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Research Article

Severe COVID-19 Among Cutaneous Melanoma Patients with COVID Seen in US Oncology Offices

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Abstract

The American Society of Clinical Oncology (ASCO) created a COVID-19 cancer registry among clinics throughout the US. Patients described here are among a cohort of cutaneous melanoma patients on active treatment or disease free for <12 months who developed COVID-19. We looked at the percentage of melanoma patients with severe COVID defined by COVID-19 outcomes of hospitalization, admission to the intensive care unit, intubation or mechanical ventilation, or death. Among these melanoma patients, 30% had severe COVID. COVID risk factors related to smoking, older age, and sex were not associated with having severe COVID in this population. Among melanoma patients with COVID-19, COVID symptoms that were associated with an increased likelihood of severe COVID included vomiting, dyspnea, nausea, weakness, cough, chest pain, chills, fever, diarrhea, loss of appetite, fatigue and body or muscle aches. This is most of the symptoms related to COVID-19 except for headache, rhinorrhea, and anosmia. Seventeen deaths were seen in this cohort, but only five COVID-related deaths. Among the 10 cancer-related deaths a higher risk was seen for those reporting COVID symptoms of nausea, chills, loss of appetite and fatigue. Overall, these ASCO data showed that melanoma patients' with COVID-19 had lower rates of severe COVID-19 and death than reported for other cancer sites, particularly hematological cancers. Yet, the association with most COVID-19 symptoms highlights the need for heightened vigilance and tailored management strategies for melanoma patients with symptoms during outbreaks of COVID-19 or similar respiratory illnesses.

Keywords: COVID-19; severe COVID; melanoma; symptoms.

Introduction

During the beginning of the severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) or COVID-19 pandemic, many clinics and hospitals delayed treatment of cancer patients secondary to capacity issues and resource management [1, 2]. The COVID-19 pandemic created delays in the screening for, diagnosis of and treatment of various cancers [3]. The complete repercussions of these delays have yet to be actualized. For some patients with COVID-19, the infection was mild, while others were hospitalized, and were admitted to the intensive care unit (ICU) due to potentially more life-threatening infection. People with cancer were reported early in the pandemic to be at increased risk for COVID-19 infection [4, 5], but most studies looked at cancer overall. While oncologists may have felt safe themselves during the pandemic, they were still reported as being worried about their patient's safety due to COVID-19 [6, 7].

Early in the pandemic, cancer patients were reported to exhibit exacerbated conditions and a higher mortality rate when exposed to the coronavirus [8-10]. One study reported that those living with cancer had a 60% increased risk of a positive COVID-19 test compared with participants without cancer [11]. CDC's National Vital Statistics System (NVSS) showed a 2-fold increase in cancer deaths with COVID as the underlying cause (2.4-fold in 2021) [12]. Clearly hematological and respiratory cancers are at higher risk of COVID-19 [13-15]. Hematologic cancers a 4.5-fold increase in deaths with COVID in NVSS as the underlying cause in 2020 and 7-fold in 2021 [12]. NVSS reported a lower increase for death

among melanoma patients (1.5-fold increase in 2020 and 1.8 in 2021) [12]. These differences suggest some risks due to COVID among cancer patients, which may be less so for solid tumors and more specifically melanoma.

While cancer overall is related to an increased risk for COVID-19 infection [4, 5], it is hypothesized that events related to immune suppression and complications of treatment are why cancer patients are at higher risk of COVID-19 and more severe outcomes [12, 16-19]. Among patients with hematological malignancies, chemotherapy showed a marked increase in mortality with a coinciding COVID-19 infection [16]. The data are less clear for other malignancies, so further research is needed. Chemotherapy, while effective in targeting cancer cells, can have a significant impact on the immune system, leading to immunosuppression.

Even with the widespread prevalence of COVID-19, the mechanistic insight of underlying pathophysiology of COVID-19 remains inadequate [20]. Individuals infected by COVID-19 present with a wide range of disease severity ranging from asymptomatic to a small but significant number of patients that develop severe disease that may lead to death [21]. Patients with certain underlying medical conditions are also at increased risk of severe COVID [22, 23] including cancer, cerebrovascular disease, chronic kidney or liver or lung disease, diabetes, disabilities, heart conditions, many blood disorders, immunocompromised conditions or weakened immune system [24]. A variety of factors influence disease severity including viral load, inflammation, and immune response stability [21].

