 Number 28 October 6, 2021

8504 Intermittent appearance of right coronary fistula and collateral circulation: A case report Long WJ, Huang X, Lu YH, Huang HM, Li GW, Wang X, He ZL 8509 Synchronous concomitant pancreatic acinar cell carcin and gastric adenocarcinoma: A case report and review of literature Fang T, Liang TT, Wang YZ, Wu HT, Liu SH, Wang C 8518 Spontaneous resolution of gallbladder hematoma in blunt traumatic injury: A case report Jang H, Park CH, Park Y, Jeong E, Lee N, Kim J, Jo Y Rupture of ovarian endometriotic cyst complicated with endometriosis: A case report 8524 Wang L, Jiang YJ 8531 Rotarex mechanical thrombectomy in renal artery thrombosis: A case report Li WR, Liu MY, Chen XM, Zhang ZW 8537 Necrotizing fasciitis of cryptoglandular infection treated with multiple incisions and thread-dragging therapy: A case report Tao XC, Hu DC, Yin LX, Wang C, Lu JG 8545 Endoscopic joint capsule and articular process excision to treat lumbar facet joint syndrome: A case report Yuan HJ, Wang CY, Wang YF 8552 Spinocerebellar ataxia type 3 with dopamine-responsive dystonia: A case report Zhang XL, Li XB, Cheng FF, Liu SL, Ni WC, Tang FF, Wang QG, Wang XQ 8557 Disseminated soft tissue diffuse large B-cell lymphoma involving multiple abdominal wall muscles: A case Lee CH, Jeon SY, Yhim HY, Kwak JY 8563 Genetic characteristics of a patient with multiple primary cancers: A case report Ouyang WW, Li QY, Yang WG, Su SF, Wu LJ, Yang Y, Lu B 8571 Hypereosinophilia with cerebral venous sinus thrombosis and intracerebral hemorrhage: A case report and review of the literature Song XH, Xu T, Zhao GH 8579 Itraconazole therapy for infant hemangioma: Two case reports Liu Z, Lv S, Wang S, Qu SM, Zhang GY, Lin YT, Yang L, Li FQ

8595 Pneumocystis jirovecii and Legionella pneumophila coinfection in a patient with diffuse large B-cell lymphoma: A case report

One-stage total hip arthroplasty for advanced hip tuberculosis combined with developmental dysplasia of

Wu WH, Hui TC, Wu QQ, Xu CA, Zhou ZW, Wang SH, Zheng W, Yin QQ, Li X, Pan HY

the hip: A case report

Zhu RT, Shen LP, Chen LL, Jin G, Jiang HT

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 9 Number 28 October 6, 2021

8602	Delayed massive cerebral infarction after perioperative period of anterior cervical discectomy and fusion:
	A case report

Jia F, Du CC, Liu XG

Cortical bone trajectory fixation in cemented vertebrae in lumbar degenerative disease: A case report 8609 Chen MM, Jia P, Tang H

8616 Primary intramedullary melanocytoma presenting with lower limbs, defecation, and erectile dysfunction: A case report and review of the literature

Liu ZQ, Liu C, Fu JX, He YQ, Wang Y, Huang TX



Contents

Thrice Monthly Volume 9 Number 28 October 6, 2021

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SYSTEMATIC REVIEWS

Clinical considerations for critically ill COVID-19 cancer patients: A systematic review

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Abstract

BACKGROUND

The World Health Organization (WHO) on March 11, 2020, had declared the novel coronavirus disease 2019 (COVID-19) outbreak a global pandemic. The COVID-19 infection continues to be a pandemic and is currently causing overwhelming challenges to healthcare across the nations. Cancer patients represent a unique population vulnerable to COVID-19 infection due to their advanced age, intrinsic frailty, medical comorbidities, immunosuppression, and frequent health care visits for their underlying disease. Robust analysis of COVID-19 infection among cancer patients is crucial to aid in the optimal management of these patients.

AIM

To identify contributors of worse outcomes in patients with malignancy and COVID-19 and to describe the role of critical care.

