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Impact of Exercise on Susceptibility and Severity of COVID-19 in Patients with Cancer: A Retrospective Study

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Abstract

Background.—Modifiable lifestyle-related factors heighten the risk and severity of coronavirus disease 2019 (COVID-19) in patients with cancer. Whether exercise lowers susceptibility or severity is not known.

Methods.—We identified 944 cancer patients from Memorial Sloan Kettering Cancer Center (mean age: 64; 85% female; 78% White) completing an exercise survey before receiving a confirmed positive or negative SARS-CoV-2 test. Exercise was defined as reporting moderate-

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intensity ≥5 days per week, ≥30 minutes/session or strenuous-intensity ≥3 days per week, ≥20 minutes/session. Multivariable logistic regression was used to determine the relationship between exercise and COVID-19 susceptibility and severity (*i.e.,* composite of hospital admission or death events) with adjustment for clinical-epidemiologic covariates.

Results.—Twenty-four percent (230 / 944) of the overall cohort were diagnosed with COVID-19 and 35% (333 / 944) were exercisers. During a median follow-up of 10 months, 26% (156 / 611) of non-exercising patients were diagnosed with COVID-19 compared with 22% (74 / 333) of exercising patients. The adjusted odds ratio (OR) for risk of COVID-19 was 0.65 (95% CI: 0.44 to 0.96, p=0.03) for exercisers compared to non-exercisers. A total of 20% (47 / 230) of COVID-19 positive patients were hospitalized or died. No difference in the risk of severe COVID-19 as a function of exercise status was observed (p>0.9).

Conclusion: Exercise may reduce the risk of COVID-19 infection in patients with a history of cancer, but not its severity.

Impact.—This study provides the first data showing that exercise might lower the risk of COVID-19 in cancer patients, but further research is required.

Keywords

Physical activity; infection; symptoms; mortality; COVID-19

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread rapidly resulting in a global pandemic.[1–3] Cancer patients represent a particularly vulnerable population at high risk of COVID-19 infection[4–6] as well as subsequent morbidity and mortality.[7] As in the general population, infection risk, disease severity, and disease course are phenotypically diverse in cancer patients, triggering considerable efforts to identify risk factors to inform screening and intervention strategies.[7–9] Non-modifiable risk factors such as older age, male sex, and certain types of malignancies (*e.g.,* hematological and lung cancer) are strong predictors of elevated susceptibility, worse disease severity, and heightened risk of death following infection.[7–10] Modifiable factors including obesity, hypertension and other chronic conditions are also strongly associated with elevated risk and worse outcomes.[7,9,11–13]

The marked impact of modifiable risk factors has generated considerable interest in whether healthy lifestyle factors such as exercise decrease COVID-19 susceptibility or improve outcomes following infection.[14–16] To our knowledge, the only studies to examine this question have all been conducted in the general population.[17–21] Overall, general physical activity, moderate-to-vigorous physical activity (*i.e.,* exercise)[17,18,21] and faster self-reported walking pace (>4 mph)[20] were associated with decreased susceptibility to COVID-19 and risk of severe COVID-19 (*i.e.,* risk of hospitalization or death). Whether these findings extend to populations at elevated risk of and worse outcomes following COVID-19 infection, such as cancer patients, is unknown.

To address this gap, we examined whether exercise was associated with susceptibility to COVID-19 in patients with a history of cancer. We also examined whether exercise influenced disease severity in those diagnosed with COVID-19.

