Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Does type of immunosupression influence the course of Covid-19 infection?

To the editor:

Minotti Chiara and colleagues and Ya Goa and colleagues have evaluated the burden of immunosupression on Covid-19 outcomes.[1,2] Coronavirus disease 19 (Covid-19) is a new challenge for physicians, especially for those who treat patients with immunocompromised status. Pathophysiology of Covid-19 is complex and a combination of factors is responsible for the hyperinflammatory state leading a cytokine release syndrome in some patients.[3] Few studies have reported that different biological features such as the cytokine release,[3] a defect in type I-interferon response[4] and/or polymorphisms of renin-angiotensin aldosterone system may play a major role in the heterogenicity of the disease.[5] As lymphopenia has been reported as a poor prognosis factor,[6] adaptative immune system might have a key role in the recovery of the disease. Only few data have reported the outcome of Covid-19 in such frail patients with cancer, organ transplant or rheumatoid condition.[7,8,9] From that hypothesis, we have compared the characteristics and outcomes of patients depending on the type of immunosupression in Besancon University Hospital from March 5th 2020 to April 30th 2020.

This retrospective case study included adults who are at least 18 years old with a diagnosis of Covid-19 infection hospitalized. All included patients have immunosupression defined by: history of neoplasia during the last five years, organ transplant, child-Pugh C cirrhosis, nephrotic syndrome, and immune related disorders or therapeutic immunosuppression (Disease-Modifying Antirheumatics Drugs (DMARDs) or steroids regimens more than 7.5 mg/day for a period superior than 3 months). Hospitalization criteria included high-grade fever, breath shortness or chest pain. Diagnosis of Covid-19 was obtained with positive reverse transcriptase polymerase chain reaction on naso-pharyngeal swab and/or pneumonia identified on chest Computed Tomography (CT). Chest CT scan was performed at the discretion of the physician and radiologist; but it was always performed when patient had spontaneous SaO2 below 94% or pulmonary embolism suspicion. In the context of the Covid-19, the French National Information Technology and Liberty Committee (Commission Nationale Informatique et Liberté, CNIL) considers that, for monocentric observational research associated with Covid-19, the information and consent of patients and families is not required.

Data have been extracted from the hospital databases and statistical analysis were performed using Prism (GraphPad, San Diego, CA, USA) (see supplementary data).

Out of 902 patients diagnosed with Covid-19, 380 patients were hospitalized. Among them, 80 patients had immunocompromised status. A total of 42 patients had solid tumor (mostly prostate cancer), 20 had hematological malignancy (mostly lymphoma) and 18 had other immunosuppression conditions (mostly organ transplant or rheumatoid conditions). The patient median age was 73.7 years old (range: 66.2-82.6) and they were mostly men (57.5%). The characteristics of patients at baseline are reported in Table 1.

The Covid-19 clinical presentation did not differ regarding the type of immunodepression. The most common symptoms were fever and cough without statistical difference between the groups ($p = 0.54$ and 0.36 respectively). At admission, hemoglobin, white count cells and lymphocytes differ between the three groups ($p < 0.01$, <0.001 and 0.03 respectively). The other biological parameters were similar except lactate dehydrogenase (LDH) ($p = 0.048$). As expected, steroids intake was more important in the non-neoplastic group ($p < 0.0001$).

Regarding radiological pattern, extended lesions on CT-scan were more frequent in non-neoplastic group and were close to reach a statistical significance ($p = 0.1070$).

Regarding the patient's outcome, almost half of patients with immunodepression had acute respiratory distress syndrome ($p = 0.64$). Mortality rate was elevated (23%) but did not differ between the groups ($p = 0.58$). Poor outcomes (ICU and or death) were frequent (38%) and tended to be more frequent in patients with hematological malignancy ($p = 0.08$) (see Table 2)

We herein report a comparative study between patients with different type of immunodepression. Our data suggest that hematological malignancy tends to be associated with poor outcomes. This outcome might be related to different Interferon-α (IFN-α) production depending on type of immunodepression. Indeed, several data report an increase of Interferon-α production in response to virus.[10]

IFN-α is produced by dendritic cells in response to infection and has a paracrine effect on lymphocytes and macrophages. It secretion induces inflammatory state via "Th1 polarization" on lymphocytes, "M-1 macrophages polarization" and lead to cytokine release syndrome. Majority of human B-lineage cell lines (B lymphoma and myeloma cells) spontaneously produce significant amounts of IFN-α and overexpression by viral stimuli may explain exacerbated cytokine release syndrome in patient with hematological malignancy. Increased IFN-α production has not been reported yet in solid tumor or rheumatoid conditions except lupus and Gougerot-Sjögren.