METHODS

In this review, we summarized the information from seminal articles on the presentation and management of patients with COVID-19 and malignancy that were published before December 10, 2020. We searched the Pub Med and Medline database for "COVID-19" and "Cancer", "Malignancy". Studies published in English, including adults with malignancy and COVID-19 infection, were eligible to be included in this review. Studies on patients that provided details on malignancy, clinical presentation, management, and outcome were included. Various details of malignancy that were included are the site of cancer, histopathological type, stage, chemotherapy, and immunotherapy. Details of COVID-19

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infection that were obtained are clinical presentation, the modality of testing, imaging, management, and outcome. Critical care details that were obtained were the type of the organ dysfunction and the requirement of organ support measures, requirement of noninvasive, invasive ventilation, management of vasopressor support, and outcome. Articles that did not have patient details, opinions, letters, and articles not published in English were excluded. All articles were reviewed by 2 independent clinicians. Articles were screened for the above terminologies by independent clinicians.

RESULTS

We identified two thousand one hundred eighty-six articles, among which fiftyfive were studies that had included patient details pertaining to COVID-19 and cancer (Figure 1). Among these, eighteen studies were eligible and were included in this review as shown in Table 1. A total of 5199 cancer patients were reported. The mean age of patients across all the studies was 64.3 years with male predominance was noted in 12 studies. The clinical presentation and diagnosis of these patients were similar to the general population. Most commonly reported malignancies with COVID-19 infection were hematological in 44% of patients, followed by thoracic malignancy in 11% of patients. The mean number of cancer patients with COVID-19 requiring critical care was 16%. The mean mortality reported was 27.4%. Among the studies that reported the presence of organ dysfunction, respiratory failure was reported in 52% of patients, of which 11.7% required mechanical ventilation. 72% of COVID-19 cancer patients required hospitalization across all the studies. The factors which are associated with the worse outcome from COVID-19 infections among the cancer patients were male gender, age ≥ 65 years, presence of higher comorbidity burden based on Charlson comorbidity index and cumulative illness reporting scale > 6, and smoking history.

CONCLUSION

The majority of the cancer patients required intensive care due to respiratory failure and the need for mechanical ventilation. Appropriate contingency planning for these patients in terms of goals of care and judicious resource allocation in the resource-poor regions is the key. The factors associated with worse outcomes from COVID-19 infections were independent of oncological features such as tumor stage, disease status, or current provision of active anticancer therapy and it could be continued with caution.

Key Words: COVID-19; Cancer; Critical care; Mortality; Pandemic

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Core Tip: Based on the analyses of 18 studies from major national and international cancer registries, it is evident that among symptomatic coronavirus disease 2019 (COVID-19) cancer patients, approximately one in six patients required intensive level of care, and one in four patients had a fatal outcome. It is crucial to identify factors associated with the worse outcome as it helps to provide prognostic enrichment while discussing the goals of care in this specific patient population. Appropriate contingency planning for these patients in terms of goals of care and judicious resource allocation in the resource-poor regions is the key. Later studies showed an absence of association between mortality from COVID-19 infection and active cytotoxic or noncytotoxic chemotherapy and it could be continued with caution.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes a wide range of illnesses ranging from mild flu-like symptoms to severe respiratory failure leading to death. The novel coronavirus disease 2019 (COVID-19) infection continues to be a pandemic and is currently causing overwhelming challenges to healthcare across the nations. As of December 28th, more than 80 million cases have been diagnosed worldwide with 18 million cases reported from the United States of America[1]. Cancer patients represent a uniquely vulnerable population due to their advanced age, intrinsic frailty, medical comorbidities, immunosuppression, and frequent health care visits for their underlying disease. Existing data suggest that patients with hematological malignancies are more susceptible to SARS-CoV-2 infection[2-5]. The literature on COVID-19 infection in patients with cancer is limited. Robust analysis of outcomes of COVID-19 disease among cancer patients is crucial to aid in the optimal management of these patients during this continuously evolving pandemic. The impact of medical management, the role of critical care, and the multidisciplinary approach in treating patients with malignancy and COVID-19 infection are mostly unknown. In this review, we aimed to study the important epidemiological parameters and predictors of the requirement of acute critical care in patients with malignancy and COVID-19. We also aimed to study the various outcomes as reported in the literature in this subgroup of patients.

