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Short communication

Circulating TNF-RII, IP-10 and HGF are associated with severity of COVID-19 in oncologic patients

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ABSTRACT

The COVID-19 patients showed hyperinflammatory response depending on the severity of the disease but little have been reported about this response in oncologic patients that also were infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Sixty-five circulating cytokines/chemokines were quantified in 15 oncologic patients, just after SARS-CoV-2 infection and fourteen days later, and their levels were compared in patients who required hospitalisation by COVID-19 versus non-hospitalised patients. A higher median age of 72 years (range 61–83) in oncologic patients after SARS-CoV-2 infection was associated with hospitalisation requirement by COVID-19 versus a median age of 49 years (20–75) observed in the non-hospitalised oncologic patients ($p = 0.008$). Moreover, oncologic patients at metastatic stage or with lung cancer were significantly associated with hospitalisation by COVID-19 ($p = 0.044$). None of these hospitalised patients required ICU treatment. Higher basal levels of tumour necrosis factor receptor II (TNF-RII), interferon-γ (IFNγ)-induced protein 10 (IP-10) and hepatocyte growth factor (HGF) in plasma were significantly observed in oncologic patients who required hospitalisation by COVID-19. Higher TNF-RII, IP-10 and HGF levels after the SARS-CoV-2 infection in oncologic patients could be used as biomarkers of COVID-19 severity associated with hospitalisation requirements.

1. Introduction

In December 2019, a new coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was spread from Wuhan (Hubei, China) to worldwide and finally was declared a global pandemic by the World Health Organisation [1]. The clinical spectrum of COVID-19 was wide and although most patients showed asymptomatic infection or mild upper respiratory tract illness, cases with severe viral pneumonia were associated with respiratory failure and a higher death risk [2]. The stage of COVID-19 severity was

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classified by the Word Health Organization (https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/) in "low" if patients showed mild COVID-19 symptoms and were hospital-treated for other reasons, "moderate" if they did not require supplemental oxygen or little and "severe" if they required high-flow oxygen, mechanical ventilation and multi-organ support.

The SARS-CoV-2 infection induced a hyperinflammatory reaction that may lead to a vascular endothelial cell injury and thrombus formation in the blood vessels of each organ, resulting finally in lung damage, acute respiratory distress syndrome and multiple organ dysfunction, specially in COVID-19 patients [3]. High blood levels of inflammatory markers like C-reactive protein (CRP), ferritin, D-dimer and neutrophils to lymphocyte ratio have been associated with severity of COVID-19 disease and higher death [1,4]. Moreover, increased serum levels of several inflammatory cytokines like IL-6, IL-8, IL-10, tumour necrosis factor receptors (TNF-RI and TNF-RII), hepatocyte growth factor (HGF) and chemokines like interferon-γ (IFN)-induced protein 10 (IP-10) have also been associated with disease severity and mortality [5–10]. These biomarkers could be used to anticipate subsequent clinical progression and to stratify patients based on risk, helping to choose the best treatment for each patient.

Oncologic patients have been particularly vulnerable during the COVID-19 outbreak due to their immunosuppressed state caused by the neoplastic disease, chemotherapy, radiotherapy or surgery treatment that increased their morbidity and mortality [11]. Lung cancer patients have often shown severe manifestation of COVID-19 after infection by SARS-CoV-2 and higher mortality than other cancer types [11,12]. However, the behaviour of these cytokines have not been analysed previously in oncologic patients after SARS-CoV-2 infection.

The aim of this study was to analyse the plasma levels of 65 cytokines in 15 oncologic patients after infection with SARS-CoV-2 virus, detecting higher levels of TNF-RII, IP-10 and HGF in oncologic patients who required hospitalisation by COVID-19.

2. Methods

2.1. Patients and samples

Fifteen oncologic patients infected with SARS-CoV-2 between July 2021 and April 2022 were enrolled in this study from three Spanish Hospitals (University Hospital General de Ciudad Real, Hospital Clínico San Carlos and University Hospital Fundación Jiménez Díaz) and grouped in Non-hospitalised and Hospitalised patients by COVID-19. Only oncologic patients over 18 years old with any type of cancer and infected with SARS-CoV-2, in whom a blood sample could be collected within the first days of infection, were enrolled. Data related to type of cancer and its stage at COVID-19 diagnosis, comorbidities and oncologic or COVID-19 treatment were collected.

