features are mostly compatible with macrophage activation syndrome (MAS) observed in other viral infections despite resulting in milder changes. Early detection and treatment of MAS may be associated with a better outcome. However, available criteria for MAS associated with other causes have not been helpful.

Objectives: To identify distinct features of MAS associated with COVID-19 using a large database enabling to assess of dynamic changes.

Methods: PCR-confirmed hospitalized COVID-19 patients followed between March and September 2020 constituted the discovery set. Patients considered to have findings of MAS by experienced physicians and given anakinra or tocilizumab were classified as the MAS group and the remaining patients as the non-MAS group. The MAS group was then re-grouped as the cases with exact-MAS and borderline-MAS cases by the study group. Clinical and laboratory data including the Ct values of the PCR test were obtained from the database, and dynamic changes were evaluated especially for the first 14 days of the hospitalization. The second set of 162 patients followed between September-December 2020 were used as the replication group to test the preliminary criteria. In the second set, hospitalization rules were changed, and all patients required oxygen support and received dexamethasone 6mg/day or equivalent glucocorticoids. Daily changes were calculated for the laboratory items in MAS, borderline, and non-MAS groups to see the days differentiating the groups, and ROC curves and lower and upper limits (10-90%) of the selected parameters were calculated to determine the cutoff values.

Results: A total of 769 PCR-confirmed hospitalized patients were analysed, and 77 of them were classified as MAS and 83 as borderline MAS patients. There was no statistically significant difference in the baseline viral loads of MAS patients compared to the non-MAS group according to the Ct values. Daily dynamic changes in the MAS group differed from the non-MAS group especially around the 6th day of hospitalization, and more than a twofold increase in ferritin and a 1.5-fold increase in D-dimer levels compared to the baseline values help to define the MAS group. Twelve items selected for the criteria are given in Table 1 below. The total score of 45 provided 79.6% sensitivity for the MAS (including borderline cases) and 81.3% specificity around days 5 and 6 in the discovery set, and a score of 60 increased the specificity to 94.9% despite a decrease in sensitivity to 40.8%. The same set provided a similar sensitivity (80.3%) in the replication, but a lower specificity (47.4-66% on days 6 to 9) due to a group of control patients with findings of MAS possibly masked by glucocorticoids.

Table 1. Preliminary Criteria for Macrophage Activation Syndrome Associated with Coronavirus Disease-19

1. Fever ($>37.0^{\circ}\text{C}$)
2. Ferritin concentration $> 550\text{ ng/mL}$
3. More than 2 times increase of ferritin concentration within 7 days of disease onset
4. Neutrophil count $> 6000\text{ cell/mm}^3$
5. Lymphopenia $< 1000\text{ cell/mm}^3$
6. Neutrophil/lymphocyte ratio > 6
7. D-dimer concentration $> 1000\text{ ng/mL}$
8. More than 50% increase of D-dimer concentration within 7 days of disease onset
9. CRP concentration $> 50\text{ mg/L}$
10. LDH concentration $> 300\text{ U/L}$
11. ALT or AST concentration $> 50\text{ U/L}$
12. Procalcitonin concentration < 1.2

1 point for each positive item assessed on Days 5-7. Score calculation: Total points / 12 x 100. Possible MAS ≥ 45 and Definite MAS ≥ 60

Conclusion: This study defined a set of preliminary criteria using the most relevant items of MAS according to the dynamic changes in the parameters in a group of COVID-19 patients. A score of 45 would be helpful to define a possible MAS group with reasonable sensitivity and specificity to start necessary treatments as early as possible.

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OP0314

DOCK8 MUTATIONS IN COVID-19 AND MIS-C CYTOKINE STORM SYNDROME

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Background: We recently identified *DOCK8* as a novel gene associated with cytokine storm syndrome (CSS)¹. Heterozygous missense mutations in *DOCK8* diminish NK cell lytic function and contribute to increased pro-inflammatory

cytokine production (CSS). CSS is a potential complication of COVID-19 with severe consequences². Children are at risk of a SARS-CoV-2 post-infectious CSS, multisystem inflammatory syndrome in children (MIS-C)³. Host genetic factors associated with COVID-19 CSS and MIS-C CSS are unknown.

Objectives: The goals are to identify and functionally study rare mutations in *DOCK8* in patients with SARS-CoV-2 COVID-19 and MIS-C.

Methods: To date, 16 adult patients enrolled in a COVID-19 CSS clinical trial at UAB had whole genome sequencing. Four (25%) had rare heterozygous *DOCK8* mutations (3 missense, 1 intronic). A COVID-19 CSS adult patient in Seattle also had a *DOCK8* missense mutation. In addition, *DOCK8* missense mutations were identified in five children (UAB & Northwell) hospitalized with MIS-C. *DOCK8* mutations, or wild-type (WT) sequence controls, were introduced into human NK-92 cells by FOAMY virus transduction. WT and mutant *DOCK8*-expressing NK-92 cells were incubated with K562 target cells and compared for cytotoxicity and degranulation (CD107a).