Early in the pandemic studies, from three meta-analyses that summarized complications across cancer and non-cancer groups [25-27], only reported having 1 to 403 cancer patients (median =11). However, among 22 of these studies of COVID patients, severe COVID was seen in 46% (mean; median 42%) of cancer cases compared to 4% (mean; median 3%) for non-cancer patients with COVID. While these early studies did not distinguish by cancer site nor adjust for confounders, they suggest cancer patients may also be at higher risk of developing severe COVID. It is unclear if this applies to all cancer sites.

Melanoma patients differ from other cancer patients due to unique characteristics related to their disease, treatment, and immune response. While the main treatment for cutaneous melanoma is surgical removal of the lesion, some melanoma patients receive immunotherapy drugs such as immune checkpoint inhibitors (e.g., anti-PD-1, anti-CTLA-4) that treat cancer by blocking proteins that regulate the immune system [28-30]. These therapies boost the immune system to fight cancer thus they could inhibit COVID development. They may also lead to an increased risk of immune-related adverse events. While such therapies may enhance antiviral immunity potentially lowering the risk of COVID-19, they can also cause systemic inflammation or immune dysregulation, potentially complicating COVID-19 outcomes [28, 30]. Melanoma treatments may result in less profound immunosuppression unlike other cancers (e.g., hematological cancers or those treated with chemotherapy). This could mean a lower risk of severe COVID-19 than other cancer patients, though the presence of immune-related side effects may still pose risks.

While melanoma like other cancers tends to occur more frequently in older adults, who are already at higher risk for severe COVID-19, melanoma can occur at any age [31]. Overall, COVID-19 outcomes (including severity and death) among melanoma patients may be more similar to the general population than the higher risk seen with other cancer patients. Understanding the potential effects of COVID-19 on melanoma patients is imperative.

Systematic data collection across U.S. oncology practices was fostered by the American Society of Clinical Oncology (ASCO)'s COVID-19 registry launched in April 2020 [32]. Prior analyses of the ASCO registry cancer cohort diagnosed with COVID-19 reported higher mortality among patients with B-cell malignancies [32]. We proposed to the Melanoma Research Foundation in conjunction with ASCO to examine how melanoma patients undergoing treatment at oncology practices are affected by having a positive COVID-19 test. This includes the frequency of severe COVID and death along with evaluating how symptoms related to COVID-19 are associated with such outcomes. The purpose of these analyses is to describe known or suspected symptoms of COVID-19 as associated with severe COVID-19 and death among the cohort of cutaneous melanoma patients on active treatment or disease free for less than 12 months who developed COVID-19.

Materials and Methods

Patients

The American Society of Clinical Oncology (ASCO) has a cancer registry among 67 oncology practices in 26 states throughout the United States designed to collect baseline and follow-up data on patients. In response to the COVID-19 pandemic, ASCO developed survey instruments for oncology practitioners to complete regarding their cancer patients with COVID-19. Participating medical oncology practices identified patients with positive SARS-CoV-2 tests and entered data in the form of surveys regarding how COVID-19 is impacting the delivery of cancer care and patient outcomes. Data from surveys were manually entered, prospectively and retrospectively, into REDCap a secure web application for building and managing databases hosted at ASCO [33]. Thus, this research is reliant on data collected from ambulatory oncology clinics [34].

The ASCO COVID-19 Registry was set up to include patients who met the following two inclusion criteria: 1) a positive SARS-CoV2 test or clinically diagnosed COVID-19, and 2) at the time of SARS-CoV2 positivity the patient must have active cancer, cancer treatment or have been cancer-free for less than 12 months (i.e., from the time of surgical resection or complete remission). Data collected by the ASCO COVID-19 Registry include cancer treatment approaches at the time of SARS-CoV-2 infection, cancer status at the time of SARS-CoV-2 infection, changes to cancer treatment plans, the status of SARS-CoV2 infection (e.g., symptoms, severity of symptoms, need for ventilator, hospitalization, recovery, long-term symptoms, and sequelae, etc.), vaccination information, and change in cancer status (e.g., cancer progression, treatment-related changes/modifications, etc.). The ASCO COVID-19 registry also asked about COVID-19 patient symptoms. Their symptom checklist included fever, headache, sore throat, cough, shortness of breath, loss of taste or smell, vomiting, diarrhea, fatigue, body or muscles aches, loss of appetite, chest pain, congestion, and/or runny nose, other (specify) or none of the above (asymptomatic). The registry involves a limited data set and requires data use agreements with participating institutions [32]. The ASCO COVID-19 registry study protocol was reviewed by the WCG institutional review board and determined it was not human subject research.