MATERIALS AND METHODS

Patients and Setting

Patients diagnosed between 1982 and 2019 with histologically confirmed cancer completing a self-reported exercise assessment as an aspect of Exercise-Oncology Service research protocols at Memorial Sloan Kettering Cancer Center (MSK) between January 01, 2018 and March 11, 2021 were eligible. Identified patients were cross-referenced with MSK's COVID-19 database to identify patients with a confirmed positive or negative SARS-CoV-2 test performed in an inpatient or outpatient setting at any of the eight MSK hospitals (located throughout New York State and New Jersey) or at a partnered institution (captured via MSK Health Information Exchange) between March 8, 2020 (the date of first documented positive COVID test) and February 19, 2021. As per MSK policy, all patients attending an in-person appointment at an MSK location were required to undergo a COVID-19 test prior to their visit. Patients with potential exposure or symptoms were also tested. SARS-CoV-2 status was determined using a nasopharyngeal swab for presence of virus-specific RNA (MSK US Food and Drug Administration Emergency Use Authorization–approved laboratory-developed test and GeneXpert; Cepheid, Sunnyvale, CA). In institutional validation data, these tests demonstrated a limit of detection of 250–500 copies/mL, a sensitivity of 97%, and specificity of 100%.[7] Follow-up data on treatment and vital status through May 14, 2021, were extracted. The protocol was approved by the MSK institutional review board (IRB#17–662). This manuscript is reported consistent with STROBE recommendations.[22]

Exercise Assessment

Exercise history was prospectively evaluated using the Godin Leisure Time Exercise Questionnaire (GLTEQ)[23] or the International Physical Activity Questionnaire Short-Form (IPAQ-SF).[24] All patients only completed one of the questionnaires, no patients completed both questionnaires. The GLTEQ survey is included as part of the standard self-assessment intake survey for all adult survivorship clinics at Memorial Sloan Kettering Cancer Center. All survey responses included in this analysis were completed via a web-application called MSK-Engage. The IPAQ-SF was collected as part of a specific study. All IPAQ surveys were completed via a self-administered paper survey. The GLTEQ contains three questions that assess the average frequency of mild, moderate, and strenuous-intensity exercise sessions of at least 15 mins/session in a typical 7-day period during leisure-time. Participants also reported the average duration of exercise within each intensity category. The IPAQ-SF contains two items that assess frequency of moderate and vigorous-intensity exercise of at least 10 minutes during the past 7 days. Exercise was defined as meeting the US Department of Health and Human Services Physical Activity Guidelines for Americans,[25] *i.e.,* moderate-intensity exercise ≥5 days per week, with each session, on average, ≥30 minutes in duration or strenuous-intensity exercise ≥3 days per week, with each session, on average, ≥20 minutes in duration or an equivalent combination. Weekly exercise minutes within each intensity category were weighted by an estimate of the metabolic equivalent of task (MET) then summed to calculate total MET hours per week (MET-h/wk). The standard MET weights for each exercise intensity are: mild (3 METs), moderate (5 METs), and strenuous (9 METs).

End Points

The primary endpoint was a positive diagnosis of COVID-19. The secondary endpoint was a severe or critical COVID-19 event. Severe COVID-19 was initially defined according to the World Health Organization (WHO) definition.[26] However, due to the low event rate when applying this criterion, we adopted an investigator-defined composite end point of any hospital admission or death within 60 days of the confirmed positive COVID-19 test date.

Statistical Analysis

Demographic and clinical characteristics were summarized using descriptive statistics. All medical and demographic data at the time of COVID-19 testing including laboratory data, medications, and anticancer therapy were programmatically extracted from the MSK EHR into an institutional COVID-19 specific database. All data pertains to the medical and demographic characteristics of study participants at the time of COVID-19 testing. Remaining data fields were manually extracted. Quality control was performed using a two-part system of cross coverage record review by two research team members together with a random record spot check by a third team member.