Blood samples were collected just after diagnosis of COVID-19 (basal) in oncologic patients with a median time of 2 days (range 0–9) and after fourteen days (day 14) from the first extraction. Plasma was purified by centrifugation of anticoagulated whole blood samples between 24 hours from the extraction, and frozen at −80 °C until assayed.

2.2. Quantification of Cytokines/chemokines

Sixty-five cytokines/chemokines/growth factors (APRIL, BAFF, CXCL13, CD30, CD40L, CXCL5, CCL11, CCL24, CCL26, FGF-2, CX3CL1, CSF-3, GM-CSF, CXCL1, HGF, IFNα, IFNγ, IL-1α, IL-1β, IL-10, IL-12p70, IL-13, IL-15, IL-16, CTLA-8, IL-18, IL-2, IL-20, IL-21, IL-22, IL-23, IL-27, IL-2R, IL-3, IL-31, IL-4, IL-5, IL-6, IL-7, CXCL8, IL-9, CXCL10, CXCL11, LIF, CCL2, CCL8, CCL7, M−CSF, MDC, MIF, CXCL9, CCL3, CCL4, CCL20, MMP-1, NGFβ, SCF, SDF-1α, TNFα, TNFβ, TNF-RII, TRIAL, TSLP, TWEAK and VEGF-A) were quantied in plasma samples using Immune Monitoring 65-Plex Human ProcartaPlex™ Panel (EPX650-16500–901, Invitrogen) in the Luminex MAXPIG Instrument according to the manufacturer's protocol.

2.3. Data analysis

Statistical analysis of clinical characteristics and plasma levels of 65 cytokines were carried out between Hospitalised and Non-hospitalised patients by COVID-19. Variables following binomial distributions (i.e.: gender) were expressed as frequencies and percentages. Comparisons between qualitative variables were done using the Fisher Exact Test. Comparisons between quantitative variables were performed through the non-parametric U of Mann-Whitney test. Statistical analysis was done using the SPSS software version 25.0 (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Patients' characteristics

Fifteen oncologic patients diagnosed with different types of cancer (3 lung cancer, 3 ovarian cancer, 2 breast cancer, 2 cervix cancer, 1 oral cancer, 1 oesophageal cancer, 1 gastric cancer, 1 thyroid cancer and 1 desmoplastic cancer), over 18 years old who were also infected with SARS-CoV-2 virus between July 2021 and April 2022 were enrolled in this study. Six of these oncologic patients required hospitalisation by COVID-19 (Table 1). The median age at COVID-19 diagnosis of 72 years (range 61–83) in the Hospitalised patients was significantly higher than 49 years (range 20–75) in the Non-hospitalised patients ($p = 0.008$). The proportion of male/female was 50/50 in the Hospitalised patients and 22.2/77.8 in the Non-hospitalised patients. The Hospitalised patients required a median time of hospitalisation from the SARS-CoV-2 infection of 9.5 days (range 8–17), who were mainly affected by lung cancer (50 %) or breast cancer (33.3 %), and diabetes (33.3 %) or chronic respiratory illness (33.3 %). Oncologic patients at metastatic stage or with lung cancer were significantly associated with hospitalisation by COVID-19 after SARS-CoV-2 infection ($p = 0.044$). None of them required ICU treatment.

Table 1
Clinical characteristics and inflammatory indexes.

Characteristics	Non-hospitalised patients (n = 9)	Hospitalised patients (n = 6)	p-value
Median Age (years)	49 (20–75)	72 (61–83)	0.008
Gender (%):			
Male	2 (22.2 %)	3 (50 %)	0.329
Female	7 (77.8 %)	3 (50 %)	
Extension of disease (%):			
Localised	5 (56 %)	0	0.044
Metastatic	4 (44 %)	6 (100 %)	
ICU treatment (%):			
No	9 (100 %)	6 (100 %)	-
Yes	0	0	
Histotype (%):			
Lung cancer	0	3 (50 %)	0.044
Breast cancer	0	2 (33.3 %)	0.143
Ovarian cancer	3 (33.3 %)	0	0.299
Cervix cancer	2 (22.2 %)	0	0.486
Oral cancer	1 (11.1 %)	0	1.000
Oesophagus cancer	0	1 (16.7 %)	0.400
Gastric cancer	1 (11.1 %)	0	1.000
Thyroid cancer	1 (11.1 %)	0	1.000
Desmoplastic small round cell tumour	1 (11.1 %)	0	1.000
Comorbidities (%):			
Hypertension	3 (33.3%)	1 (16.6 %)	0.604
Smoker	4 (44.4 %)	3 (50 %)	1.000
Diabetes	0	2 (33.3 %)	0.143
Chronic respiratory Illness	0	2 (33.3 %)	0.143

