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Dimensionality reduction for stepwise analysis of immune response dynamics in COVID19

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BACKGROUND

Our understanding behind the heterogeneity of responses to severe SARS-CoV-2 infection is incomplete.

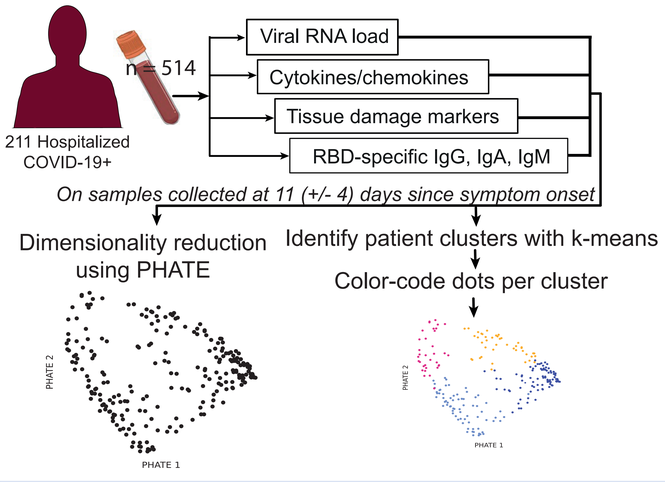
- Combining plasma measurements uncovers greater granularity among patients than clinical severity (Liu et al., Cell 2021)
- In plasma, multiple markers of immune dysregulation are associated with fatal outcome :
  - SARS-CoV-2 vRNA
  - Delayed antibody response and
  - Elevated cytokines and
  - Elevated tissue damage markers

Hypothesis : Integrating fatality-associated markers will uncover a subgroup of high-risk patients, and help better delineate mechanisms associated with fatal outcome to COVID-19.

Aims :

1. Delineate "types" of plasma profiles through unsupervised dimensionality reduction of features associated to fatal outcome
2. Characterize kinetics differences in immunovirological parameters
3. Compare transcriptomic profiles uniquely associated to fatal outcome, within patients with similar immune responses.

METHODS



Cytokines	CCL2	CXCL13	CXCL8	IL1ra	IL23	IL6	TNFa
Tissue damage markers	Angio-2	RAGE	SP-D				
RBD-specific	IgG	IgM	IgA				
SARS-CoV-2	N gene						

Enrichment Depleted

Chi2	Age	Female	Obesity	Chronic_renal_insufficiency	Chronic_Heart_Insufficiency	Chronic_liver_insufficiency	Hypertension	Dyslipidemia	Chronic_Lung_Insufficiency
1	0.52	0.46	0.07	0.00	0.46	1.00	0.21	0.59	0.06
2	0.86	0.74	0.50	0.96	0.33	1.00	0.93	0.11	0.29
3	0.15	0.30	0.06	0.86	0.08	1.00	0.44	0.08	0.54
4	0.32	1.000	0.77	0.02	0.15	1.00	0.85	0.98	0.84

