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Research Article

The impact of routine molecular screening for SARS-CoV-2 in patients receiving anti-cancer therapy: an interim analysis of the observational COICA study

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Short Title: Molecular screening for SARS-CoV-2 in patients receiving anti-cancer therapy

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Abstract

Introduction: Cancer aggravates COVID-19 prognosis. Nosocomial transmission of SARS-CoV-2 is particularly frequent in cancer patients, who need to attend hospitals regularly. Since March, 2020, all cancer patients having access to the Oncology Unit at the "Andrea Tortora" Hospital (Pagani, Salerno - referred to as "the Hospital") as inpatients or outpatients receiving intravenous therapy have been screened for SARS-CoV-2 using RT-PCR nasal swab. The ongoing COICA (COVID-19 Infection in Cancer Patients) study is an ambispective, multicenter, observational study designed to assess the prognosis of SARS-CoV-2 infection in cancer patients. The aim of the study presented here was to explore potential differences in COVID-19 related outcomes among screening-detected vs. non-screening detected SARS-CoV-2 infected patients. **Methods:** The COICA study enrolled cancer patients who had received any anti-cancer systemic therapy within 3 months since the day they tested positive for SARS-CoV-2 on RT-PCR. The target accrual is 128 patients, and the study was approved by the competent Ethics Committee. Only the sub-group of patients enrolled at the Hospital was considered in this unplanned interim analysis. Logistic regression analysis was used to evaluate the association of screening-based vs. non screening based diagnosis. **Results:** Since March, 15 2020 until August, 15 2021, a total of 931 outpatients and 230 inpatients were repeatedly screened for SARS-CoV-2 using RT-PCR nasal swab at the Hospital. Among these, 71 asymptomatic patients were positive on routine screening and five patients were positive for SARS-CoV-2 outside the institutional screening. Seven patients died because of COVID-19. At univariate analysis, non-screening vs. screening detected SARS-CoV-2 infection was associated with significantly higher odds of O_2 Therapy (OR= 16.2; 95% CI =2.2 to 117.1; p =0.006),hospital admission (OR=31.5; 95% CI=3.1 to 317.8; p=0.003), admission to ICU (OR=23.0; 95% CI = 2.4 to 223.8; p= 0.007) and Death (OR=8.8; 95%CI= 1.2 to 65.5; p =0.034). **Conclusion**: Routine screening with RT-PCR may represent a feasible and effective strategy in reducing viral circulation and possibly COVID-19 mortality in patients with active cancer having repeated access to hospital facilities.

Introduction

The COVID-19 pandemic has profoundly affected all aspects of healthcare, posing a multitude of challenges for patients, physicians, as well as public health policy makers. In cancer patients, COVID-19 prevalence was reported to be higher compared to regional community prevalence[2]. Cancer patients are more likely to be infected with SARS-CoV-2 [3], to require intubation [4], and to die because of COVID-19[3], which is likely the result of a complex interplay of multiple factors, including the effects of reduced organ and immune system function due to the underlying malignancy and anti-cancer medications[2]. Commonly accepted recommendations for COVID-19 management and prevention in cancer patients include reducing office visits, improving telemedicine services, preferring oral compared to intravenous medications, among others[5][6]. Nosocomial transmission of SARS-CoV-2 is particularly frequent in cancer patients, who need to attend hospitals regularly for intravenous administration of anti-cancer therapies, office visits, management of uncontrolled symptoms or adverse events due to therapy[7]. In this regard, according to the European Society for Medical Oncology, all cancer patients requiring hospital admission may be screened by using a RT-PCR pharyngeal swab to be performed within 48 hours before admission[8]. Asymptomatic carriers of SARS-CoV-2 are likely to provide a major contribution to spreading the infection[9]. In this regard, the value of a molecular or serological screening in asymptomatic patients attending hospital facilities is likely to be critically dependent on the local epidemiological scenario, although no conclusive evidence obtained in prospective clinical trials supports its effects in terms of reduced COVID-19 mortality[10][11].

