

# The Karolinska KI/K COVID-19 immune atlas: An open resource for immunological research and educational purposes

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## Abstract

The Karolinska KI/K COVID-19 Immune Atlas project was conceptualized in March 2020 as a part of the academic research response to the developing SARS-CoV-2 pandemic. The aim was to rapidly provide a curated dataset covering the acute immune response towards SARS-CoV-2 infection in humans, as it occurred during the first wave. The Immune Atlas was built as an open resource for broad research and educational purposes. It contains a presentation of the response evoked by different immune and inflammatory cells in defined naïve

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patient-groups as they presented with moderate and severe COVID-19 disease. The present Resource Article describes how the Karolinska KI/K COVID-19 Immune Atlas allows scientists, students, and other interested parties to freely explore the nature of the immune response towards human SARS-CoV-2 infection in an online setting.

## 1 | INTRODUCTION

The COVID-19 pandemic struck Stockholm, Sweden, in the beginning of March 2020. In response to the pandemic, a group of physician scientists in intensive care, infectious diseases, clinical microbiology and laboratory scientists with experience in immunology, inflammation, and viral diseases rapidly formed a group referred to as the Karolinska KI/K COVID-19 Resource Group. The group commenced a number of immediate tasks, including the exploration of strategies for: (1) antiviral and (2) anti-inflammatory treatments for patients newly arrived to the Karolinska University Hospital, and (3) strategies for clinical sampling of blood and other body fluids for immediate microbiological and clinical chemistry analyses as well as for establishing clinical sample collections organized in a biobank for immediate, short-term, and long-term research purposes.<sup>1</sup> One task in this process was to undertake immediate immunological research on clinical samples from newly arrived COVID-19 patients. SARS-CoV-2, at the time, was a novel pathogen and, accordingly, COVID-19 was a new disease. The need for insights into immunological and inflammatory responses was immense. The idea was not only to rapidly publish data resulting from the project but also to make curated data publicly available as an open resource for research and educational purposes. In this Resource Article, we recollect the above-mentioned process and present the current content of the Karolinska KI/K COVID-19 Immune Atlas (hereafter referred to as the “Immune Atlas” when not otherwise noted; [www.covid19cellatlas.com](http://www.covid19cellatlas.com)) set up in an immediate response to the developing pandemic in the spring of 2020. We describe how the Immune Atlas can be used to explore the immune response to naïve individuals exposed to the SARS-CoV-2 virus. We also discuss how the Immune Atlas can be further developed.

## 2 | IMMUNE ATLAS OVERVIEW

The Karolinska KI/K COVID-19 Immune Atlas was set up in the spring of 2020 during the very first phase of the COVID-19 pandemic and went public in the summer of 2020. Data was subsequently added to it as they

were rapidly gained and published. The overall structure of the Karolinska KI/K COVID-19 Immune Atlas web interface, patient cohorts, and the flow cytometry panels upon which all cellular analyses were based, are depicted in [Figure 1](#). In this section, we describe the patient cohort on which the Immune Atlas data is based. We then describe the clinical sample collection strategy, analyses performed, publication outcome and the assembly of data for the Immune Atlas. This is followed by a description of cell counting and immunophenotyping data obtained through the project as well as of data on soluble factors. This is followed by a description of specific methodological aspects of the data generation, followed by strategies employed for data presentation. Finally, we briefly described the construction of the Immune Atlas web application.