MATERIALS AND METHODS

In this review, we summarized the information from seminal articles on the presentation and management of patients with COVID-19 and malignancy that were published before December 10, 2020. We searched the Pub Med and, Medline database for "COVID-19" and "Cancer", "Malignancy". Studies published in English, including adults with malignancy and COVID-19 infection, were eligible to be included in this review. Studies on patients that provided details on malignancy, clinical presentation, management, and outcome were included. Various details of malignancy that were included are the site of cancer, histopathological type, stage, chemotherapy, and immunotherapy. Details of COVID-19 infection that were obtained are clinical presentation, the modality of testing, imaging, management, and outcome. Critical care details that were obtained were the type of the organ dysfunction and the requirement of organ support measures, requirement of noninvasive, invasive ventilation, management of vasopressor support, and outcome. Articles that did not have patient details, opinions, letters, and articles not published in English were excluded. All articles were reviewed by 2 independent clinicians. Articles were screened for the above terminologies by independent clinicians.

RESULTS

Studies from major national and international cancer registries and large single-center retrospective studies were included and interpreted. We identified two thousand one hundred eighty-six articles, among which fifty-five were studies that had included patient details on COVID-19 and cancer (Figure 1). Among these, eighteen studies were eligible and were included in this review as shown in Table 1. Eight of these studies were prospective in nature. These studies included patients from around eleven countries, from all over the world and five of these studies were multinational as shown in Figure 2. A total of five thousand one hundred ninety-nine patients were reported in the above studies. The mean age of patients across all the studies was 64.3 years. Male predominance among the study participants was noted in twelve (67%)

The four most common presenting symptoms of COVID-19 were fever (64%), cough (61%), fatigue or malaise (43%), and dyspnea (41%) and were similar to the general population[6]. The diagnosis was uniformly established with reverse transcriptasepolymerase chain reaction and/or radiological finding suggestive of COVID-19 infection (100%)[7,8]. However, the diagnosis which was solely based on the clinical symptoms were excluded in these studies due to the high risk of bias. Most commonly reported malignancies with COVID-19 infection were hematological in 44% of patients, followed by thoracic in 11%, gastrointestinal, and breast cancer 10% each (Figure 3).

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Ref.	Country	Study type	Mean age (yr)	Gender	COVID-19 diagnosis	No. of patients	ICU admission rates ¹	Mortality rates ¹
Garassino et al[13] (TERAVOLT)	Multinational (8 countries)	Observational-cross sectional	68	M: 141 (70%); F: 59 (30%)	RT-PCR, or imaging	200	13 (9%)	33%
Passamonti et al[2]	Italy	Retrospective	66.8	M: 340 (63%); F: 196 (37%)	RT-PCR	536	82 (15%)	37%
García-Suárez et al [3]	Spain	Prospective observational cohort study	72	M: 413 (60%); F: 277 (40)	RT-PCR	697	55 (8%)	33%
Lee et al[8] (UKCCMP)	United Kingdom	Prospective- observational	69	M: 449 (56%); F:349 (44%)	RT -PCR	800	53 (7%)	28%
Mato et al[9]	United States and Europe	Retrospective cohort	70.5	M: 125 (63%); F: 73 (37%)	RT-PCR	198	70 (35%)	33%
Fürstenau et al[5]	Europe and Israel	Randomized control trial	61	M: 4 (57%); F:3 (43%)	RT-PCR	7	2 (29%)	29%
He et al[4]	China	Case control study	35	M: 7 (56%); F: 6 (44%)	RT-PCR or imaging	13	NA	61%
Fattizzo et al[30]	Italy	Case series	77	M: 10 (63%); F: 6 (37%)	RT-PCR	16	2 (12%)	31%
de Joode <i>et al</i> [14]	Netherlands	Observational cohort study	70	M: 187 (53%); F: 164 (47%)	RT-PCR or imaging	351	NA	32%
Pinato et al[24]	Europe, United Kingdom, Italy, Spain	Retrospective observational	69.3	M: 127 (62%); F:77 (38%)	RT-PCR	204	36 (18%)	29%
Kuderer et al[6] (CCC19)	United States, Canada, Spain	Retrospective	66	M: 468 (50%); F: 460 (50%)	RT-PCR	928	132 (14%)	13%
Robilotti et al[21]	United Sates	Retrospective	NA	M: 212 (50%); F: 211 (50%)	RT-PCR	423	NA	12%
Ramaswamy et al [11]	India	Prospective observational	42	M: 124 (54%); F: 106 (46%)	RT-PCR	230	8 (3%)	10%
Nichetti et al[12]	Italy	Prospective observational	61	M: 4 (36%); F: 7 (64%)	RT-PCR	11	1 (9%)	55%
Kuderer et al[6]	Canada	Prospective observational	73	M: 127 (50%); F: 150 (50%)	RT-PCR	252	71 (28%)	13%
Lara et al[17]	United States	Retrospective	64	F: 121 (100%)	RT-PCR	121	20 (16%)	14%
Zhang et al[16]	China	Retrospective	66	M: 60 (56%); F: 47 (44%)	RT-PCR or imaging	107	NA	22%
Dai <i>et al</i> [15]	China	Case control study	64	M: 57 (55%); F: 48 (46%)	RT-PCR or imaging	105	20 (19%)	11%