In the Campania Region, large population-based screening campaigns have been conducted by assessing anti-SARS-CoV-2 antibodies in peripheral blood, as in the case of the locked down town of Ariano Irpino[12], while some facilities have used lateral flow chromatographic immunoassays to assess presence of anti-SARS-CoV-2 immunoglobulin (Ig)G and IgM antibodies in fingerstick whole-blood specimens for initial screening of asymptomatic cancer patients, followed by RT-PCR nasal swab in case of positivity[6]. The Oncology Unit at the “Andrea Tortora” Hospital(Pagani, Salerno referred to as “the Hospital” here) is the main Oncology Unit of Azienda Sanitaria Locale of Salerno (Campania Region, Italy), a public company that provides community-based health services to over 1 million citizens. Since March 2020, all cancer patients having access to the Hospital as inpatients or outpatients receiving intravenous therapy have been screened for SARS-CoV-2 as per Hospital policy using RT-PCR nasal swab.

We here report an unplanned analysis involving patients recruited at the Hospital in the ongoing COICA (COVID-19 Infection in Cancer Patients) study, an ambispective, multicenter, observational study designed to assess the prognosis of SARS-CoV-2 infection in cancer patients. In this work, we analyzed COVID-19 outcomes in cancer patients to explore potential differences among screening-detected vs. non-screening detected SARS-CoV-2 infected patients, with the intent to gather evidence regarding the potential utility of routine screening for SARS-CoV-2 in cancer patients.

Materials and Methods

The COICA study is an ongoing, multi-center, ambispective observational study including cancer patients who had received any anti-cancer systemic therapy within 3 months since the day they tested positive for SARS-CoV-2 on RT-PCR. COICA was mainly designed to capture the clinical course of SARS-CoV-2 infection in patients being treated for cancer and its full results will be published once the accrual has been completed. Briefly, enrolled patients are required to sign an informed consent and are observed from the time of diagnosis of SARS-CoV-2 to confirmed recovery (defined as two negative RT-PCR tests in a raw performed at least 24 hours apart) or death. RT-PCR must be performed following WHO guidelines[13]. The COICA study, with a target accrual of 128 patients, was approved by the competent Ethics Committee and conducted according to the principles of the Helsinki Declaration.

We here report a preliminary analysis of patients enrolled at the Hospital, updated as of 1st October, 2021. The unplanned analysis presented here was conceived to assess potential differences in COVID-19 outcomes among screening-based vs. non-screening based SARS-CoV-2 diagnosis. Institutional screening for SARS-CoV-2 was conducted for all cancer patients having access to the Hospital as either inpatients or outpatients receiving intravenous therapy, who had to be screened for SARS-CoV-2 using RT-PCR nasal swab the day before they were admitted to the Hospital. Screening was omitted if the patient was asymptomatic and had tested negative for SARS-CoV-2 on RT-PCR within the previous 20 days. Only patients enrolled at the Hospital, where >90% of patients had been recruited in the COICA study, were considered in this analysis, in order to minimize potential sources of distortion associated with different institutional screening protocols. Screening-diagnosed patients were defined as those asymptomatic patients who were diagnosed with SARS-CoV-2 following the Institutional screening program. Non-screening diagnosed patients were defined as those who had been diagnosed outside the Institutional screening for any reason. Asymptomatic patients were defined as individuals without a recent history of cough or fever and with no more than a single symptom among diarrhea, joint pain, headache vomiting, asthenia, sore throat, muscle pain, and loss of taste or smell, as others have done[12].

Descriptive statistics and frequency counts were used to summarize characteristics of the study population. Median numbers were presented with interquartile ranges, unless specified otherwise (IQR). Logistic regression analysis was used to evaluate the association of screening-based vs. non screening based diagnosis along with other available variable of potential interest with SARS-CoV-2-related outcomes. All tests were 2-sided, and a value of $P \leq 0.05$ was considered statistically significant. All statistical analyses were conducted using R 3.5.2.