### 2.1 | Patient cohort

The immunological data presented are derived from two groups of COVID-19 patients (27 patients in total), stratified as moderately and severely sick according to set inclusion and exclusion criteria. All included patients (ages 18-78 years old) were SARS-CoV-2 RNA positive and sampled within 24 days after symptom debut and within 8 days after hospital admission. Moderately sick patients were defined as having an oxygen saturation level of 90%-94% or needing oxygen at 0.5-3.0 L/min at sampling. Severely sick patients were defined by needing treatment in an intensive care or high-dependency unit. Patients with current malignancies or immunomodulatory treatment prior to hospitalization were excluded. Clinical characteristics of the groups presented in the Immune Atlas include information on group size, known risk factors for severe disease, information on pre-existing conditions, comorbidities and organ failure, viremia at sampling time point, symptoms at admission, peak supportive oxygen therapy, treatment prior to sampling, clinical course, and outcome. Clinical laboratory results included clinical chemistry data before study sampling, at study sampling (+/- 24 hours), or in applicable cases at study sampling (+/- 5 days) ([Figure 1](#)). Non-COVID-19 age- and sex-matched controls were also included, all of whom were SARS-CoV-2 IgG seronegative at time of inclusion.

## 2.2 | Clinical sample collection

Peripheral blood samples were collected once a week for three consecutive weeks from the end of April to mid-May 2020, at the Karolinska University Hospital Infectious Diseases and Intensive Care Units. This time period came to represent the first wave of the COVID-19 pandemic, a time point when all patients were naïve towards exposure to the SARS-CoV-2 virus and were unvaccinated (no

SARS-CoV-2 vaccines were available at the time). Clinical samples were transported to the Center for Infectious Medicine, Karolinska Institutet, and directly processed for immediate immunological research. Results from the studies were rapidly put together and presented in a series of publications.<sup>2-9</sup> In parallel with acceptance of published papers, curated data were assembled and presented in an aggregated form in the Immune Atlas database, rapidly made available as an open resource (Figure 1).



**FIGURE 1** Structure of the Immune Atlas web interface, patient cohort, and flow cytometry panels used for immunophenotyping. A, Overview of the head menu of the Immune Atlas. Below the toolbar appears the different immune cell populations studied from peripheral blood of defined groups of COVID-19 patients and healthy controls. B, Under the section “Project”, the item “Cohort” provides clinical information of the patients included in the Immune Atlas project. C, Under the section “Project”, the item “Panels” provides details on the flow cytometry panels used to immunophenotype each of the cellular populations

## 2.3 | Cellular data and soluble factors

Cell data displayed included flow cytometry data from indepth studies of innate lymphocytes including natural killer (NK) cells,<sup>2</sup> innate lymphoid cells,<sup>5</sup> and unconventional T cells including mucosal-associated invariant T (MAIT) cells,  $\gamma\delta$  T cells, and invariant natural killer T (iNKT)<sup>4</sup>; adaptive lymphocytes including conventional T cells<sup>3</sup> and B cells<sup>7</sup>; and myeloid cells including granulocytes<sup>8</sup> as well as monocytes and dendritic cells (DCs).<sup>6</sup> Soluble factors displayed include extensive proteomic data from serum (unpublished data). References cited above refer to original papers in which Immune Atlas-related data were first published. It shall be noted that additional studies of the present patient cohort have been performed, not available in the present version of the Immune Atlas; e.g. an in-depth assessment of >1000 unique metabolites. These results have been integrated with available proteomic and immunology data to capture multiorgan system perturbations.<sup>9</sup>

## 2.4 | Data presentation

Data in the Immune Atlas are presented in an aggregated manner. This allows for comparison of different patient groups and healthy controls in a manner where distinct cellular characteristics of specific immune cell subsets from each specific cell track can be visualized by different means including box plots, volcano plots, radar charts, and with applicable statistical measures (Figures 2 and 3).