Patients were diagnosed with cancer between 2009-2021 and COVID-19 infection between April 2020 and March 2022. With these data, the ASCO Registry aims to help the cancer community learn more about the patterns of symptoms and severity of COVID-19 infection and the impact on treatment among patients with cancer. The ASCO Registry collects baseline and follow-up data on how the COVID-19 virus impacts cancer care and patient outcomes during the pandemic and for up to two years after a patient with cancer is infected with SARS-Cov-2.

We examined outcomes among a cohort of 73 cutaneous melanoma patients who were infected with COVID-19. Among the 73 melanoma cases with COVID- identified in oncology practices, 22 had severe COVID-19 and 17 died of COVID or of their cancer or other reasons. Severe COVID was coded (as yes) based on the CDC definition of having any of the COVID-19 outcomes of hospitalization, admission to the intensive care unit (ICU), intubation or mechanical ventilation, or death [35]; otherwise severe COVID was coded as no. It was also important to consider if patients might be immunocompromised for reasons other than having melanoma or COVID-19. Patients were coded (yes) as possibly being immunocompromised if they had any of the following conditions: HIV/AIDS (N=0), history of solid organ transplant (N=0), diabetes (N=6), cirrhosis (N=0), hepatitis (N=1), sepsis (N=1), chronic renal insufficiency (N=5), chronic obstructive pulmonary disease (COPD)/emphysema (N=8), coagulation defect (N=1), or noted they were immuno-suppressed due to non-cancer related treatment or chemotherapy (N=0). Eighteen subjects were coded as being immunocompromised. Age was collected in 5-year age groups. To estimate the mean age, we assigned the midpoint of each 5-year age group. We did not include smoking in this list as we looked at smoking separately.

Statistical Analyses

Relative risks (RR) were assessed in this cohort of melanoma patients with COVID-19 to look at factors associated with severe COVID (22 as yes, 51 as no) and death (N=17). These analyses provide RRs and 95% confidence intervals (CI) [36, 37]. Factors related to severe COVID and those related to any death were examined for confounding by age, sex and being immunocompromised based on a change in the RR of more than 20% (not 10% due to the smaller sample size). If adjustment is not stated, then no confounding was seen. Deaths due to COVID and cancer progression/treatment were not examined for confounding due to the small number of deaths. When confounding was seen, adjustments are noted in the results; otherwise, unadjusted RR are presented. Race/ethnicity had too little variation to consider adjusting for it. Data were analyzed using Cochran-Mantel-Haenszel statistics in SAS 9.4.

Results

Of the 73 ASCO registry melanoma cases that were COVID-19 positive identified between April 2020 and March 2022, 30% had severe COVID infections. Overall, 58% had metastatic disease, 6% had regional stage disease,16% had localized disease, 18% had unknown stage of melanoma and 3% were cancer-free with adjunct therapy. These patients were ages 25+ with an estimated mean age of 63 (median=67; interquartile range of 52-72). Five died of COVID-19 complications, ten died of complication due to their melanoma and to of other underlying causes. Only 17 subjects were diagnosed after the COVID-19 vaccines were available and only 11 had the vaccine at baseline, therefore it could not be examined. Thus, we could not look at the association between severe COVID and prior COVID-19 vaccination with any power.

Table 1 describes demographics or host characteristics along with cancer status among the ASCO melanoma cases by those with and without severe COVID. Those with severe COVID were more likely to have cancer that was progressing (R=7.28). No clear trends were seen for severity of COVID-19 by age, or body mass index with a non-significant increase for males and a 2-fold increase for Hispanics and non-Whites combined.

Characteristics	Overall Frequency		Severe COVID[a]				
	N	%	Yes	No	Crude RR	95% CI	
Sex:							
female	26	35.6	6	20	ref		
male	47	64.4	16	31	1.48	0.66	3.31
Race/Ethnicity:							
Non-Hispanic White	64	87.7	17	47	ref		
Hispanics and non-Whites[b]	9	12.3	5	4	2.09	1.03	4.26
Age:							
18-49	14	19.2	3	11	ref		
50-59	13	17.8	6	7	3.14	0.59	16.84
60-69	22	30.1	4	18	0.82	0.15	4.35
70+	24	32.9	9	15	2.2	0.48	10.07
Body Mass Index:							
17-<25 kg/m^2	17	23.3	8	9	ref		
25-<30 kg/m^2	22	30.1	6	16	0.42	0.11	1.61
30-49 kg/m^2	33	45.2	8	25	0.36	0.1	1.25
missing	1	1.37	0	1			
Prior/concurrent other malignant cancer:							
no	57	78.1	16	41			
yes	16	21.9	6	10	1.34	0.62	2.85
Cancer extent:							
cancer free w/adjunct therapy	2	2.7	0	2			
Local/regional	16	21.9	3	50	ref		
metastatic	42	57.5	14	28	2.17	0.53	8.87
unknown	13	17.8	5	8	2.71	0.5	14.54
Cancer status:							
progressing	16	21.9	9	7	7.28	1.51	35.21
responding to treatment	10	13.7	3	7	2.43	0.39	15.08
stable	20	27.4	3	17	ref		
unknown/missing	27	36	7	15			