Results

Since March, 15 2020 until August, 15 2021, a total of 76 patients were enrolled in the COICA study at the Hospital and represent the study cohort assessed in this work. Of these, the majority (71%) were enrolled in 2020. Among these, 71 asymptomatic patients were found to be positive on routine screening among a total of 931 outpatients and 230 inpatients who were repeatedly screened for SARS-CoV-2 using RT-PCR nasal swab at the “Andrea Tortora” Hospital in Pagani during the same time period. Only five patients were found to be positive for SARS-CoV-2 outside the institutional screening after being tested either because symptomatic (four cases) or because of incidental finding of interstitial pneumonia on CT scans. With the exception of one patient who was enrolled in August, 2021, all patients were enrolled before April, 2021. All patients were followed-up until confirmed negative RT-PCR or death. None of the patients had been vaccinated against SARS-CoV-2, which is consistent with the fact that the vaccination campaign for cancer patients started in Campania in March, 2021. Breast (19.74%) and prostate cancer (19.74%) were the two most frequent malignancies in the cohort. The cohort consisted of 47 males (61.84%). Median age was 62 years (IQR, 55-72). Approximately half of the patients had received some anti-neoplastic systemic therapy within 30 days of diagnosis. Approximately seventy-two per cent of patients presented metastatic cancer and about seventy-seven per cent presented some SARS-CoV-2 related symptoms during the observation. CT-confirmed lung pneumonitis was reported in 15 patients (19.74%), while 12 (18.82%) had to be admitted to the hospital. O2 therapy was required in 9 patients (11.84%), while four had to be admitted to the ICU (5.26%). Seven patients died because of COVID-19 after a median of 19 days (IQR, 11-28). These seven patients (2 males, 5 females) had been respectively diagnosed with ovarian (2 patients), head-and-neck (1 patient), kidney (1 patient), uterine (1 patient), breast (1 patient) and lung cancer (1 patient) and six of them had metastatic disease. Furthermore, six of them had to be admitted to the hospital and four of them had to be admitted to the intensive care unit. Antibiotics, heparin and corticosteroids were administered to all of them.

Median time to confirmed negative test was 20 days (95% CI = 17 – 24), as shown in Figure 1. Any anti COVID-19 treatment was administered in 49 (64.47%) patients. Among these, antibiotics (67.3%), heparin (30.6%) , and corticosteroids (40.8%) were commonly administered.

At univariate analysis, non-screening vs. screening detected SARS-CoV-2 infection was associated with significantly higher odds of requiring O2 therapy (OR= 16.2; 95% CI =2.2 to 117.21; p =0.006),hospital admission (OR=31.5; 95% CI=3.1 to 317.8; p=0.003), admission to ICU (OR=23.0; 95% CI = 2.4 to 223.8; p= 0.007) and death (OR=8.8; 95%CI= 1.2 to 65.5; p =0.034). None of the other potential predictors explored were significant (Table 2).

Discussion

The main objective of the COICA study was to add evidence to the existing body of literature suggesting that COVID-19 prognosis is negatively affected by a previous or concomitant cancer diagnosis. In fact, in one retrospective analysis of 557 consecutive COVID-19 patients, of whom 46 had active cancer, an overall fatality rate of 50% (CI 95%: 34.9;65.1) vs. 20.2% (CI 95%: 16.8;23.9) in patients with vs. without cancer was reported, with a median OS of 14 vs. 35 days, respectively[14]. Consistent results have been obtained by other researchers [15] [16]. Finally, in a retrospective case-control study conducted by analyzing medical records of 2,523,920 cancer patients, patients with cancer and COVID-19 had significantly worse outcomes (hospitalization rate, 47.46%; death rate, 14.93%) compared to non- oncological patients with COVID-19 (hospitalization rate, 24.26%; death rate, 5.26%) (P < .001) [17].