¹Percentage in decimals were rounded to the nearest whole number. RT-PCR: Reverse transcriptase polymerase chain reaction; M: Male; F: Female; UKCCMP: The United Kingdom Coronavirus Cancer Monitoring Project; CCC19: Coronavirus disease 2019 and Cancer Consortium; COVID-19: Coronavirus disease 2019; ICU: Intensive care unit; NA: Not available.

> Fourteen (78%) studies reported the requirement of inpatient critical care management among patients and all of these studies reported mortality (100%). The mean number of cancer patients with COVID-19 requiring critical care was 16% with the minimum and maximum being 3% and 35% respectively. The mean mortality reported was 27.4%, with the minimum and maximum being 10% and 61.5%

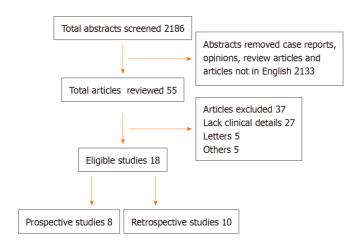


Figure 1 PRISMA diagram showing the details of the study.

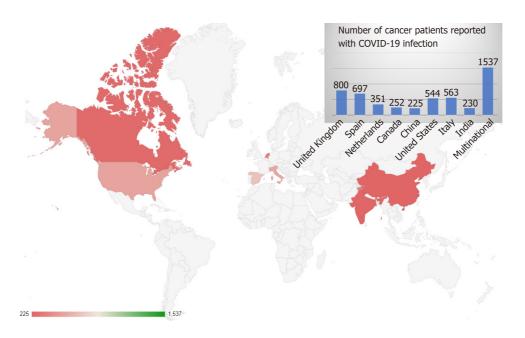


Figure 2 Showing the geographical distribution of reporting of cancer and coronavirus disease 2019 coinfection. COVID-19: Coronavirus disease 2019.

8445

respectively. The description of the various patterns of organ dysfunction was not uniform. The presence of acute hypoxic respiratory failure and requirement of mechanical ventilation was reported in 9 (50%) of the studies. Renal dysfunction, shock, and cardiac injury were reported in only 4 (22%), 2 (11%), 2 (11%) of the studies. Among the studies that reported the presence of organ dysfunction, respiratory failure was reported in 52% of patients, of which 11.7% required mechanical ventilation. The presence of renal dysfunction, shock, and cardiac injury was noted in 8%, 14.5%, and 4.3% respectively. The requirement of hospitalization was reported in 9 (50%) of the studies, with around 72% of patients requiring hospitalization across all the studies. There were significant differences in the study design, data collection, and measured outcomes among the studies which made the comparison of data difficult.

DISCUSSION

In this review, we summarized the role of intensive care in patients with COVID-19 and active malignancy. We identified that only very few studies discussed the medical management of sick patients with COVID-19 in the background of active malignancy. We identified that overall, 16% of COVID-19 cancer patients were admitted to the intensive care unit [the specific reasons for intensive care unit (ICU) admission were

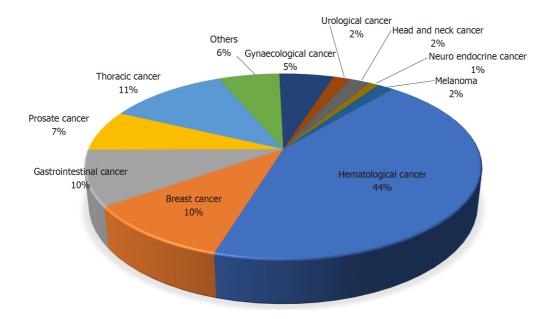


Figure 3 Pie chart showing the reported coronavirus disease 2019 infections among various types of cancers.