Univariable associations between COVID-19 susceptibility or severity and meeting exercise guidelines, demographic characteristics, and cancer characteristics were assessed using logistic regression. Variables significant in analyses adjusted only for the covariate of interest and age at a p-value threshold of 0.2 were included in the multivariable logistic regression models. The final model for COVID-19 diagnosis was adjusted for age (on March 1st, 2020), sex (female, male), race (Asian, Indian, Black, White, other), body mass index (BMI; ≤29.9 kg/m^2, ≥30 kg/m^2), cancer stage (stage I-II, stage III-IV), current cancer treatment (receiving active cancer treatment (non-hormonal), disease-free but receiving hormonal treatments, or other), and any comorbidities (*e.g.,* chronic obstructive pulmonary disease, hyperlipidemia, etc.). A complete case analysis (n=807) was performed for the final model assuming that data for BMI and stage are missing completely at random; the distribution of missingness for these variables was similar across COVID infection status and exercise status. Collinearity among covariates in the final model was assessed by computing variance inflation factors, none which indicated collinearity. BMI, current cancer treatment and comorbidities were recorded at the time of COVID-19 testing. Interaction effects between exercise status and age, cancer stage, BMI, sex, and comorbid conditions were considered based on a model including exercise status, age, the covariate of interest, and the interaction between exercise status and the covariate of interest. A similar analytic approach was adopted to examine the relationship between exercise status and COVID-19 severity. Patients diagnosed with COVID-19 and at least 60 days of follow-up were included in the analysis. Patients with an unknown admission status were considered not admitted. Odds ratios (OR) and 95% confidence intervals (CI) are reported. Analyses were performed in R version 4.0.3.

Data availability statement

The data generated in this study are available upon request from the corresponding author.

RESULTS

A total of 1,209 patients completed an exercise assessment between January 01, 2018 and March 11, 2021 and had a confirmed positive or negative SARS-CoV-2 test between March 08, 2020 and February 19, 2021; 265 were excluded due to either a lack of a confirmed histologic diagnosis of cancer or insufficient documentation, including the absence of follow-up to determine the severity of COVID-19 clinical course, or the date of SARS-CoV-2 PCR occurring prior to exercise survey completion date. Hence, the final cohort comprised 944 patients (230 positive and 714 negative patients; Figure 1). The median time between exercise survey completion and date of the SARS-CoV-2 index test was 10 months [interquartile range (IQR), 6, 14 months]. Characteristics for the overall cohort (n=944) and those testing positive for COVID-19 (n=230) are provided in Table 1. In brief, the median age of the overall cohort was 64 years (IQR: 56 to 71) and the median time from cancer diagnosis to exercise survey completion was 7.3 (IQR: 4.4 to 10.9) months. The cohort mostly consisted of White female patients diagnosed with breast cancer. Less than 10% of the overall cohort was receiving definitive anticancer therapy at the time of study entry.

Exercise and COVID-19 susceptibility

In the overall cohort, 35% (333 / 944) were defined as exercisers. During follow-up, 26% (156 / 611) of non-exercising patients were diagnosed with COVID-19 compared with 22% (74 / 333) of exercising patients. Table 2 presents the age-adjusted and multivariable-adjusted estimates of COVID-19 risk stratified by exercise status. Age-adjusted analysis indicated that exercisers had a non-significant lower risk of COVID-19 (OR, 0.77, 95% CI, 0.56 to 1.06; p=0.11). In the multivariable adjusted model, exercisers had a significantly lower risk of COVID-19 susceptibility in comparison to non-exercisers (OR, 0.65, 95% CI, 0.44 to 0.96; p=0.03; Figure 2). Male sex was strongly associated with higher risk of COVID-19 (Figure 2). Interaction analyses indicated that the relationship between exercise status and reduction in COVID-19 susceptibility did not differ based on stratification by age, sex, cancer stage, BMI, or comorbid conditions (all p>0.05; data not presented).

Exercise and COVID-19 severity

Within 60 days of the index COVID-19 positive test date, 20% (47 / 230) of COVID-19 positive patients developed the primary end point of severe COVID-19 [46 / 230 (20%) were admitted to hospital and 16 / 230 (7%) died]. Of patients with severe COVID-19, 34% (16 / 47) were exercisers. In age-adjusted analysis, there was no association between exercise status and risk of severe or critical COVID-19 (OR 1.33, 95% CI 0.64 to 2.68; p=0.4). Findings remained non-significant in multivariable-adjusted model (OR 0.99, 95% CI 0.38 to 2.51; p>0.9; Figure 3). Increasing age was the only variable associated with elevated risk of severe or critical COVID-19 (Figure 3). Interaction analyses indicated that the relationship between exercise status and COVID-19 severity did not differ by age (p=0.13) (data not presented).