Based on these findings, the optimal strategy for early detection of SARS-CoV-2 in patients who periodically have access to hospital facilities to receive anti-cancer therapy remains to be established and contextualized in the evolving epidemiologic scenario. In this work, we presented clinical outcomes related to SARS-COV-2 infection in patients receiving systemic anti-neoplastic treatment at the coordinating center of the COICA study and reported a 9.21% death rate, with 11.84 % of patients requiring O_2 therapy, 15.79% requiring to be admitted to the hospital and 5.26 % being admitted to the intensive care unit. These findings appear to be more favorable compared to those mentioned above[14][15][16][17]. When we explored potential predictors of COVID-19 related outcomes, we found that non-screening vs. screening detected SARS-CoV-2 infection was associated with significantly higher odds of death, needing O_2 therapy, being admitted to hospital as well as being admitted to ICU. Although definitive conclusions can be drawn only in the context of a randomized interventional trial, our data seem to support the benefits of routine screening for SARS-CoV-2. In fact, the institutional screening policy adopted at the Hospital allowed to identify 71 asymptomatic cases overall, that is approximately 6% of the 1161 screened patients in the period considered. Our positive test rate was higher compared to other experiences. In fact, in a retrospective study including 1,226 cancer patients who were offered to be screened for SARS-CoV-2, a positive test was identified only in 10 patients (approximately 1%), with only seven patients being asymptomatic at the time of testing, which translated into an asymptomatic infection prevalence of 0.6% (95% CI [0.15–0.99][2]. Similarly, in another study conducted in 2691 cancer patients who underwent asymptomatic screening, only 1.6% of patients were SARS-CoV-2 positive, with 11.6% of the cohort developing COVID-19-related symptoms during the course of the disease [18]. Differently from these findings, we reported that in our cohort of initially 71 asymptomatic patients, 76% developed symptoms over the course of the disease, which suggests that our approach may have represented a truly effective strategy leading to early SARS-CoV-2 diagnosis. One possible interpretation of this unexpected finding is that patients might have been more frequently exposed to the virus just before they were screened, considering that patients on active therapy at the Hospital generally preferred to take a blood draw in any external laboratory next to their home a few

days before and were screened for SARS-CoV-2 the day before they were scheduled for therapy at the Hospital.

We recognize that our study presents multiple limitations. First of all, it is an unplanned analysis of an observational study, which therefore does not allow to draw any conclusion about the efficacy of the screening strategy adopted, and it can only provide hypothesis-generating results. Second, the COICA trial was not designed to include all patients diagnosed at any participating center, which may have been responsible for a selection bias. In fact, only 5 cancer patients were diagnosed outside the Institutional screening. To the best of the investigators' knowledge all patients with a SARS-CoV-2 diagnosis at the Hospital were offered to participate to the COICA trial and were ultimately included, although we are unaware of how many SARS-CoV-2 cases among cancer patients treated at the Hospital were missed. Third, the data presented were collected in a pre-vaccination scenario, with none of the enrolled patients being vaccinated, so they cannot be extrapolated in the current epidemiologic scenario, with the majority of patients being vaccinated. Fourth, the sample size of 76 patients, with only 5 patients diagnosed outside the institutional screening, is limited. Nevertheless, this analysis presented here has the strength to reflect the results obtained as a single center where a single screening protocol was followed, with all enrolled patients followed-up until recovery or death.

In conclusion, this unplanned analysis of the COICA trial performed at a single center reported an unexpected high rate of screening-detected SARS-CoV-2 infections in cancer patients. The potential implications for COVID-19 associated outcomes are unknown and the generalizability of our results is limited. Routine screening with RT-PCR may represent a feasible and effective strategy in reducing viral circulation and possibly COVID-19 mortality in patients with active cancer having repeated access to hospital facilities.

Statement of Ethics

Written informed consent was obtained from participants (or their parent/legal guardian/next of kin) to participate in the study. This study protocol was reviewed and approved by the local Ethics Committee Campania Sud, approval number 2020-3JF. The study was conducted according to the criteria set by the declaration of Helsinki

Conflict of Interest Statement

Dr. Di Lorenzo serves as an editorial board member of Oncology. All the other authors have no conflicts of interest to declare.