There are some limitations to this study. First of all, it is a retrospective study with data collection based on the information available on the patient's records. Another limit is the suspension of oncological activity including some chemotherapy during the pandemic. Thus we could not evaluate if cancer activity or chemotherapy was more responsible for outcome of Covid-19.

Our major strength is that data was derived from a tertiary care center in Europe with high prevalence of COVID-19 infection.

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Table 1
Demographics, clinical characteristics of patients at baseline.

	All patient (n=80)	Solid cancer (n=42)	Hématological malignancy (n=20)	Non neoplastic immunodeficiency (n=18)
Mean age (range)	72.4 ((±13.8)	75.6 (±12.0)	68.8 (±10.2)	68.2 (±19.2)
Sex M	46	27	13	8
Coexisting conditions				
HTA (n)	29	16	5	6
Cardiovascular conditions (n)	40	23	9	8
Current smoker (n)	9	6	3	1
BMI>40 (n)	3	2	0	1
Diabetes (n)	14	6	3	4
Respiratory disease (n)	15	7	4	3
Type of ID (n)		Prostate:11 Breast:8 Lungs:5 Colon:4 ENT:3 Pancreas:2 Ovary:2 Skin:2 Kidney: 2 Bladder:1 Liver:1 Stomach:1	B lymphoma : 8 Myeloma : 4 Secondary acute leukemia : 2 Chronic lymphoid leukemia: 2 Primary acute leukemia:1 Chronic myeloid leukemia: 1 T lymphoma : 1 Myelodysplastic syndrom :1	Organ transplant : 5 Polymyalgia rheumatica:3 Vasculitis: 3 Nephrotic syndrome : 2 Child Pugh C cirrhosis: 2 Rheumatoid arthritis: 2 Spondyloarthritis:1
Local treatment for cancer (n)	29	29	0	0
Hormonotherapy (n)	12	12	0	0
Chemotherapy (n)	38	18	20	0
Targeted therapies (n)	2	2	0	0
Monoclonal antibodies for solid tumor (n)	3	3	0	0
Anti-Cd20 monoclonal antibodies (n)	10	0	8	2
Hematological stern cell (n)		0	4	0
CAR-T cells (n)	1	0	1	0
Proteasome inhibitor (n)	5	0	5	0
Venetoclax	3	0	3	0
Immunosuppressive therapies except steroids (n)				Tacrolimus:5 Mycophenolate Mofetil: 3 JAK-inhibitor:1 Leflunomide: 1 Methotrexate: 1 Salazopyrine: 1 Azathioprine: 1

Table 2
Characteristic and outcomes of patients with immunosupression.