Abbreviations: BMI, body mass index; CI, Confidence interval; kg, kilograms; m, meters; RR, relative risk; ref, reference category.
a COVID-19 diagnosis within 12 months of melanoma diagnosis or treatment. Severe COVID defined by CDC to include hospitalization, admission to the intensive care unit, intubation or mechanical ventilation, or death.
b This includes white Hispanics, and black, other races and unknown race.

Table 1: Host characteristics and cancer status of melanoma patients diagnosed with COVID-19 within 12 months of their melanoma diagnosis or treatment.

Several patient experiences that may be related to complications of their COVID-19 illness were associated with severe COVID likely due to such conditions required hospitalization which is part of the definition of severe COVID. Patient experiences following complications of their COVID-19 illness (likely due to requiring hospitalization) that were significantly related to severe COVID included COVID pneumonia (RR = 3.82), bleeding (RR = 3.53), sepsis (RR = 3.77), acute respiratory distress syndrome (RR = 3.26), respiratory failure (RR = 3.77), cardiac arrythmia (RR = 3.26), cerebrovascular accident (e.g., stroke) (RR = 2.67 adjusted for sex), and encephalopathy (RR = 3.53). None of the melanoma cases reported disseminated intravascular coagulation, pulmonary embolism, congestive heart failure, deep venous thrombosis, myocardial infarction, acute hepatic injury, bowel perforation, peritonitis, or seizures and only one reported acute renal failure.

Risk of severe COVID-19 among the 73 melanoma patients with COVID-19 diagnosed within 12 months of their melanoma diagnosis or treatment was not related to drug treatments for cancer including Pembrolizumab, Binimetinib, Encorafenib, Nivolumab, Ipilimumab, Trametinib, or Dabrafenib. However, those who reported being tested for COVID due to patient symptoms had 8.72 increased risk of severe COVID (95% CI of 2.20-34.61). Some risk factors related to developing COVID were not significantly related to having severe COVID among melanoma patients with COVID including current smoking (RR=0.89), past smoking (RR=1.18), being over age 65 (RR=1.26), and obesity (RR=0.68). Severe COVID was also not related to pneumonitis (RR = 2.18), diabetes (RR = 1.83), hypertension (RR = 1.81), COPD (RR = 1.59) or chronic kidney insufficiency (RR = 2.25).

Table 2 describes COVID-19 symptoms among melanoma patients as related to severe COVID. No asymptomatic melanoma patients had severe COVID. The strongest associations were seen with vomiting (Rr=5.17) and chills (RR=4.7). Patients who manifested symptoms shortness of breath (dyspnea), cough, chest pain, fever, diarrhea loss of appetite, and body or muscle aches also showed an increased risk of severe COVID among melanoma patients who developed COVID-19 within 12 months of cancer treatment or diagnosis (Table 2). Among "other symptoms" that were specified, severe COVID was associated with nausea, weakness, and chills.

COVID-19 symptoms		Severe COVID				
		Yes	No	RR	95% CI	
Vomiting	no	19	51	ref[b]		
	yes	3	0	5.17	2.52	10.6
Shortness of breath (dyspnea)	no	10	46	ref		
	yes	12	5	3.95	2.08	7.5
Nausea (other symptom)	no	18	51	ref		
	yes	4	0	3.83	2.58	5.7
Weakness (other symptom)	no	19	51	ref		
	yes	3	0	3.68	2.51	5.41
Cough	no	8	41	ref		
	yes	14	10	3.57	1.74	7.33
Chest pain	no	20	51	ref		
	yes	2	0	3.55	2.45	5.15
Chills (other symptom)	no	20	51	ref[b]		
	yes	2	0	4.57	2.38	8
Fever	no	11	45	ref		
	yes	11	6	3.29	1.74	6.22
Diarrhea	no	18	50	ref		
	yes	4	1	3.02	1.67	5.46

Loss of appetite	no	17	49	ref		
	yes	5	2	2.77	1.49	5.17
Fatigue	no	13	42	ref		
	yes	9	9	2.11	1.09	4.1
Body or muscle aches	no	16	46	ref		
	yes	6	5	2.11	1.07	4.19
Sore throat	no	21	49	ref		
	yes	1	2	1.11	0.22	5.73
Headache	no	20	45	ref		
	yes	2	6	0.81	0.23	2.85
Rhinorrhea	no	21	45	ref		
	yes	1	6	0.45	0.07	2.85
Loss of taste or smell	no	22	28	ref		
	yes	0	5	ID		

Abbreviations: CI, Confidence interval; ID, indeterminable RR; ref, reference category; RR, relative risk.
a COVID-19 diagnosis within 12 months of melanoma diagnosis or treatment. Severe COVID defined by CDC to include hospitalization, admission to the intensive care unit, intubation or mechanical ventilation, or death.
b Adjusted for age < 65 and 65+.