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Author Contributions

Study concept and design: Giuseppe Di Lorenzo, Luciana Buonerba, Concetta Ingenito, Carlo Buonerba.

Acquisition of data: all authors.

Analysis of data: Giuseppe Di Lorenzo, Carlo Buonerba

Interpretration of data: All authors.

Drafting of the manuscript: Giuseppe Di Lorenzo, Carlo Buonerba.

Critical revision of the manuscript for important intellectual content: all authors.

Data Availability Statement

Anonymized data are available upon request to the corresponding author without any restrictions.

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Figure Legends

Fig. 1. Time to confirmed negative RT-PCR

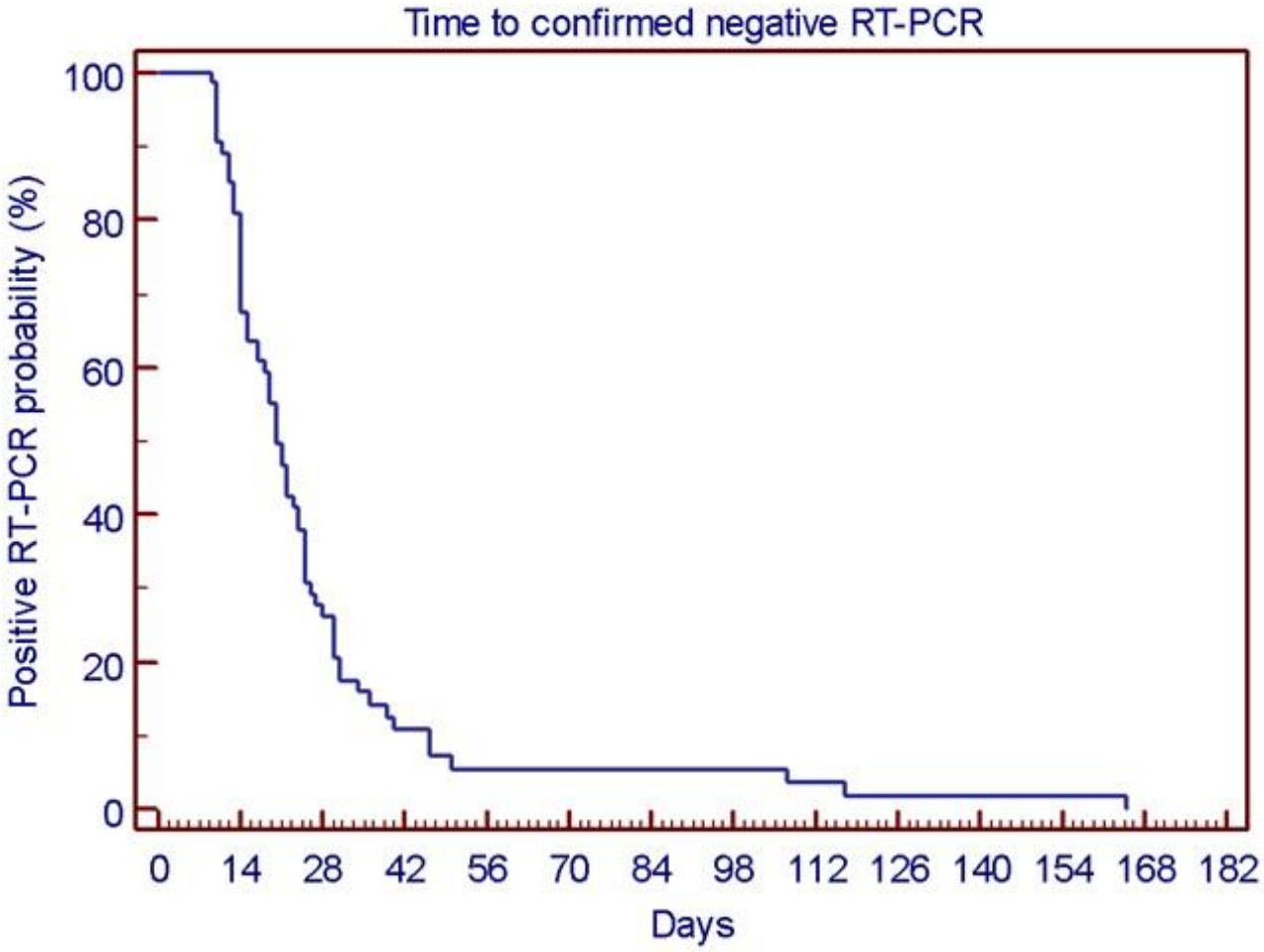
Time to confirmed negative RT-PCR
Positive RT-PCR probability (%)
100
80
60
40
20
0
0
14
28
42
56
70
84
98
112
126
140
154
168
182
Days