	Mean value all ID patientsn=80	Solid tumorn=42	Hematological malignancyn=20	Non neoplastic immunodeficiencyn=18	P value
Signs and symptoms at baseline					
Temperature°C	37.7 (± 1.11)	37.7 (± 1.09)	37.6 (± 1.15)	37.5 (± 1.11)	0.8535
Fever	65 (81)	36 (85)	15 (75)	14 (77)	0.5475
Respiratory rate	21.8 (± 6.58)	19.8 (± 4.51)	24.8 (± 10.9)	23.7 (± 5.05)	0.0618
Sao2	93.9 (± 2.69)	94 (± 2.60)	93.7 (±3.30)	93.9 (± 2.31)	0.0938
Cough	58 (72)	33 (78)	14 (70)	11 (61)	0.3660
Shortness of breath	28 (35)	16 (38)	5 (25)	7 (38)	0.555
Abnormal auscultation	49 (61)	25 (59)	12 (60)	12 (66)	0.8657
Digestive symptoms (nausea/vomiting/diarrhea).	24 (30)	11 (26)	6 (30)	7 (38)	0.6165
Fatigue/syncope	50 (62)	34 (80)	11 (55)	15 (83)	0.0571
Biological status at baseline					
Hb	11.9 (± 2.18)	11.9 (±2.06)	10.7 (±1.94)	12.8 (±2.19)	**0.0093**
GB	11.7 (± 21.7)	6.24 (± 3.44)*	26.0 (± 39.7)#	7.36 (± 3.77)	**0.0061**
Ly	4.35 (± 19.6)	0.947(±0.485)	14.5 (±38.6)	1.05 (±0.454)	**0.0352**
ASAT	57.5 (48.8)	51.5(±33.5)	49.6 (±48.3)	73.7 (±68.9)	0.2177
ALAT	41.4 (± 63.1)	36.3 (±26.2)	35.8 (±36.5)	58.6 (±115)	0.3681
LDH	366 (± 181)	316 (±122)	352 (±233)	448 (±197)	**0.0475**
Bilirubin	8.42 (± 3.85)	8.55 (±4.10)	8.24 (±3.55)	8.33(±3.53)	0.9575
creatinine	108 (± 113)	119(±146)	89.4(±38.9)	96.0 (±56.2)	0.5799
CRP	101 (± 84.2)	98.1(±82.2)	106(±90.1)	103(±82.3)	0.9398
Ferritin	1607 (± 1774)	1470(±1628)	2597(±2744)	1371(±997)	0.0929
Fibrinogen	6.10 (± 1.53)	6.14(±1.33)	5.87(±1.87)	6.13(±1.57)	0.8467
D-dimer	2060 (± 1873)	1960(±1377)	2512(±2569)	1415(±1412)	0.3092
lactate	1.70 (±0.922)	1.65(±0.774)	1.74(±1.41)	1.75(±0.734)	0.9497
PaO2/FiO2	318(±90.5)	316.29 (±84)	309.22(±131)	316.40 (±89)	0.9755
Treatment					
Steroids before admission	16 (20)	4 (9)	2 (10)	10 (55)	**0.0001**
Antibiotic	50 (62)	27 (64)	12 (60)	11 (61)	0.9393
Anticoagulation therapy	56 (70)	31 (73)	13 (65)	12 (66)	0.7321
Hydroxychloroquine	9 (11)	4 (9)	1 (5)	4 (22)	0.2146
Radiological findings					
CT-scan	47 (58)	21(50)	14 (70)	12 (66)	0.2421
Covid-19 pattern on CT-scan	34 (42)	16 (38)	11 (55)	7 (38)	0.4256
Extended lesions on CT-scan	18 (22)	6 (14)	5 (25)	7 (38)	0.1070
Pulmonary embolism	6 (7)	3 (7)	1 (5)	2 (11)	0.7686
Diagnosis of pneumonia	64 (80)	34 (80)	14 (70)	16 (88)	0.3391
0utcomes					
ARDS	33 (41)	17 (40)	7 (35)	9 (50)	0.6372
ICU admission	12 (15)	3 (7)	5 (25)	4 (22)	0.1143
Death	19 (23)	8 (19)	6 (30)	5 (27)	0.5754
Poor outcome	31 (38)	11 (26)	11 (55)	9 (50)	0.0823

* $p < 0.05$ vs patients with hematological malignancy
# $p < 0.05$ vs patients with non-neoplastic immunodeficiencyAbbreviations: Sa02: saturation of arterial blood with oxygen, Hb: hemoglobin, GB: white count cells, Ly: lymphocytes counts

This data reinforce the burden of immunodepression regarding Covid-19 infection; and our results correlate with Minotti Chiara[1] Ya Gao.[2]

Patient with hematological malignancy are the most fragile patient regarding covid-19 infection but our results could not reach statistical significance.

Declaration of Competing Interest

The authors declare no competing financial interest and received no grants related to this study.

Authors contribution

JR, KB designed the study. ASB, KB and JR and collected the data and JR wrote the initial draft. JR, KB and TS performed the statistical analysis. All authors participate in editing and approved the final version of the manuscript.

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