DISCUSSION

In this single institution study, cancer patients meeting national exercise guidelines had lower susceptibility to COVID-19 relative to their sedentary counterparts even after adjustment for important clinical and epidemiologic covariates. Exercise was not associated with COVID-19 severity. Nevertheless, our sample size was too small to draw definitive conclusions regarding the link between exercise and risk / severity and our findings generate interesting hypotheses for future testing in larger cohorts.

To our knowledge, only four studies have examined the relationship between physical activity reported prior to the pandemic and risk and severity of COVID-19.[17–21] All were conducted in the general population, with three using the same cohort study (*i.e.,* UK Biobank).[17–20] In the largest and most comprehensive study to date, Sallis and colleagues identified 48 440 adult patients with a COVID-19 diagnosis and self-reported physical activity two years prior to the pandemic.[21] Patients meeting exercise guidelines (*i.e.,* 150 minutes of moderate or vigorous-intensity exercise per week) had significantly lower risk of hospitalization, ICU admission and death in comparison with inactive patients after adjustment for known risk factors. These data corroborate the reports from the UK Biobank, a population-based prospective cohort of >500,000 adults age 40–69 years in the UK.[11,19,27] Our data extend this evidence base by showing the protective impact of exercise extends to patients with cancer, a high-risk population at elevated risk of both diagnosis and worse outcomes following COVID-19 infection.[28–30] We also extend prior work by being the first to include individuals with a confirmed negative COVID-19 test. Although exercise was associated with a reduction in COVID-19 risk, these estimates may be underestimated since we adjusted for pathologic conditions (*e.g.,* obesity, comorbid conditions) strongly associated with elevated risk and worse outcomes following a COVID-19 diagnosis in cancer patients[7,9,11–13] but also strongly influenced by exercise. While exercise reduced susceptibility, infection severity was similar to non-exercising patients. These findings should be interpreted with caution given the low number of events and further work is required.

The potential protective effect of exercise on COVID-19 susceptibility is biologically plausible. Heightened susceptibility and severity of COVID-19 in individuals with comorbidities such as obesity and type 2 diabetes has been linked to shared pathophysiological impairments including heightened basal inflammatory tone, endothelial dysfunction, greater risk for coagulation-related complications, and impaired adaptive immune response.[31] Obesity and insulin resistance are linked to impairments in host inflammatory and immune function in a complex manner.[32] Elevated glucose and sustained aerobic glycolysis in monocytes directly promote COVID-19 viral replication, cytokine production, and the subsequent T cell dysfunction and lung epithelial cell death.[33] Conversely, the prevalence of metabolic disorders are significantly lower in exercisers in the general population and in patients with cancer.[26,34,35] Exercising individuals may have heightened protection against COVID-19 secondary to normal physiologic regulation of basal inflammation, endothelial function / coagulation, and host immunity. Indeed, in a series of randomized controlled trials, our group has demonstrated short-term (12 to 15 weeks) structured aerobic training is associated with improvements in metabolic profile,[36,37] endothelial function,[38] and host inflammatory-immune profile[38–40] in patients with solid malignancies. Further, in the normal lung, exercise enhances homeostasis in response to infection and other pathologic exposures.[41–43] Although biologically plausible, the important influence of residual confounding on findings in the present study must be considered. Indeed, adherence to national exercise guidelines may be associated with better adherence to other health behaviors (*e.g.,* diet, alcohol consumption) as well as established COVID-19 protective measures (*e.g.,* hand washing, social distancing, mask wearing). It was not possible to assess the effect of these factors in our study and residual confounding could potentially explain why exercise was only associated with reduced risk but not severity of COVID-19 in this study. Investigation of the exercise - COVID-19 link in larger cohorts together with translational studies testing exercise biological effects and mechanisms would be of significant interest.