Table 2: COVID-19 symptoms among melanoma patients with COVID-19[a] as related to risk of severe COVID, strongest associations first[a].

Among the cohort, there were 17 deaths (23.3%) with five from COVID-19 (6.8%) and 10 related to cancer prognosis and treatment (13.7%) and two due to other causes. We had planned to evaluate how COVID-19 severity changes survival by stage of melanoma, but the high survival rate and lack of association with stage in this cohort prohibited such analyses. Instead, we looked at death. While the data on deaths among these melanoma patients with COVID-19 should be interpreted with caution due to the small numbers reported, overall deaths were related to having severe COVID, COVID-pneumonia, and symptoms of shortness of breath (dyspnea), nausea, vomiting, chills, and weakness (Table 3). Deaths due to COVID-19 were all in hospitalized males requiring supplemental oxygen, and exhibiting symptoms of shortness of breath. They were linked to having COVID pneumonia, vomiting and chest pain in this cohort of patients (Table 3). Non-COVID deaths were related to reporting chills and loss of appetite.

Effect	all 17 deaths				5 COVID deaths[b]				10 Cancer deaths[b]			
	% dead exp	Crude RR	95% CI		% dead exp	Crude RR	95% CI		% dead exp	Crude RR	95% CI	
Severe COVID	65%	4.25	1.8	10.04	100%				40%	1.55	0.48	4.94
COVID related Condition or Symptoms												
COVID-pneumonia	53%	3.02	1.35	6.77	80%	10.57	1.29	86.61	25%	0.88	0.2	3.86
Dyspnea	59%	4.71	2.12	10.46	100%				40%	2.2	0.7	6.89
Nausea	18%	3.7	1.77	7.7	20%	4.31	0.62	30.18	20%	4.31	1.33	14
Vomiting	18%	6.50[b]	3.43	12.3	40%	15.56	3.97	60.97	10%	2.59	0.47	14.37
Weakness	12%	3.11	1.24	7.79	20%	5.83	0.91	37.54	10%	2.59	0.47	14.37
Cough	47%	1.81	0.8	4.11	40%	1.36	0.24	7.61	50%	2.04	0.65	6.38
Chest pain	6%	2.22	0.52	9.47	20%	8.87	1.65	47.68	0%			
Chills	12%	4.73	3.02	7.42	0%				20%	8.88	4.62	17.05
Fever	29%	1.37	0.56	3.35	20%	0.82	0.1	6.88	20%	0.82	0.19	3.52
Diarrhea	12%	1.81	0.57	5.8	0%				20%	3.4	0.97	11.93
Loss of appetite	24%	2.9	1.3	6.49	20%	2.36	0.3	18.28	30%	4.04	1.34	12.21
Fatigue	35%	1.67	0.72	3.86	20%	0.76	0.1	6.4	50%	3.06	1	9.36
Body or muscle aches	18%	1.21	0.41	3.52	20%	1.41	0.17	11.45	20%	1.41	0.34	5.77

Abbreviations: CI, Confidence interval; exp, exposed; RR, relative risk; ref, reference category.
a COVID-19 diagnosis within 12 months of melanoma diagnosis or treatment; none were vaccinated prior to developing COVID, or reported weakness or chest pain.
b Other deaths were coded as missing. Among the 17 deaths, 5 were from COVID, 10 were related to their cancer (1 from cancer treatment, 9 from cancer prognosis), and 2 other deaths were not related to COVID-19 or their cancer. b Adjusted for being immunocompromised (having diabetes, hepatitis, sepsis, chronic renal insufficiency, COPD (chronic obstructive pulmonary disease), or a coagulation defect.

Table 3: Multivariate models for 17 deaths among melanoma patients with COVID-19[a].