3.2. TNF-RII, IP-10 and HGF plasma levels as predictive biomarkers of severe disease by COVID-19 in oncologic patients

Plasma levels of sixty-five cytokines/chemokines were quantified in the fifteen oncologic patients just after SARS-CoV-2 infection and 14 days later. Fifteen cytokines/chemokines (CXCL13, CCL8, MDC, CD30, TNF-RII, CCL7, IL-4, IP-10, IL-7, CCL11, HGF, CCL2, IL-15, IL-18 and VEGF-A) were detected in all the patients at the basal time and their levels were compared in patients who required hospitalisation by COVID-19 versus Non-hospitalised patients at the different times (Table S1). Among them, basal TNF-RII, IP-10 and HGF levels were significantly higher in the Hospitalised patients with a median concentration of 194.5 pg/ml, 59.5 pg/ml and 97 pg/ml, respectively, versus 84 pg/ml, 22 pg/ml and 44.5 pg/ml ($p = 0.013$, $p = 0.033$ and $p = 0.008$) in the Non-hospitalised patients (Fig. 1 and Table S1). TNF-RII, IP-10 and HGF plasma levels increased quickly after SARS-CoV-2 infection in the Hospitalised patients and decreased at day 14, achieving similar levels detected in the Non-hospitalised patients. Basal TNFR-II, IP-10 levels and HGF did not show a significant Spearman correlation with age ($r_S = 0.368$, $p = 0.177$; $r_S = 0.332$, $p = 0.226$ and $r_S = 0.370$, $p = 0.193$, respectively). The other cytokines/chemokines were under the limit of detection of the assay in the majority of samples.

4. Discussion

In this study the plasma levels of sixty-five cytokines/chemokines were quantified in fifteen oncologic patients just after SARS-CoV-2 infection and their levels were compared in patients who required hospitalisation by COVID-19 versus Non-hospitalised patients. Lung cancer or breast cancer cases were more represented in this study probably because they are among the most prevalent in the population. However, ovarian or cervix cancer cases were more represented than expected probably because there were twice as many cases of females as males. A higher median age was associated significantly to the Hospitalised patients, which has also been previously associated with a higher mortality [11]. Moreover, the presence of metastatic disease or lung cancer were significantly associated with hospitalisation by COVID-19, as it has been reported in previous studies [12]. However, different comorbidities observed in these oncologic patients such as hypertension, smoking, diabetes and chronic respiratory illness were not significantly associated with hospitalisation by COVID-19.

Among the sixty-five cytokines analysed, TNF-RII, IP-10 and HGF levels were significantly increased just after SARS-CoV-2 infection in oncologic patients who required hospitalisation by COVID-19. Higher TNF-RII levels have been previously associated with disease severity and mortality in COVID-19 patients [5] and higher levels of its ligand TNFα and the other receptor, TNF-RI, have also been reported in hospitalised COVID-19 patients who required ICU treatment [9,10]. Therefore, the TNFα signalling pathway developed an important role in the hyper-inflammatory response and its blockage has improved clinical outcomes [13]. Higher levels of the chemokine IP-10, together with CCL2 and other cytokines like IL6, IL8 or IL10 have been reported in the COVID-19 patients and related to disease severity [6], specially in cases who required ICU treatment [7]. IP-10 is a cytokine mainly responsible for the lung cell damage which has been proposed as a biomarker for a higher susceptibility and fatality of lung cancer patients toward SARS-CoV-2 infection [14]. Finally, higher HGF levels, a pleiotropic cytokine with anti-inflammatory properties, together with CXCL13 levels