not available due to lack of data granularity]. The commonest cause of admission to ICU was an acute hypoxemic respiratory failure which is also the cardinal presentation of a typical symptomatic COVID-19 patient [8,9]. The reported intensive care unit admission rates among COVID-19 patients with chronic lymphomatous leukemia was 35 % which was higher than 7% and 14% reported by the United Kingdom Coronavirus Cancer Monitoring Project (UKCCMP) and the COVID-19 and Cancer Consortium (CCC19) respectively [6,8,9]. The differences in the ICU admission rates among those patients may be multifactorial. These could be related to the intrinsic immune defect secondary to chronic lymphomatous leukemia, cultural and geographical differences in the practice and ICU admission criteria, and differences in the predisposing factors such as age and comorbidities. Most of the literature that we reviewed lacked detailed information about advance care directives. Variation of inhospital mortality and ICU mortality at least in part can be attributed to do-notintubate/do-not-resuscitate status for at least some of these patients.

COVID-19 and malignancy

The real burden of COVID-19 among cancer patients was unknown as the studies were done mostly in symptomatic patients requiring treatment. Asymptomatic cancer patients were not routinely tested for COVID-19 due to resource limitations during the initial phase of the pandemic. This is hypothesis-generating and further incites the discussion about how frequently should cancer patients be treated in the absence of symptoms if at all[10,11].

During the initial stages of the COVID-19 outbreak, due to the high risks of infection and limited medical resources, prioritization of certain anticancer treatments over others, temporary chemotherapy discontinuation was routinely practiced in Europe [12]. Initial data showed that chemotherapy was associated with fatal outcomes from COVID-19 infections among the cancer patients but later this association was not confirmed by later studies from national registries[8,13,14]. The United Kingdom cancer registry reported that 172 patients (22% of analyzed subjects) received interruption In their anti-cancer treatment due to potential fear from immunosuppression. They found active chemotherapy has no significant impact on mortality from COVID -19 infection (27% mortality observed on active chemotherapy patients vs 29% on non-chemotherapy patients; P = 0.467) after adjusting for age, comorbidities[8]. The absence of association between mortality and active cytotoxic or noncytotoxic chemotherapy, recent surgery within 4 wk suggests curative surgical resection, adjuvant chemotherapy, and maintenance chemotherapy could be continued during the pandemic with extreme caution[15-17]. Randomized clinical trials are necessary to confirm this hypothesis.

Interestingly, it was reported that thoracic malignancy and chronic lymphomatous leukemia patients with COVID-19 treated with tyrosine kinase inhibitors were less likely to develop severe COVID-19 infection requiring hospitalization, the requirement

of oxygen support, and mechanical ventilation[9,13]. However, tyrosine kinase inhibitor does not appear to impact survival [9]. It is hypothesized that tyrosine kinase inhibitors modulate the immune response by blocking pro-inflammatory and chemoattractant cytokines in the lungs thereby mitigating hyperinflammatory immune response. Randomized clinical trials of tyrosine kinase inhibitor for the treatment of COVID-19 are ongoing and will provide more definitive evidence of the effect of these drugs in COVID-19 (NCT04375397 and NCT04380688)[9,18].

Role of critical care in patients with malignancy and COVID-19

Outcomes from SARS-CoV-2 are influenced by ceilings of medical care. In cancer patients, escalation beyond ward-based care requires careful case-by-case evaluation. The decision to provide organ support to acutely ill cancer patients is made even harder in the context of a global pandemic, where saturation of clinical services imposes an often difficult prioritization of critical care resources in favor of younger and less co-morbid critically ill patients [3,6,19].

Dutch Oncology COVID-19 Consortium (DOCC) encouraged early discussion of advanced care planning and treatment strategies (do not intubate) among the vulnerable populations during the ongoing pandemic. They reported more than 80% of patients who had fatal outcomes with COVID-19 had previously discussed with their care team regarding goals of care and had opted for non-heroic measures in acute decompensation from a respiratory failure point of view (do not intubate or do not resuscitate)[14]. In the Netherlands, based on DOCC registry, cancer patients with COVID-19 infections were mainly admitted to the intensive care unit solely for mechanical ventilation. They provided most of the supportive care other than the mechanical ventilation, outside the intensive care unit. Their mortality rate of 32.4% of analyzed patients was comparable to the other national registries [4,6,8,13].