Overall, data from the present study together with those from the general population provides suggestive evidence that in addition to lowering the risk of non-communicable diseases,[44] exercise consistent with national and international guidelines may also reduce susceptibility to COVID-19. Our data also add to the oncology – COVID-19 literature base. Identification of predictive factors to inform screening / risk stratification as well as preventive, treatment, and recovery strategies are of clinical importance in this vulnerable population. To date, both cancer-specific factors (*e.g.,* diagnosis of hematologic or lung cancer, metastatic cancer)[7,29] and factors of importance in general populations (*e.g.,* obesity, advanced age, comorbidities)[28,45] are associated with higher COVID-19 susceptibility and poorer clinical outcomes. Our data suggest that exercise status may also warrant consideration when advising cancer patients on factors associated with COVID-19 risk.

Our study has important limitations. Exercise was assessed by a self-administered questionnaire with well-known limitations, and therefore some misclassification of exposure is likely. Our sample largely consisted of white female patients with breast cancer, limiting generalizability. We were only able to determine whether patients were admitted to hospital for COVID-19 via the MSK electronic medical record (EMR). As such, not all admissions at outside hospitals were captured, leading to potential under reporting of such events. Finally, the generalizability of our findings is also limited by the unique structure of MSK, a dedicated cancer center in which patients are followed longitudinally. These patients may therefore report symptoms earlier in the course of illness. MSK also has a dedicated COVID-19 nursing response team, which ensured close follow-up of patients after COVID-19 diagnosis.[7]

In summary, exercise may influence susceptibility of COVID-19 in patients with cancer. However, our findings are hypothesis-generating and further research in a broader cancer population is required.

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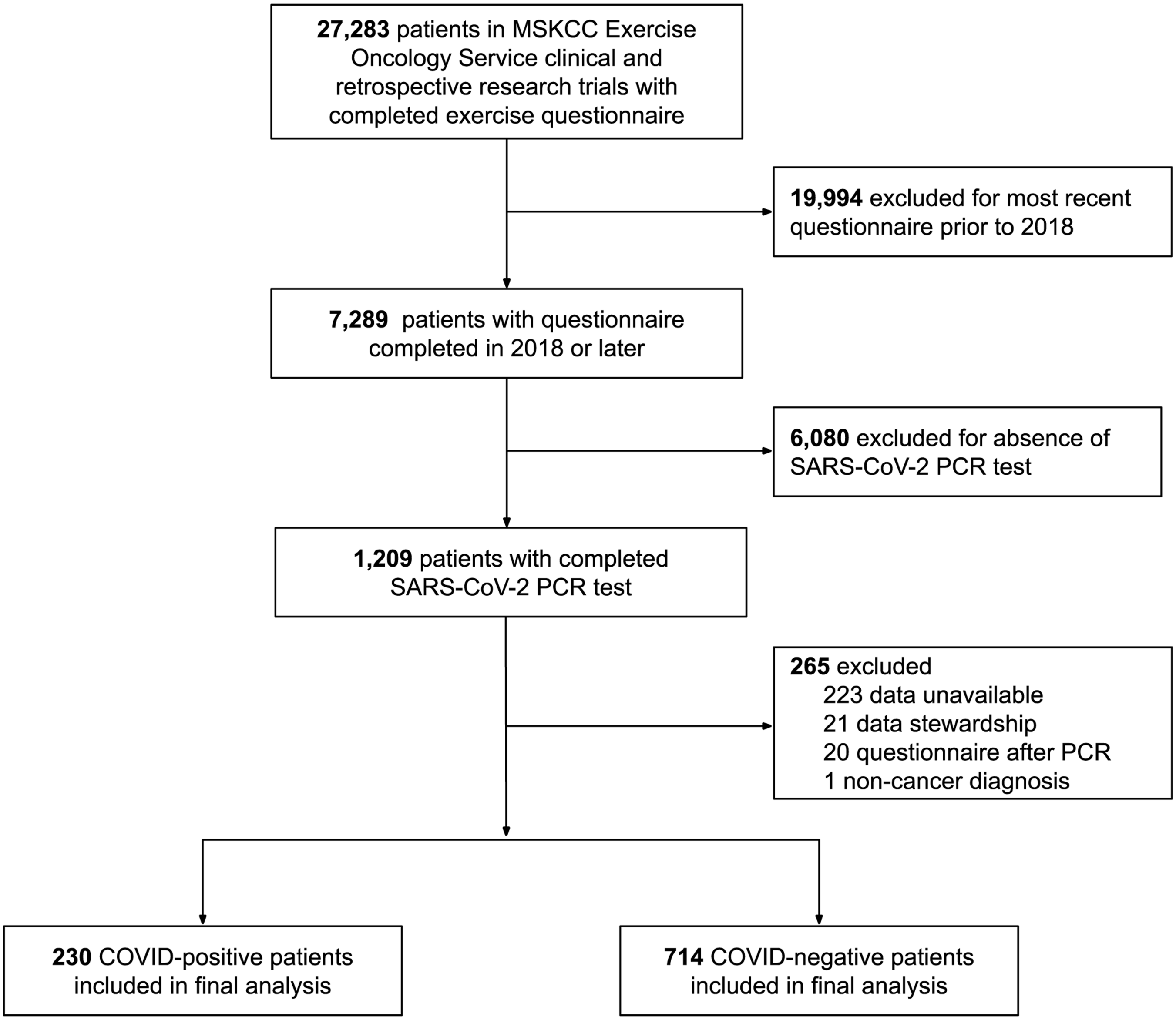