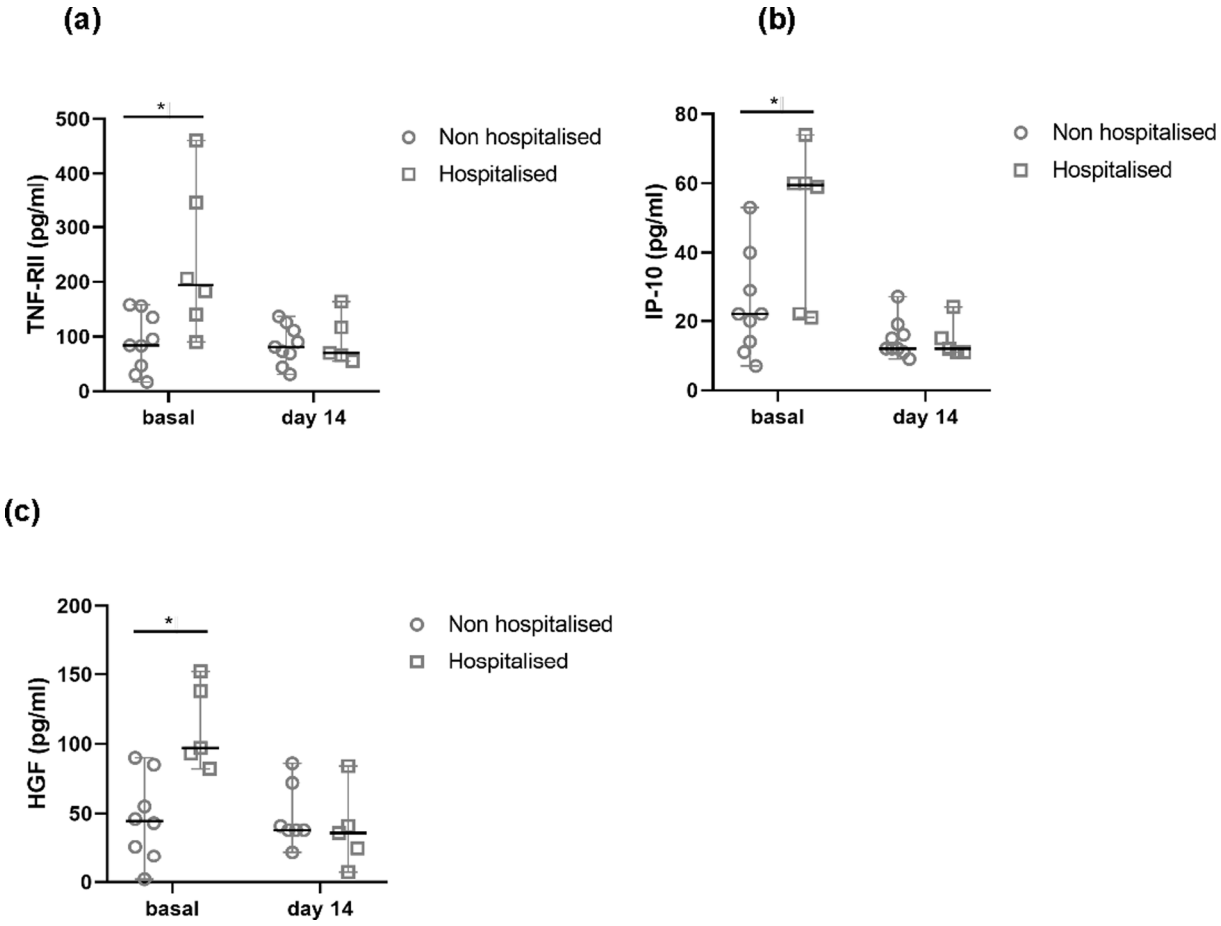

Fig. 1. Plasma TNF-RII, IP-10 and HGF levels along the time in Non-hospitalised or Hospitalised oncologic patients. Plasma concentration (pg/ml) of TNF-RII (a), IP-10 (b) and HGF (c) for each patient from the Non-hospitalised or Hospitalised patients are shown along the time (basal and day 14), *$p < 0.05$.

have also been reported in the COVID-19 patients who required ICU treatment [8]. However, higher TNF-RII, IP-10 and HGF levels were significantly associated with COVID-19 severity in the oncologic patients enrolled in this study and not the other cytokines and chemokines previously reported in the COVID-19 patients. According to the WHO classification of COVID-19 patients, our Non-hospitalised patients corresponds to patients with low severity and the Hospitalised patients to patients with moderate severity because none of them required ICU treatment, so probably a higher number of cytokines/chemokines would have been upregulated and with higher level in oncologic patients with requirement of ICU treatment as it has been described for COVID-19 patients, but none of these cases was enrolled in our study. Some studies showed that only 14 % of hospitalised COVID-19 patients required ICU treatment [15] so the low number of hospitalised patients in our study would explain that no cases who required ICU treatment were enrolled in this study.