COVID-19 and mortality

The overall reported mortality among the COVID-19 cancer patients ranges from 12% to 37% which is higher than the general population. UKCCMP, a registry spanning the United Kingdom reported a mortality rate of 28% based on the analysis of 800 cancer patients which was similar to the other European studies [teravolt study group (33%), Italian hematology alliance (37%) and Spain cancer registry (33%)][2,3,8,13]. Whereas the COVID-19 and CCC19, a multi-institution registry mainly from North America reported a mortality rate of 13% based on analysis of 928 patients [6]. This was similar to two single-center retrospective analyses from large healthcare systems in New York City, one at Mount Sinai (11%), another (12%) from analysis of 423 COVID-19 cancer patients at Memorial Sloan Kettering Cancer Center[20,21].

Overall, 7% to 35% of patients were treated in the intensive care unit. The mortality rates seen were as high as 50%[22]. The most common reported reason for the requirement of intensive care unit admission was acute hypoxic respiratory failure needing non-invasive or invasive mechanical ventilation[23]. The reason for intensive care unit admission was not included in most of the analyses and lack of granularity on the data point remains to be the constraint associated with retrospective studies [24]. Information condensed in studies such as above and our extensive review helps to provide prognostic enrichment while discussing the goals of care in this specific patient population.

Contributors of worse outcome in patients with malignancy and COVID-19

The factors which are associated with the worse outcome from COVID-19 infections among the cancer patients were male gender, age ≥ 65 years, presence of higher comorbidity burden based on Charlson comorbidity index and cumulative illness reporting scale > 6, and smoking history (Figure 4). These factors are significantly associated with the patient's mortality independent of oncological features such as tumor stage, disease status, or current provision of active anticancer therapy[14,24]. The higher levels of inflammatory markers such as CRP, D-dimer, ferritin, and procalcitonin were associated with severe and critical COVID-19 infections[8,16].

Some of the observations reported in the studies have a biological basis in the pathogenesis of SARS-CoV-2 infection. Male gender and history of smoking are associated with the worse outcome from COVID-19 infection. In the general population, evidence regarding the history of smoking and the risk of COVID-19 infection is equivocal[25,26]. Based on the previous human and animal studies, it has been reported that angiotensin-converting enzyme2 (ACE2) receptor expression is increased among smokers which facilitates the viral entry to cells. The angiotensinconverting-enzyme 2 converts biologically active angiotensin II to angiotensin (1-9)

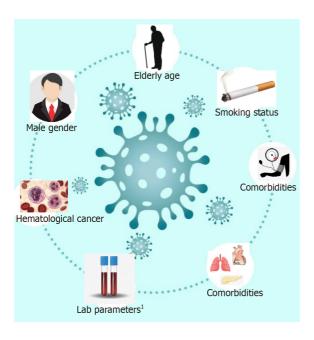


Figure 4 Contributors of worse outcome of among cancer patients with coronavirus disease 2019 infection. 'Higher levels of C-reactive protein, D-dimer, ferritin and procalcitonin.

thereby acting as a physiological counter renin-angiotensin-aldosterone system activation. The binding of the virus to the ACE2 receptor leads to its downregulation and reduced clearance of angiotensin II. It has been postulated that acute lung injury secondary to the viral infection could be due to increased levels of unbound angiotensin II and downregulation of ACE2[27].

The SARS-CoV-2 virus also depends on the proteolytic effects of transmembrane serine protease 2 (TMPRSS2)[28]. TMPRSS2 mediated cleavage of viral glycoprotein S results in the fusion of the virus with the host cell membrane. The alveolar expression of TMPRSS2 is androgen-dependent and prostate-specific [29]. The observed gender differences with a worse outcome of COVID-19 could be due to biological differences in the expression of the enzyme in addition to the difference in exposures to the virus (for example high-risk jobs, professional exposure, cigarette smoking).

Passamonti et al[2] and García-Suárez et al[3] based on the descriptive analysis reported that 50% to 62% of severe and critical COVID-19 infections among hematological cancer when compared to 26% to 43% among solid tumors vs 15% among noncancer. In their analysis, they found that non-survivors had significantly higher baseline D-dimer levels at disease onset than survivors (0.6 mg/L vs 1.3 mg/L, P =0.03).

Among the COVID-19 hematological malignancy patients, the lower levels of hemoglobin, lymphocyte, and platelet concentrations possibly due to the effect of hematologic therapies or attributable to COVID-19 infection itself which may predict worse outcomes[4].