Results: One COVID-19 patient *DOCK8* mutation (Gly523Arg) reduced NK cell degranulation by 30% and cytotoxicity by 23% (n=3) (Figure 1). Similar studies of 3 MIS-C patients with *DOCK8* missense mutations (Arg899Trp, Ala2Thr, Pro-687Leu) revealed up to 31% reduced NK cell degranulation and 48% reduction in cytotoxicity by 3 distinct mutations (n=3). Two-way ANOVA analysis revealed statistically significant ($p<0.05$) differences in NK cell degranulation and lysis for four unique *DOCK8* mutations.

Conclusion: Heterozygous *DOCK8* missense mutations may contribute to severe COVID-19 and MIS-C CSS by partial dominant-negative effects yielding decreased NK cell cytotoxicity.

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Metabolic pathways during the regulation of inflammation and immunity

OP0315

EFFECTOR CD4 T CELLS REQUIRE SURVIVIN FOR REGULATION OF GLUCOSE METABOLISM AND IFNG PRODUCTION

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Background: Interferon-gamma (IFN γ) producing effector T cells play the leading role in triggering and perpetuation of inflammation in rheumatoid arthritis. Inflammation leads to metabolic reprogramming of T cells and high energy consumption supporting proliferation and IFN γ production. Being a part of chromosomal passenger complex, oncoprotein survivin is essential for cell proliferation. It has also been identified as a marker of severe therapy-resistant rheumatoid

arthritis. Thus, we aimed to explore the association between survivin and IFN γ producing phenotype of CD4 T cells.

Objectives: We study if survivin mediates the glucose dependent mechanism of IFN γ production in CD4 T cells.

Methods: CD4 cells were sorted from the peripheral blood of RA patients and healthy controls, activated with aCD3, cultured in presence of survivin inhibitor YM155 and subjected to RNA sequencing (Illumina, Life Science). IFN γ levels in supernatants were measured by ELISA. To study glucose uptake in presence of YM155, CD4 cells were treated with IFN γ +aCD3 overnight followed by 2NBD-glucose challenge for 30 min. Uptake of fluorescent 2NBD-glucose probe was measured by flow cytometry. Statistical analysis of RNAseq was performed in R-studio using the Bioconductor package DESeq2.

Results: Comparison of the whole-genome transcription profile of CD4 cells different by levels of BIRC5, coding for survivin, demonstrated that the BIRC5hi group expressed significantly higher levels of IFN γ (mRNA, $p=10^{-26}$ and protein, $p=10^{-4}$). Also, BIRC5hi CD4 cells had higher expression of glucose transporter GLUT1 (SLC2A1, $p=0.0064$) and of glycolytic enzymes glucose-6-phosphate dehydrogenase (G6PD, $p=10^{-6}$), pyruvate kinase (PFKP, $p=10^{-6}$), and lactate dehydrogenase (LDHA, $p=10^{-14}$). On the contrary, expression of the key regulator of glycolysis 6-phosphofructo-2-kinase (PFKFB3) was significantly lower in the BIRC5hi group ($p=4.4 \times 10^{-5}$). Notably, expression of glycolytic enzymes G6PD and PFKFB3 correlated strongly to IFN γ ($r=0.880$ and -0.698 , respectively), TBX21 ($r=0.811$ and -0.698) and perforin ($r=0.781$ and -0.698). To demonstrate functional relevance of the connection between BIRC5 and glucose metabolism, survivin was inhibited in CD4 cell cultures. Survivin inhibition resulted in significant increase of PFKFB3 ($p=7 \times 10^{-6}$) and LDHA ($p=0.0089$), leading to inhibition of phosphoglycerate mutase PGAM1 and ATF citrate lyase ACLY ($p=0.021$ and $p=0.0074$, respectively), which dignify the restoration of aerobic glycolysis. Importantly, inhibition of survivin decreased 2NBD-glucose uptake by CD4 cells ($p=0.031$) and reduced expression of GLUT1 ($p=0.034$). These changes in glucose metabolism were followed by decreased IFN γ production in supernatants ($p=0.037$).

Conclusion: The study demonstrates a strong connection between IFN γ production and glucose metabolism in CD4 cells. Survivin emerges as an important regulator of glycolysis acting through expression of glycolytic enzymes and glucose transport.

Disclosure of Interests: None declared.

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Let's work. Together.