Table 1. Characteristics of the study population (n=76 cases)

Variable		Absolute Number / Evaluable cases (%)
Gender	Males	47/76 (61.84%)
	Females	29/76 (38.16%)
Any antineoplastic treatment within 30 days	Yes	37/76 (48.68%)
	No	39/76 (51.32%)
Last cancer diagnosis	Prostate cancer	15/76 (19.74%)
	Ovarian cancer	5/76 (6.58%)
	Merkel cell carcinoma	1/76 (1.32%)
	Lung cancer	7/76 (9.21%)
	Breast cancer	15/76 (19.74%)
	Colon cancer	7/76 (9.21%)
	Hepatocellular carcinoma	1/76 (1.32%)
	Kidney cancer	7/76 (9.21 %)
	Bladder cancer	6/76 (7.89%)
	Laryngeal cancer	1/76 (1.32%)
	Kaposi's sarcoma	1/76 (1.32%)
	Pancreatic cancer	1/76 (1.32%)
	Testicular cancer	3/76 (3.95%)
	Head and Neck cancer (tongue cancer)	1/76 (1.32%)
	Uterus cancer	2/76 (2.63%)
	Gastric cancer	2/76 (2.63%)
	Urothelial carcinoma	1/76 (1.32%)

Antineoplastic agent(s) administered within 30 days	Chemotherapy-based	Carboplatin- Paclitaxel	2/37 (5.41%)
		FOLFOX- Bevacizumab	2/37 (5.41%)
		Cisplatin- Pemetrexed- Pembrolizumab	1/37 (2.70%)
		Cabazitaxel	1/37 (2.70%)
		Carboplatin- Gemcitabine	3/37 (8.11%)
		Cisplatin	1/37 (2.70%)
		Doxorubicin	2/37 (5.41%)
		Cetuximab- FOLFOX	1/37 (2.70%)
		Paclitaxel- Gemcitabine	1/37 (2.70%)
		Bevacizumab-Paclitaxel	1/37 (2.70%)
		Pertuzumab- Trastuzumab- Docetaxel	1/37 (2.70%)
		Paclitaxel	1/37 (2.70%)
		Gemcitabine	1/37 (2.70%)
		Paclitaxel- Ramucirumab	1/37 (2.70%)
		Epirubicin- Cyclophosphamide	1/37 (2.70%)
		Docetaxel- Cyclophosphamide	1/37 (2.70%)
	Hormonal therapy	Abiraterone	3/37 (8.11%)
		Enzalutamide	3/37 (8.11%)
	Immunotherapy-based	Nivolumab	2/37 (5.41%)
		Atezolizumab	1/37 (2.70%)
		Pembrolizumab- Axitinib	1/37 (2.70%)
	Targeted therapy	Pertuzumab-Trastuzumab	4/37 (10.81%)
		Alectinib	1/37 (2.70%)
		Pazopanib	1/37 (2.70%)
Metastatic	Yes		55/76 (72.37%)
	No		21/76 (27.63%)
Symptomatic	Yes		59/76 (77.63%)
	No		17/76 (22.37 %)
Diagnosis	Screening		71/76 (93.42%)
	Non-screening		5/76 (6.58%)
CT-confirmed lung pneumonitis	Yes		15/76 (19.74%)
	No		4/76 (5.26%)
Admitted to Hospital	Yes		12/76 (15.79%)
	No		64/76 (84.21%)
Dead because of COVID-19	Yes		7/76 (9.21%)
	No with a confirmed negative RT-PCR		69/76 (90.79%)
Any Anti-Covid19 treatment	Yes		49/76 (64.47%)
	No		27/76 (35.53%)
o_2 therapy required	Yes		9/76 (11.84%)
	No		67/76 (88.16%)
Intensive Care Unit	Yes		4/76 (5.26%)
	No		72/76 (94.74%)