Discussion

This study found 30% of melanoma patients with COVID-19 had severe COVID, which is slightly higher than seen for non-cancer studies (26%) [38], but is lower than seen for all cancer patients of 45% (range 17-84%) based on 22 studies published through April 2020 [39]. Among studies on only hematological cancer, the mean percentage of cancer patients with COVID who have severe COVID was higher at 59% (range 45-84%) based on six studies [40]. In our ASCO patients with melanoma and COVID, having only 30% with severe COVID suggests less severe complications due to COVID-19 among melanoma patients than other cancer patients. However, 30% is still a substantial burden of severe illness in this population.

A meta-analysis of 17 studies found that COVID infected cancer patients who recently received active cancer treatment did not observe a higher risk of exacerbation and mortality, but saw an increased risk (OR=1.45) specifically with chemotherapy in the last 28 days [41]. However, a subsequent meta-analysis of 52 cohort studies reported a small significantly increased risk among patients on anti-cancer therapy for death (OR=1.21), severe COVID (OR=1.19) with age, sex, hypertension, COPD, smoking and lung cancer as potential prognostic factors for both death and severe COVID [41]. The other two meta-analyses also found cancer patients with COVID who died was on average 28% (range 7-56%) based on 47 studies published from 2020 to March 2021 [40, 41], however it was not clear if this was any death or death due to COVID but as data collection was only through March 2021 it is likely that COVID was the underlying cause of death. Among studies on only hematological cancer, the mean and median percentage of cancer patients with COVID who died was 35% and 38%, respectively (range 24-56%) based on 11 studies [40]. In our study of melanoma patients, we saw 23% of patients died, with only 7% due to COVID-19, which also suggests a lower rate of death among melanoma patients. This would be consistent with less severe outcomes due to COVID among melanoma patients.

Other studies of COVID among melanoma patients had a wide range in reported percentage of their population that had severe COVID ranging from 7-8% in populations in Greece and Switzerland [28, 29], to 27% in France [30] and 68% in Spain [42] with the percentages of deaths ranging from 4-26%. Our findings of 30% of melanoma patients with severe COVID and 7% dying of COVID-19 are within these ranges. However, the wide range for severe COVID needs to be better understood as the 68% of melanoma patients with COVID having severe COVID in Spain is higher than seen among other cancers. It is of note, that the study from France reported a similar percentage as we did for melanoma patients with COVID having severe COVID [30].

Among ASCO melanoma patients with a COVID-19 infection, 73% had symptoms. Indicators of severe COVID included most symptoms for COVID-19. COVID symptoms that we found to be related to severe COVID, shortness of breath, nausea, vomiting, weakness, chills, and loss of appetite were also related to any death. However, only vomiting and chest pain were significantly related to deaths due to COVID, whereas, nausea, chills, loss of appetite and fatigue were related to deaths related to the cancer progression or treatment. None of these who died had reported a sore throat or loss of taste or smell. A French study screened all of their melanoma patients for COVID symptoms with 45.2% reporting any symptoms compared to 60% among melanoma patients with COVID-19 [30]. This is a bit lower than what we saw. In this study in France, only fever, anosmia and shortness of breath were significantly higher among COVID cases than non-COVID melanoma cases with no differences in the symptoms for chills, nasal congestion, headache (higher in those without COVID), sore throat, nausea, vomiting, and diarrhea (Chi-square p-value > 50%).

COVID studies have looked at a variety of COVID-19 symptoms [43, 44]. A recent review of mobile health applications (apps) for monitoring COVID-19 symptoms found almost all apps asked about fever, dry cough, tiredness, aches and pains (myalgias), sore throat (pharyngitis), diarrhea, headache, loss of taste or smell, difficulty breathing or shortness of breath (dyspnea), chest pain/pressure and a few asked about skin rash [43]. Laracy et al., [44] looked at eight of these symptoms along with abdominal pain, chills, fatigue, nausea/vomiting, and running nose (rhinorrhea) among healthcare personnel. The ASCO registry asked many of the same questions about COVID-19 symptoms as other studies, but the distribution of a few main symptoms seems to vary across different populations [43, 44]. We saw that the most commonly reported COVID-19 symptom among all melanoma patients with COVID-19 was a cough (33%) followed by fatigue (25%), fever (23%), shortness of breath (23%), muscle and body pain (15%), headache (11%), and runny nose (10%). The symptoms reported among ASCO melanoma patients are similar to what Laracy et al. [44] reported to be the most common COVID-19 symptoms in their study of healthcare personnel who developed COVID-19 infections including cough (61%), sore throat (61%), fatigue (54%), headache (53%), runny nose (52%), and muscle pain (46%)], though healthcare workers reported higher rates of these symptoms than the melanoma patients. However, symptoms were higher in ASCO melanoma patients with severe COVID including cough (64%), fatigue (41%), and muscle pain (27%) but not sore throat, headache, or runny nose. Similarly, a study of COVID-19 hospitalizations in the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) cohort study reported frequencies of 69% for fever, 68% for cough, 66% for shortness of breath, and 46% for fatigue [45]. One study reported chest distress