This study has the limitation of the very few recruited patients by the difficulty to activate the specific protocol at the peak of the pandemic, limited access to the hospital of the cancer patients, difficulty to identify oncologic patients infected by SARS-CoV-2 just in the first days of the infection and rapid decrease of cases due to the effect of the vaccination campaign. Moreover, the high heterogeneity among the oncologic patients because they were affected by different types of cancer and were treated with different chemotherapeutic regimens. Even so, not all the types of cancer were represented. Finally, the absence of viral data which could be associated with the cytokine/chemokine response. Nevertheless, we found three cytokines/chemokines which were upregulated in oncologic patients who required hospitalisation by COVID-19.

In conclusion, higher TNF-RII, IP-10 and HGF levels could be used as predictive biomarkers of COVID-19 severity in oncologic patients after SARS-CoV-2 infection, anticipating the requirement of treatment like hospitalisation and specific therapies for each one.

Author Contributions

J.C.-G. and S.L. contributed equally to this work. Conceptualization, J.M.-B.; Investigation, J.C.-G., S.L., M.R. and J.L.M.-H.; Formal analysis, J.C-G., D.D.L and A. G.; Writing—original draft preparation, J.C.-G., D.S. M. and J.M.-B.; Resources, G.M., D.P.C., J.O., J.M.C.C. and S.H.; Writing—review and editing, J.C.-G., S.L., N.H., D.S.M., G.M., J.M.C.C., S. H., A.C., A.M. and J.M.-B.; Supervision, J.M.-B.; Funding acquisition, J. M.-B. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Drug Research Ethics Committees (CEIms) of the participating centres, University Hospital General de Ciudad Real (9 Feb 2021, C.I.-C-431), Hospital Clínico San Carlos and University Hospital Fundación Jiménez Díaz (22 Dec 2020, C.I.-20/829/E)).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

CRediT authorship contribution statement

Jaime Carrillo-García: Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Serena Lacerenza:** Investigation, Writing – review & editing. **Nadia Hindi:** Writing – review & editing. **David S. Moura:** Writing – original draft, Writing – review & editing. **Gloria Marquina:** Resources, Writing – review & editing. **Daniel Parra Corral:** Resources. **Jennifer Olalla:** Resources. **Juana María Cano Cano:** Writing – review & editing, Resources. **Sergio Hoyos:** Resources, Writing – review & editing. **Marta Renshaw:** Investigation. **Jose L Mondaza-Hernández:** Investigation. **Davide Di Lernia:** Writing – original draft, Writing – review & editing. **Antonio Casado:** Formal analysis. **Arantxa Manzano:** Writing – review & editing. **Antonio Gutierrez:** Formal analysis. **Javier Martin-Broto:** Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Javier Martin Broto reports financial support was provided by Pfizer and Consejería de Salud de Andalucía. Jaime Carrillo Garcia reports a relationship with Pharmamar and Karyopharm that includes: funding grants. David da Silva Moura reports a relationship with Pharmamar, Eisai, Immix Biopharma, Novartis, Celgene, Bayer and Pfizer that includes: funding grants and travel reimbursement. Nadia Hindi reports a relationship with Pharmamar, Eisai, Immix Biopharma, Novartis, Eli Lilly, Arog, Bayer, Lixte, Karyopharm, Deciphera, GSK, Novartis, Blueprint, Nektar, Forma, Amgen and Daichii-Sankyo that includes: consulting or advisory, funding grants, and non-financial support. Javier Martin Broto reports a relationship with Pharmamar, Eisai, Immix Biopharma, Novartis, Eli Lilly, Bayer, Arog, Lixte, Karyopharm, Deciphera, GSK, Novartis, Blueprint, Nektar, Forma, Amgen and Daichii-Sankyo that includes: consulting or advisory and funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.].

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2024.156542.

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