Strengths and limitations

Our review is timely and has certain strengths such as; it included studies with patients having COVID-19 in the background of active malignancy from major national and international cancer registries. We also attempted to identify the predictors of morbidity, worse clinical outcomes, and the role of intensive care therapy in these patients.

At the same time, our study acknowledges several limitations. There are regional and geographical differences in the threshold for testing COVID-19 infection which may add to the selection bias of not testing the asymptomatic cancer patients. Studies included in this review were retrospective and lack overall granularity of information such as details on the severity of disease, details of malignancy, and details of medical treatment, details of comorbidities, drug interactions, and outcome. Details of COVID-19 infection on the management of malignancy and vice versa were also not uniformly addressed. Details of treatment of COVID-19, duration of therapy, length of hospital stay, the long-term outcome were not uniformly available, especially at the beginning of the pandemic. Details of intensive care treatment including mode of ventilation, vasopressors of choice, renal replacement therapies, the role of sedatives and

paralytics on this subgroup of populations were also not discussed. Studies with larger sample size and longer-term follow-up are needed. These limitations may also serve as hypothesis-generating questions for future studies.

CONCLUSION

As COVID-19 infection continues to affect the outcome of patients with malignancy on treatment, treating physicians need to be aware of the potential differences and contributors to outcome in patients with malignancy and COVID-19. Patients with hematological cancer and lung cancer are more vulnerable to complications of COVID-19 infections [13,14]. Superimposed bacterial infections seem to play an important role in outcomes among the hematological cancer population[4]. Limiting the exposure to novel coronavirus and prioritizing the vaccinations for these vulnerable populations should be considered. So far there is a paucity of focused data with regards to the efficacy and timing of vaccination among active cancer patients getting chemotherapy.

In this review, we identified that in the setting of active malignancy cytotoxic treatments can be continued with caution[8]. Interestingly, cancer patients treated with tyrosine kinase inhibitors were less likely to develop severe forms of COVID-19 infection. Two randomized control trials are ongoing to provide more definitive evidence. Another interesting finding was that majority of the cancer patients required intensive care due to respiratory failure and the need for mechanical ventilation. Appropriate contingency planning for these patients in terms of goals of care and judicious resource allocation in the resource-poor regions is the key.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndromecoronavirus 2 has led to an unprecedented global public health crisis. Patients with cancers are particularly suspectable to morbidity and mortality from COVID-19 infection due to their medical risk factors, immune dysfunction, and frequent health care visits for their underlying disease.

Research motivation

To analyze the characteristics of COVID-19 infection among cancer patients which would help treating physicians in optimal management of COVID-19 cancer patients.

Research objectives

In this review article, authors intend to describe the role of critical care in COVID-19 cancer patients and to analyze the various factors which determine the outcome in patients with malignancy and COVID-19.

Research methods

Authors searched the PubMed and, Medline database for "COVID-19" and "Cancer", "Malignancy". Studies published in English, including adults with malignancy and COVID-19 infection, were eligible to be included in this review. We identified two thousand one hundred eighty-six articles, among which eighteen studies were eligible and were included in this review.

Research results

A total of 5199 cancer patients were reported. Male predominance was noted in 12 studies. Most reported malignancies with COVID-19 infection were hematological in 44% of patients, followed by thoracic malignancy in 11% of patients. The mean number of cancer patients with COVID-19 requiring critical care was 16%. The mean mortality reported was 27.4%. 72% of COVID-19 cancer patients required hospitalization across all the studies. Majority of the cancer patients required intensive care due to respiratory failure and the need for mechanical ventilation. Male gender, age ≥ 65 years, presence of higher comorbidity burden and smoking history are associated with the worse outcome from COVID-19 infections among the cancer patients. These factors are significantly associated with the patient's worse outcome independent of oncological features such as tumor stage, disease status, or current provision of active anticancer therapy.

Research conclusions

Among symptomatic COVID-19 cancer patients, approximately one in six patients required intensive level of care, and one in four patients had a fatal outcome. It is crucial to identify factors associated with the worse outcome as it helps to provide prognostic enrichment while discussing the goals of care in this specific patient population. Appropriate contingency planning for these patients in terms of goals of care and judicious resource allocation in the resource-poor regions is the key.

Research perspectives

In this review, we identified that in the setting of active malignancy cytotoxic treatments can be continued with caution. Cancer patients treated with tyrosine kinase inhibitors were less likely to develop severe forms of COVID-19 infection. Two randomized control trials are ongoing to provide more definitive evidence.

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