among 14% of cancer patients with COVID but only 6% among COVID patients without cancer [46], we saw fewer patients (9% of melanoma) with COVID having chest pain. The COVID symptom frequency among healthcare workers were similar to melanoma patients for fatigue and cough, but were 6 to 13 times as common among health care workers for headache, rhinorrhea and sore throat suggesting milder symptoms among these melanoma patients. Laracy et al. [44] found symptoms with the Omicron variant and variants that predated Omicron were somewhat similar though more Omicron patients reported sore throats and less frequently reported rhinorrhea, diarrhea and loss of smell or taste. For cases during the Omicron variant breakthrough, patients were more likely to have symptoms if they had not a booster vaccine [44]. Few studies have reported COVID-19 symptoms among cancer patients. The higher frequency of symptoms reported among healthcare workers could be skewed as healthcare workers are (in general) more aware of potential COVID-19 symptoms and/or COVID-19 symptoms may be underreported in cancer patients due to being masked by cancer-related symptoms consciously or subconsciously. In another study, a community-based cohort of adults who developed COVID-19 symptoms, most commonly reported symptoms of cough, fever, headache, and muscle ache, which is similar to both the healthcare worker study and melanoma patients in this study [47]. These studies show similar symptoms among melanoma patients, healthcare workers, community-based adults and hospitalized patients diagnosed with COVID-19.

Some inconsistencies remain when surveying patients about the COVID-19 symptoms [44]. The World Health Organization's clinical definition of COVID-19 infection is the manifestation of 3 symptoms, whereas the Centers for Disease Control breaks up their definition using 3 symptoms into specific groups of 1 and 2 symptoms. The organizations agree that the possible symptoms include fever, cough, headache, dyspnea, myalgias and sore throat. However, their symptom lists differ on the inclusion of chills, nausea/vomiting, diarrhea, difficulty breathing, and an altered mental status as typical COVID-19 symptoms [45]. Other studies have inconsistently reported these COVID-19 symptoms. More analyses of existing studies are needed to clarify the COVID symptom lists and their significance.

Another review of COVID patients found the most prevalent symptoms or clinical manifestations were fever (78%), cough (65%), fatigue (41%), and dyspnea (39%) [48]. They compared prevalent clinical manifestations between severe and non-severe COVID patients finding the significant associations with dyspnea (OR: 4.20, 95% CI: 3.09–5.72), cough (OR: 1.45, 95% CI: 1.18–1.78), and fatigue (OR: 1.40, 95% CI: 1.14-1.72) based on pooling 34 studies [48]. While we saw less frequent fever (23%), cough (33%), fatigue (25%), and dyspnea (23%) among ASCO melanoma patients within 12 months of diagnosis or treatment, we saw also saw significant associations with dyspnea (OR: 3.95), cough (OR: 3.57), and fatigue (OR: 2.11) along with other factors (Table 2).

Impact of Comorbidities

A meta-analysis [49] of studies published December 2019-July 2020 looked at the impact of coronary heart disease, hypertension and diabetes on the prevalence of severe COVID-19 finding ORs of 3.21 (95% CI of 2.58-3.99), 2.27 (95% CI of 1.79-2.90), and 2.34 (95% CI of 1.79-3.05), respectively. A review of clinical factors related to severe COVID among 41 studies in China found male sex, diabetes, cerebrovascular disease (crude OR=3.34; N=7 studies), hypertension (OR=2.63; N=18 studies), COPD (OR=6.92; N=6 studies), other lung diseases and cancer to be related to severe COVID [50]. Another review of 41 studies throughout the world (including 16 from China) found similar significant results for severe COVID and cerebrovascular disease (crude OR=2.78; N=31 studies), hypertension (OR=1.98; N=35 studies), with lower risk for COPD (OR=1.90; N=28 studies), but also found significant results for chronic kidney disease(OR=2.74; N=20 studies), diabetes (OR=2.04; N=37 studies), and cancer (OR=1.75; N=28 studies) [48]. Among our ASCO melanoma patient experiencing complications of COVID we found a similar risk for cerebrovascular accident (e.g., stroke) (crude RR of 3.21; RR=2.67 adjusted for sex) that were significantly related to severe COVID, but not too hypertension, COPD, chronic kidney insufficiency or diabetes.