RESULTS

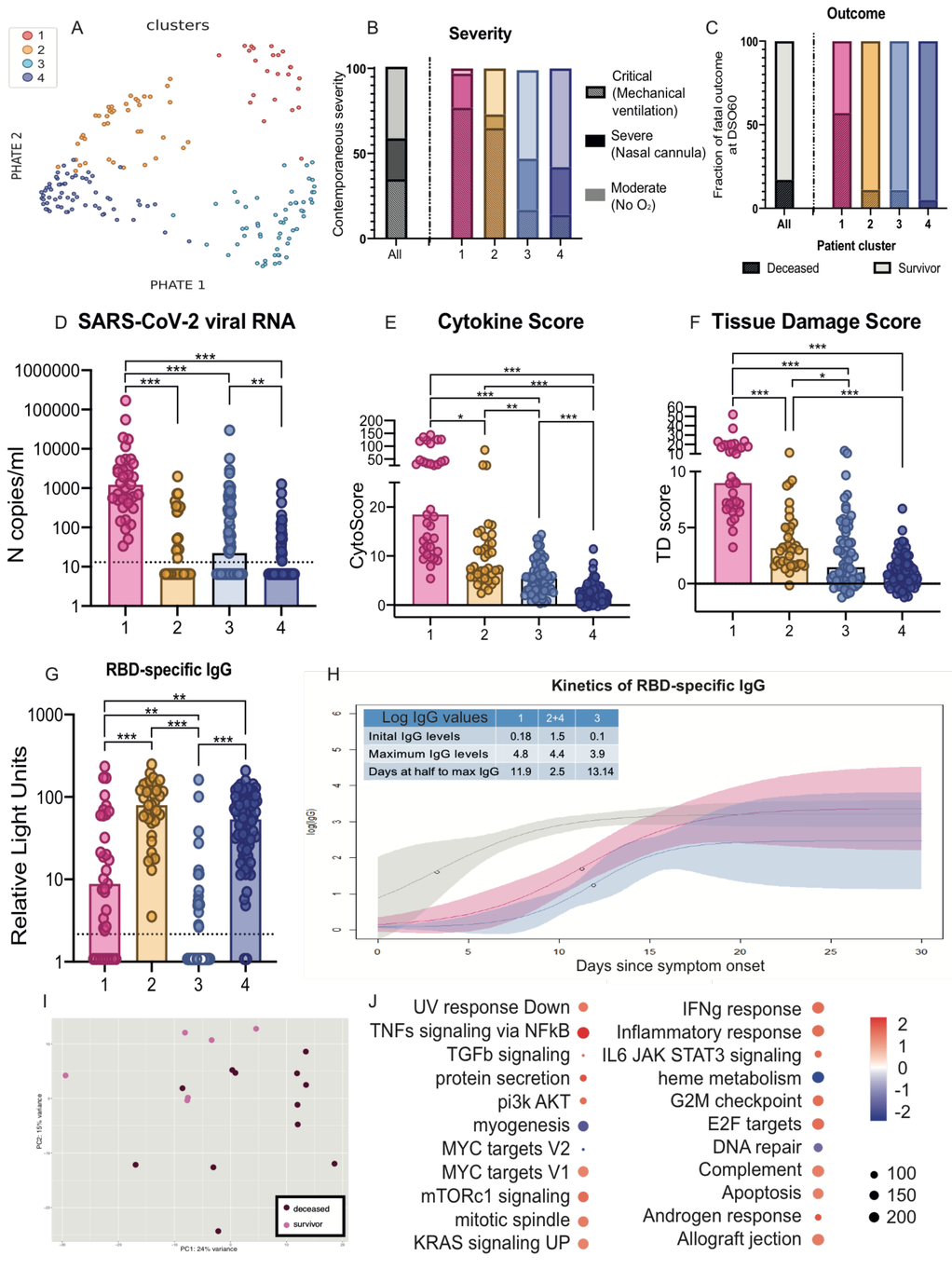


FIGURE. Integrative analysis of fatality-associated plasma markers measured at DSO11 reveal four types of early immune response, with one strongly associated to fatal outcome. A) PHATE embedding with color-coding using k-means clustering using all 14 parameters identifies 4 patient clusters (see methods). **B**) Contemporaneous severity, based on requirement of respiratory support, per patient cluster. **C**) Proportion of patient cluster with fatal outcome within 60 days since symptom onset. Comparison, among all 4 patients clusters at DSO11, of **D**) levels of SARS-CoV-2 viral RNA ; **E)** score based on linear combination of 7 cytokines ; **F**) score based on linear combination of 3 markers of tissue damage ; **G**) levels of RDB-specific IgG. **H**) Logistic curves of RBD-specific IgG response per patient cluster. Curves calculated using 514 samples collected longitudinally on all 211 patients. Table includes variables extracted from models. Within the high-fatality cluster 1, **I**) principal component analysis of survivors and deceased based on whole blood RNA Seq gene expression; **J**) GSEA on Hallmark collection, using genes differentially expressed between survivors and deceased.

DISCUSSION

- Unbiased identification of four "types" of plasma profiles early in infection, which align with severity and outcome.
- Two types of responses characterized by more than 10-day delay in generation of SARS-CoV-2-specific antibody response
- One of these clusters is highly enriched in fatal outcome, and further characterized by strong and sustained levels of viral RNA and cytokine levels.
- Within high-fatality cluster, non-survivors have transcriptomic signatures of inflammation, complement activation and apoptosis.

This unbiased approach gives an integrated view of dysregulated immune response components in fatal COVID-19, which may be explained through differences in molecular pathways. This approach allows to efficiently target detailed investigations on very high-risk patient subgroups who may most likely benefit from new therapeutic interventions.

ADDITIONAL KEY INFORMATION

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