Anti- Covid19 treatment	Antibiotics	Azithromycin	21/49 (42.86%)
		Ceftriaxone	2/49 (4.08%)
		Levofloxacin	2/49 (4.08%)
		Amoxicillin/Clavulanic acid	2/49 (4.08%)
		Ciprofloxacin	1/49 (2.04%)
		Clarithromycin	1/49 (2.04%)
		Cefixime	1/49 (2.04%)
		Piperacillin/Tazobactam	1/49 (2.04%)
		Doxycycline	1/49 (2.04%)
		Sulphametoxazole- trimethoprim	1/49 (2.04%)
	Corticosteroids	Prednisone	10/49 (20.41%)
		Dexamethasone	7/49 (14.29%)
		Betamethasone	3/49 (6.12%)
	FANS	Ibuprofen	3/49 (6.12%)
		Ketoprofen	1/49 (2.04%)
	Heparin	Enoxaparin	11/49 (22.44%)
		Nadroparin	3/49 (6.12%)
		Parnaparin	1/49 (2.04%)
	Other therapies	Lopinavir/Ritonavir	2/49 (4.08%)
		Omeprazole	1/49 (2.04%)
		Tocilizumab	1/49 (2.04%)
		Vitamin C	1/49 (2.04%)
		Acetilsalicilic acid	1/49 (2.04%)
		Paracetamol	5/49 (10.20%)

Table 2. Univariate analysis of COVID-19 related outcomes

Predictor	Outcome	Odds ratio (95% CI)	P value*
Non screening diagnosed vs. screening diagnosed	Need of O2 Therapy	16.2 (2.2 to 117.1)	**0.006**
	Admitted to Hospital	31.5 (3.1 to 317.8)	**0.003**
	Admission to ICU	23.0 (2.4 to 223.8)	**0.007**
	Death	8.8 (1.2 to 65.5)	**0.034**
Age	Need of O2 Therapy	1.0 (0.9 to 1.0)	0.313
	Admitted to Hospital	1.0 (1.0 to 1.1)	0.152
	ICU	1.0 (0.9 to 1.1)	0.706
	Death	1.0 (0.9 to 1.1)	0.136
Sex Females vs. Males	Need of O2 Therapy	1.1 (0.2 to 4.6)	0.833
	Admitted to Hospital	1.8 (0.5 to 6.2)	0.361
	ICU	4.5 (0.4 to 46.1)	0.195
	Death	4.0 (0.7 to 21,9)	0.110

Metastatic vs. non metastatic	Need of O2 Therapy	2.9 (0.3 to 24.7)	0.328
	Admitted to Hospital	2.1 (0.4 to 10,6)	0.363
	ICU	1.0 (0.0 to 10.1)	1.000
	Death	2.1 (0.2 to 18.5)	0.502
Anti-cancer treatment within 30 days	Need of O2 Therapy	1.1 (0.2 to 4.6)	0.840
	Admitted to Hospital	0.7 (0,2 to 2,5)	0.597
	ICU	0.2 (0.0 to 2.8)	0.288
	Death	0.6 (0.1 to 3.1)	0.600

ICU= Intensive Care Unit. *Significant P values are highlighted in bold.