Inflammatory pathways associated with COVID-19 severity differ based on obesity status

277

Stefano Savinelli[1,2], Grace Kenny [1,2], Colm O'Brien [1], Kathleen McCann[1], Alejandro A Garcia Leon[2], Gurvin Saini[2], Colette M Gaillard[2], Riya Negi[2], Dana Alalwan[2], Alan L Landay[3], Cecilia M O'Kane[4], Aoife Cotter[2,5], Patrick WG Mallon[1,2], Eoin R Feeney[1,2] on behalf of the AIID cohort study investigators.

[1]St Vincent's University Hospital, Dublin, Ireland [2]Centre for Experimental Pathogen Host Research (CEPHR), University College Dublin (UCD), School of Medicine, Dublin, Ireland [3]Department of Internal Medicine, Rush University Medical Centre, Chicago, Illinois [4]Wellcome Wolfson Institute for Experimental Medicine, Queen's University Belfast, Northern Ireland, UK [5]Mater Misericordiae University Hospital, Dublin, Ireland

Background

- Severe COVID-19 is characterized by a hyperinflammatory response associated with high morbidity and mortality[1].
- People with obesity have features of persistent low-grade inflammation[2].
- A higher degree of inflammation in people with obesity and COVID-19 is thought to contribute to the worse clinical outcomes in this population during SARS-CoV-2 infection[3-5].
- The aim of our study was to explore how patterns of inflammation differ between SARS-CoV-2 infected people with and without obesity, and the association between these patterns and COVID-19 disease severity.

Methods

- People with (Ob) and without (NOb) obesity (BMI ≥30 kg/m^2) and COVID-19 were recruited from the AIID multicentre, prospective cohort, matched for age, sex and WHO COVID-19 disease severity[6].
- Blood samples collected early after the diagnosis were used to measure 57 biomarkers (chemiluminescence) covering the pathways outlined below.

Biomarker functional group	Biomarkers
Innate immune activation	IL-28A/B, CXCL10, S100B, sCD163, CCL2, TGF-α, IL-33, CCL22, sCD14, IL-12, IFN-α/β/γ/λ
Immune regulation	PD-L1, IL-1RA, IL-10, IL-13, IL-4, IL-5
Systemic inflammation	IL-8, EGF, VEGF, CCL3, GM-CSF, IL-18, PCT, TSLP, CRP, IL-15, TNFR1, TNFR2, TNF-α, IL-17, IL-1β, IL-2, IL-6
Coagulation	D-dimer, TPO, PDGF-AA/AB, CD40L, SERPINE1, vWF
Endothelial activation	E-selectin, P-selectin, ICAM-1, VCAM-1
Immune metabolism	FABP4, resistin, leptin, adiponectin
Microbial translocation	LBP, I-FABP, zonulin, BDG

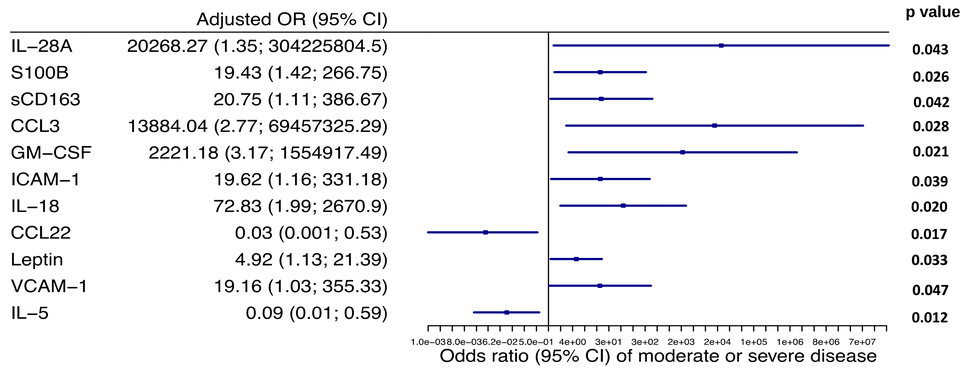
- Between-group differences were assessed by Mann-Whitney. Associations between subsequent maximal COVID-19 severity (mild vs moderate/severe/critical) and biomarkers were explored by logistic regression adjusted for age, sex, hypertension (HTN) and diabetes (DM).
- Data are median pg/mL [IQR] or n [%], unless stated.

People with COVID-19 and obesity had significantly higher markers of inflammation, coagulation and microbial translocation compared to matched controls. However, in adjusted analyses these markers were not associated with disease severity in people with obesity, in contrast to people without obesity. This suggests generalised immune dysregulation across this population, which may explain some of the higher morbidity and mortality seen with COVID-19.