Figure 1.

Study cohort. Composition diagram of eligible patients and final analytic cohort.

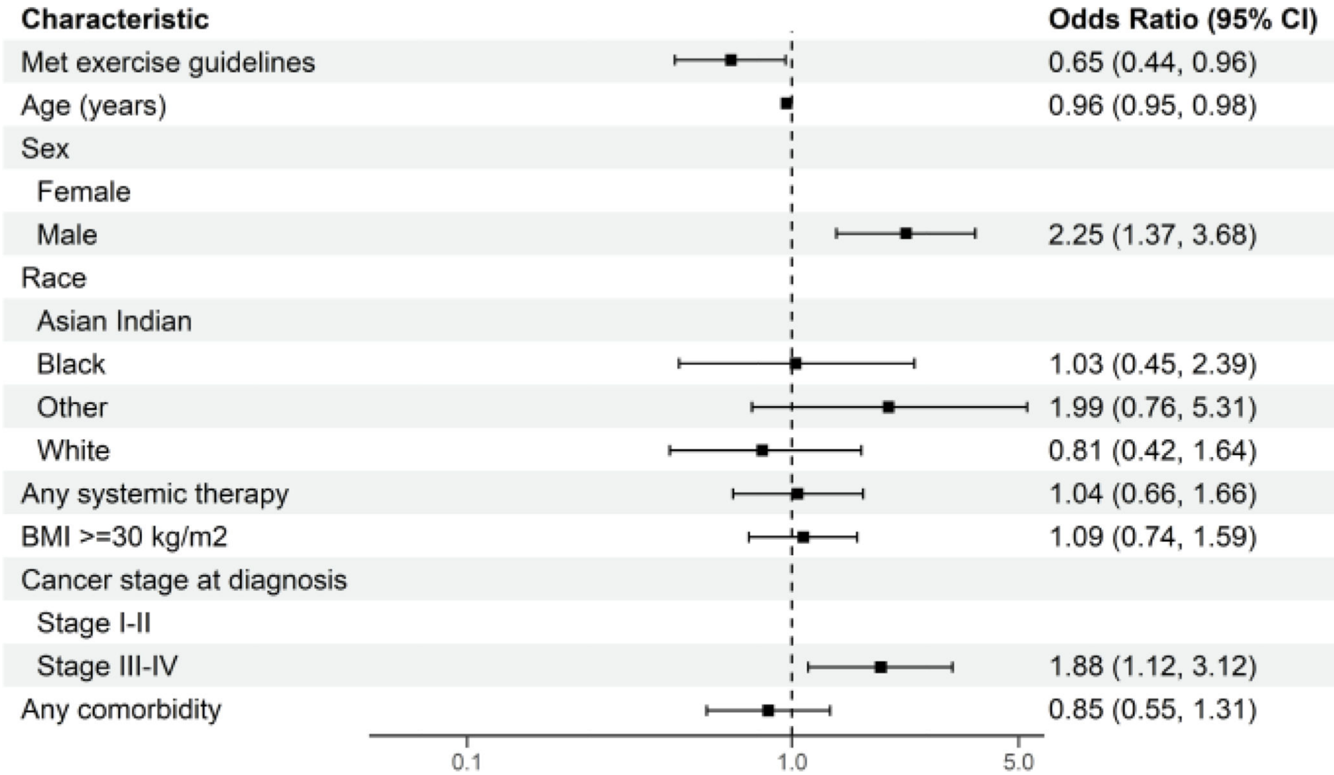

Figure 2.

Adjusted risk factors for COVID-19 susceptibility in