OP0316

ASSOCIATION BETWEEN INDIVIDUAL AND COUNTRY-LEVEL SOCIOECONOMIC FACTORS AND WORK PARTICIPATION IN PERIPHERAL AND AXIAL SPONDYLOARTHRITIS: ANALYSIS OF THE ASAS PERSPA STUDY

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Background: Work outcomes in spondyloarthritis (SpA) have mostly been studied in axSpA, less in peripheral SpA (pSpA) or PsA. The ASAS-COMOSPA study showed that lower education, female gender and lower healthcare expenditures (HCE) are associated with lower odds of employment in SpA. However, it is unknown whether country-level factors or SpA phenotype (axSpA/pSpA/PsA) modify the effect of individual-level socioeconomic factors.

Objectives: To examine whether associations between socioeconomic factors and work outcomes differ across SpA phenotype and whether associations for individual-level socioeconomic factors are modified by country-level factors.

Methods: Working age patients (18-65 years) from the ASAS-perSpA (peripheral involvement in SpA) study were included. Associations between individual- (age, gender, education, marital status) and country-level socioeconomic factors (Human Development Index (HDI), HCE) with work outcomes (employment status (binary), absenteeism, presenteeism (tertiles)) were assessed using

mixed-effects logistic and ordinal logistic models. Models were adjusted for confounders. Separate models for ASDAS, BASFI and BASDAI were created in turn due to collinearity. Effect modification by SpA phenotype and country-level factors was tested using interaction terms.

Results: A total of 3835 patients (mean age 42 years, 61% males) from 23 countries worldwide were included (66% axSpA, 10% pSpA, 23% PsA). Being employed was associated with gender (male vs female OR 2.5; 95%CI 1.9-3.2), education (university vs primary OR 3.7; 2.9-4.7) and being married (vs single OR 1.3; 1.04-1.6) (Table 1). University (vs primary) education was associated with lower odds of absenteeism (OR 0.7; 0.5-0.7) and presenteeism (OR 0.5; 0.3-0.7). Associations were not statistically different across SpA phenotypes. HCE was significantly associated with all work outcomes: employment (OR 2.5; 1.5-4.1), absenteeism (OR 0.6; 0.4-0.9) and presenteeism (OR 0.6; 0.3-0.9). HDI results were similar. Gender discrepancy in odds of employment was greater in countries with lower socioeconomic development; eg, males had 3.5 higher odds of employment than females in countries with low HCE, whereas the difference was 1.8 fold in high HCE countries.

Table 1. Effect of individual socio-economic factors on work outcomes.

	Employment status	Absenteeism	Presenteeism
	OR (95% CI)	OR (95% CI)	OR (95% CI)
N	3780	2218	2127
Age	1.43 (1.36,1.51)	1.00 (0.99,1.01)	1.00 (0.99,1.01)
Age ²	0.996 (0.995, 0.996)	NS - uni	NS - uni
Male (vs female)	2.48 (1.92,3.21)	1.22 (0.96,1.56)	0.97 (0.78,1.20)
Education			
Primary	ref	ref	ref
Secondary	1.86 (1.48,2.35)	0.69 (0.49,0.99)	0.69 (0.49,0.99)
University	3.68 (2.87,4.72)	0.67 (0.47,0.96)	0.49 (0.34,0.69)
Marital status			
Single	ref	ref	ref
Married	1.27 (1.04,1.56)	0.95 (0.73,1.22)	0.98 (0.78,1.22)
Divorced or Widowed	1.39 (0.98,1.97)	1.39 (0.88,2.18)	1.16 (0.74,1.82)
ASDAS	0.78 (0.72,0.84)	1.51 (1.33,1.72)	2.31 (2.04,2.61)
Fatigue	NS - multi	1.14 (1.09,1.21)	1.30 (1.24,1.36)
Depression	0.70 (0.59,0.82)	1.45 (1.15,1.82)	1.95 (1.59,2.39)
Fibromyalgia	NS - multi	1.62 (1.11,2.35)	1.58 (1.03,2.41)
BMI	NS - multi	0.99 (0.97,1.02)	NS - multi
Dactylitis	1.41 (1.12,1.76)	NS - uni	NS - uni
Uveitis	NS - multi	0.62 (0.46,0.84)	NS - uni
NSAIDs	NS - multi	1.53 (1.18,1.99)	1.32 (1.07,1.64)
bDMARDs	NS - multi	NS - uni	1.23 (1.01,1.51)

Models used ASDAS rather than BASDAI/BASFI, which are collinear. NS, not significant in the univariable or multivariable model.

Conclusion: Individual- (lower education) and country-level socioeconomic factors (lower healthcare expenditure) were both associated with (lower) work participation, independently of SpA phenotype. The disadvantageous effect of female gender on employment is particularly strong in countries with lower socioeconomic development. This highlights the need for wider societal interventions, such as improving education and healthcare investment, to improve work outcomes.

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OP0317-PARE

THE CONTEMPORARY WORK-RELATED BURDEN OF DISEASE FOR PEOPLE WITH RHEUMATIC DISEASES IN GREECE

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