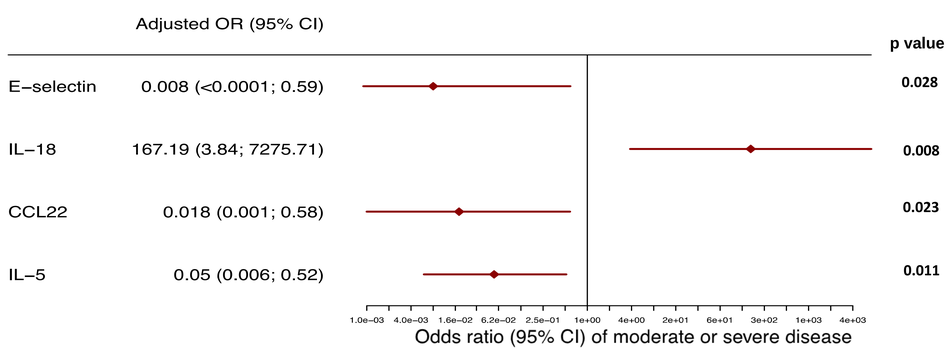
Results

- A total of 50 Ob and 50 NOb presenting between April 2020 and March 2021 were included in the analysis. Patients' characteristics are summarized in Table 1.
- Compared to NOb, Ob had higher circulating levels of markers of innate immune activation (IFN-α), systemic inflammation (CRP), immune regulation (IL-1RA, IL-4), coagulation (vWF), microbial translocation (zonulin), and immune metabolism (resistin, leptin), while adiponectin (anti-inflammatory immune metabolism marker) was lower. Median [IQR] and p-values for these differences in biomarkers are summarized in Table 2.

People Without Obesity



People With Obesity



Results (cont)

Table 1. Patient characteristics.

Patients' characteristics n (%) or median [IQR]	People with obesity (n=50)	People without obesity (n=50)
Age (years)	65 [23-91]	65 [21-95]
Sex (female)	27 (48%)	28 (56%)
BMI (kg/m^2)	33.7 [30.0-71.8]	23.3 [15.3-25.9]
WHO disease severity	Mild 22 [48%] Moderate 15 [30%] Severe/critical 6 [12%]	Mild 23 [46%] Moderate 13 [26%] Severe/critical 7 [14%]
Comorbidities	Hypertension 30 (60%) Diabetes 19 [38%]	Hypertension 17 (34%) Diabetes 6 [12%]
Days from symptom onset	7 [2-17]	8 [1-15]
Vaccinated	3 (6%)	0 (0%)

Table 2. Between-group difference in biomarkers.

Biomarkers median [IQR]	People with obesity	People without obesity	p value for between-group difference
IFN-α (pg/mL)	1.8 [0.6; 11]	0.9 [0.1; 4.7]	0.02
CRP (mAU/mL)	10 [9.6; 10.2]	9.7 [7.2; 10]	0.02
IL-1RA (pg/mL)	197 [122; 399]	138 [88; 253]	0.02
IL-4 (AU/mL)	288 [161; 424]	205 [82; 333]	0.04
vWF (pg/mL)	252 [166; 383]	163 [96; 318]	0.03
Zonulin (ng/mL)	114 [77; 131]	57 [18; 106]	<0.001
Resistin (pg/mL)	956 [569; 1153]	727 [712; 1525]	0.02
Leptin (pg/mL)	3482 [1513; 5738]	848 [249; 2114]	<0.001
Adiponectin (mg/L)	1.12 [0.09; 1.5]	1.5 [1.18; 1.93]	0.002

- In both groups higher proinflammatory IL-18 and lower levels of anti-inflammatory CCL22 and IL-5 were associated with higher odds of disease severity, and lower E-selectin with higher disease severity only in Ob (see figure to the left).
- However, in NOb higher type 3 interferons (IL-28A), macrophage activation (sCD163, CCL3) and vascular inflammation markers (ICAM-1, VCAM-1), along with higher S100B, GM-CSF and leptin were also associated with disease severity, a pattern not observed in Ob.

Conclusions

- Although Ob had higher overall levels of inflammation than NOb, these biomarkers did not predict subsequent COVID-19 severity in Ob.
- These differences in patterns of innate immune activation, macrophage activation, vascular and systemic inflammation suggest dysregulated immune responses in Ob with COVID-19. How these differences impact on clinical outcomes needs to be explored in future research.

REFERENCES

1. Leisman DE et al. *Lancet Respir Med* 2020; 2. Apostolopoulos V et al. *Mol Nutr Food Res* 2016; 3. Petrilli CM et al., *BMJ* 2020; 4. Hajifathalian K et al., *Obesity* 2020; 5. Foulkes AS et al., J *Clin Endocrinol Metab*. 2022; 6. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. *Lancet Infect Dis*. 2020

ACKNOWLEDGEMENTS

The authors would like to acknowledge all the study participants and all the collaborators for the All Ireland Infectious Diseases (AIID) Cohort study. This study was funded through the Science Foundation Ireland (SFI) grant number 20/COV/8566