patients with cancer. BMI, body mass index. Adjusted for: age, sex, race, body mass index, cancer stage, cancer treatment, and any comorbidities.

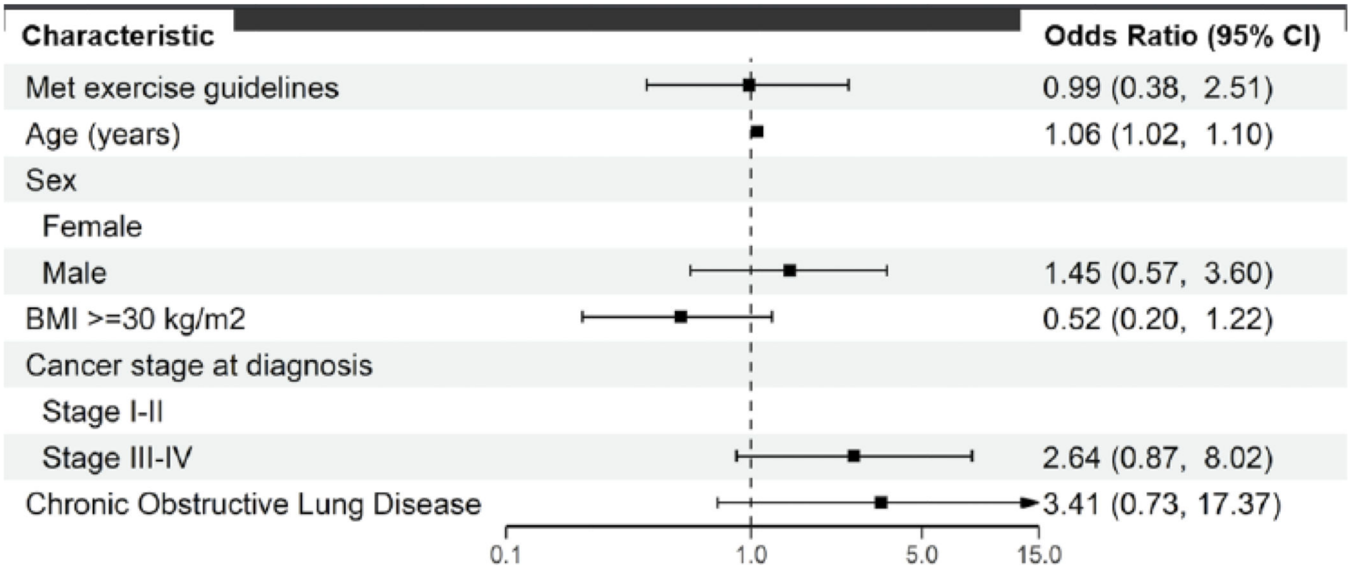

Figure 3.