Two melanoma studies reported no association with such immune checkpoint inhibitors and severe COVID [28, 30]. Similarly, we did not see an association with severe COVID and immune checkpoint inhibitors including Nivolumab, Pembrolizumab, and Ipilimumab. We also did not see associations with severe COVID and MEK inhibitors (Binimetinib, or Trametinib) or BRAF kinase inhibitors (Encorafenib, Dabrafenib). While severe COVID among these ASCO melanoma patients with COVID was not related to their cancer drugs, it was related to complications of COVID including bleeding, sepsis, acute respiratory distress syndrome (ARDS), respiratory failure, cardiac arrythmia, cerebrovascular accident, and encephalopathy. Cutaneous melanoma patients seen by oncologists often present with more advanced melanoma including metastases as seen here. This is due to referral patterns, where patients with early-stage melanoma are often managed by dermatologists or surgeons, while those with more advanced disease require systemic therapies, such as immunotherapy or targeted treatments, which fall under the expertise of medical oncologists. The high proportion of metastatic cases among oncology melanoma patients reflects this trend.

Various host factors may put individuals at higher risk of severe COVID-19. As previously mentioned, underlying medical

conditions are related to an increase in severe COVID [22, 23] along with being immunocompromised [21]. Microbiome dysbiosis is an imbalance in the microorganisms that live in the human body [51]. Symptoms of microbiome dysbiosis that are also COVID-19 symptoms include diarrhea. Among the ASCO melanoma patients with COVID-19, a 3-fold increased risk was seen with diarrhea and severe COVID. Among these melanoma patients with COVID, 7% reported diarrhea. This is higher than symptoms of diarrhea in a nationwide study in Iran that only had 4% of COVID patients whether with or without cancer reporting diarrhea [52]. Whereas a study in China reported higher rates of diarrhea with 19% among cancer patients with COVID and 20% among other COVID patients [18]. This wide range of symptoms rates but similar among those with and without cancer does not support microbiome dysbiosis as a potential mechanism that differentiates melanoma or cancer patients.

Racial, ethnic, and socioeconomic disparities have been highlighted in COVID-19 infections, hospitalizations, and deaths [53-55]. We did see a 2-fold increase among Hispanics or non-Whites in this study, which is a little surprising as melanoma is primarily a disease among people with light white skin. But this accounts for the small racial/ethnic diversity in these cancer cases. As severe COVID is partially defined by hospitalization, we might expect severe COVID to be higher in some racial/ethnic groups, as we saw here. However, these data cannot provide insight into if such an increase in severe COVID is related to access to care, cultural differences, or other factors.

As this cohort of subjects all have melanoma and COVID-19, the study is not able to look at how the diagnosis of melanoma influences COVID-19. But it looks at factors that are related to developing severe COVID. One of the limitations of this study is the small number of COVID-19 positive melanoma patients identified among 67 oncology practices in 26 states throughout the United States. The majority of early-stage melanoma are seen and treated by dermatologists and surgeons, thus will not be seen in n medical oncology practice unless they are referred with lymph node involvement or metastatic disease. However, this population seen by oncologists may represent more advanced melanoma cases. This observational research study is reliant largely on data collected from ambulatory oncology clinics that are part of ASCO, which is a limitation. As a result, real-time reliant access to inpatient and clinical data not directly related to oncological treatment varies. We recognize that this patient cohort had a small sample size and may not be representative of all patients with cutaneous melanoma but as the pandemic evolved, the registry and data matured. Thus, the findings from the ASCO registry continue to be relevant.

Conclusion

Overall, these ASCO melanoma patients with COVID-19 had lower rates of severe COVID and death than reported for other cancer sites, particularly hematological cancers. A lower percentage of severe outcomes due to COVID-19 among melanoma patients is not surprising as surgical removal of melanoma is the main treatment and can often be performed in a dermatologists' office. Even so, melanoma patients had an increased risk of severe COVID (compared to non-cancer patients). They reported most COVID-19 symptoms to be associated with sever COVID and many were associated with death, both of which are clinically relevant to primary care physicians and dermatologists for future outbreaks. Nevertheless, within the context of other cancer patients with COVID, melanoma patients seem to have better outcomes partially due to younger patient demographics, treatment with immune checkpoint inhibitors and fewer immunosuppressive treatments.

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Institutional Review Board Statement: "The Institutional Review Board of WCG reviewed the ASCO Survey on COVID-19 in Oncology Registry and determined the study was exempt from IRB review because it did not meet the definition of human subject as defined by 45 CRF 46.102." The date received by the University of Arizona was further de-identified from names, addresses with only a study ID provided and determined "Not applicable" for not involving humans or animals.

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