Adjusted risk factors for COVID-19 severity in patients with cancer. Adjusted for age, sex, stage, BMI, cancer treatment and chronic obstructive pulmonary disease.

Table 1.

Characteristics of the overall cohort and COVID-19 positive patients

Characteristic[1]	Overall Cohort N = 944	Covid Positive Patients N = 230
Age – median (IQR)[2]	64 (56, 71)	62 (53, 69)
Sex – number (%)		
Female	798 (85)	170 (74)
Male	146 (15)	60 (26)
Race – number (%)		
White	741 (78)	166 (72)
Asian Indian	62 (7)	16 (7)
Black	102 (11)	30 (13)
Other	39 (4)	18 (7.8)
Cancer type		
Breast	555 (59)	111 (48)
Colorectal	47 (5)	18 (8)
Lung	81 (9)	25 (11)
Hematologic	38 (4)	26 (11)
Other	223 (24)	50 (22)
Stage – number (%)		
I-II	624 (73)	138 (67)
III-IV	98 (11)	44 (21)
Stage not applicable	134 (16)	23 (11)
Unknown	88	25
Current cancer treatment status – number (%)[2]		
Receiving definitive therapy[3]	81 (9)	40 (17)
Receiving adjuvant hormonal therapy only	198 (21)	49 (21)
Not receiving any anticancer therapy	665 (70)	141 (61)
Comorbidities – number (%)[2]		
Any comorbidity (not including obesity)	642 (68)	158 (69)
Any cardiovascular comorbidity	417 (44)	88 (38)
Chronic obstructive pulmonary disease	43 (5)	12 (5)
Diabetes mellitus type 2	104 (11)	24 (10)
Hyperlipidemia	227 (24)	67 (29)
Hypertension	339 (36)	73 (32)
Obesity, body mass index ≥30 kg/m^2	301 (34)	84 (40)

[1] values may not equal 100% due to missing data

[2] values recorded at the time of COVID-19 testing

[3]defined as receiving chemotherapy, radiotherapy or any other systemic therapy other than hormonal therapy.

Table 2.

Age-adjusted and multivariable odds ratios for a positive diagnosis of COVID-19 according to exercise status

		Exercise Status		
	Non-Exercise [1] (N = 611)		**Exercise[2] (N = 333)**	**P**
Median MET-h/wk (IQR)[3]	5 (2, 10)		31 (23, 47)	
COVID-19 diagnosis				
Patients testing positive for COVID-19 – number (%)	156 (26%)		74 (22%)	
Age-adjusted, OR (95% CI)	1.0 (reference)		0.77 (0.56 to 1.06)	0.11
Multivariable-adjusted, OR (95% CI)[4]	1.0 (reference)		0.65 (0.44 to 0.96)	0.03

Abbreviations: MET, metabolic equivalent task; OR, odds ratio

[1]Not meeting national exercise guidelines (*i.e.,* moderate-intensity exercise <5 days per week, with each session, on average, <30 minutes in duration or strenuous-intensity exercise <3 days per week, with each session, on average, <20 minutes in duration or an equivalent combination.

[2]Meeting national exercise guidelines (i.e., moderate-intensity exercise ≥5 days per week, with each session, on average, ≥30 minutes in duration or strenuous-intensity exercise ≥3 days per week, with each session, on average, ≥20 minutes in duration or an equivalent combination).

[3]Weekly exercise minutes within each intensity category were weighted by an estimate of the metabolic equivalent of task (MET) then summed to calculate total MET hours per week (MET-h/wk). The standard MET weights for each exercise intensity are: mild (3 METs), moderate (5 METs), and strenuous (9 METs).

[4]Adjusted for age, sex, race, body mass index, cancer stage, cancer treatment, and any comorbidities.