## 2.5 | Methodological aspects

Flow cytometry represented the key immunological method employed for cellular data acquisition. Many factors were considered when designing the panels for flow cytometry-based analyses including biomarker selection, instrument configuration, fluorochrome brightness, spectral overlap, antigen density, antigen co-expression, and reagent availability. Up to 29 different parameters were analysed depending on cell types and specific information desired. Complete panels used for the analyses

are shown in the Immune Atlas by cell track and include information of the lasers, filters, specific antigens, and fluorochromes used in the analyses (Figure 1). Staining was performed on freshly isolated peripheral blood mononuclear cells after conventional Ficoll isolation, except granulocyte analysis which was performed on whole blood. Data on soluble factors were generated by analysing patient and healthy control serum using a Proximity Extension Assay (Olink) (Figure 4). The Normalized Protein Expression unit, which is an arbitrary unit on the log<sub>2</sub> scale, is used for all protein-expression values. The volcano plots display absolute differences in the medians of the two groups, plotted against the non-adjusted p-value of a Mann–Whitney U test. A complete list of proteins can be found on the Soluble Factors page. Protein names and gene symbols were retrieved from the UniProt database.

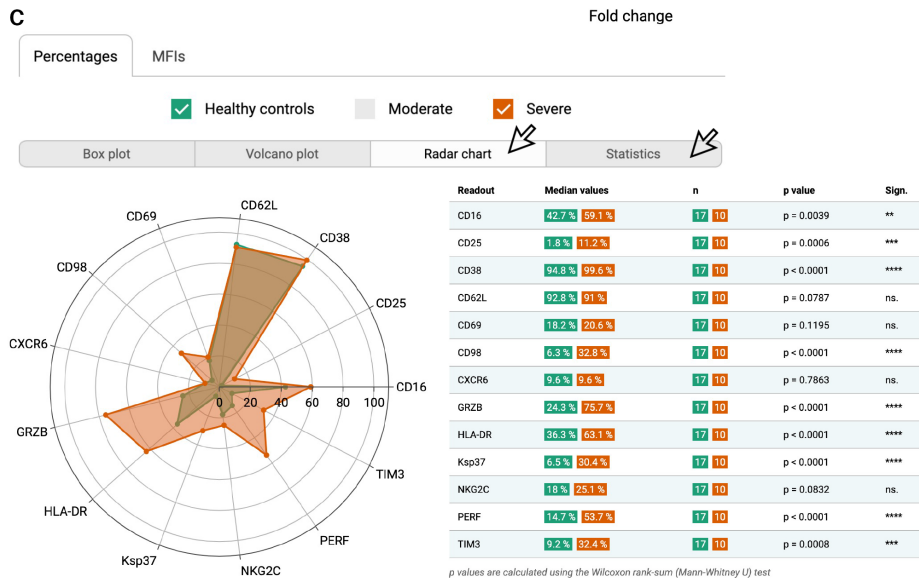
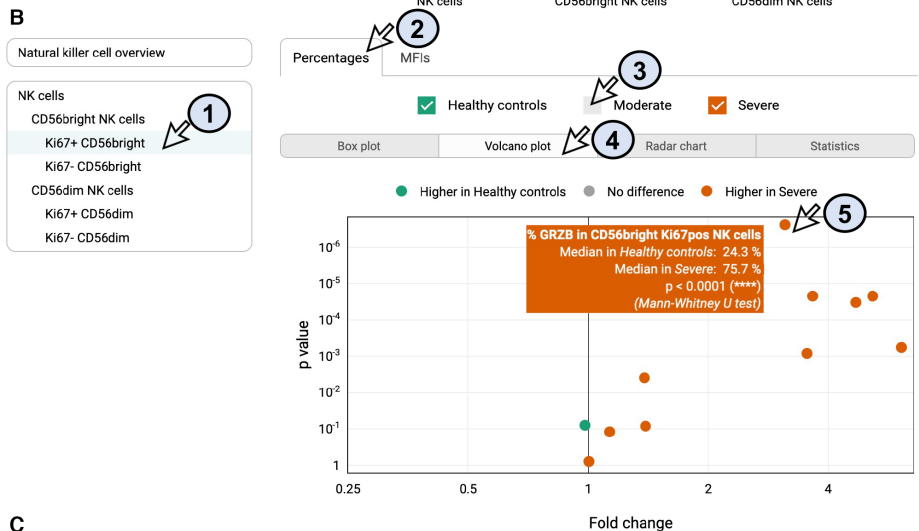
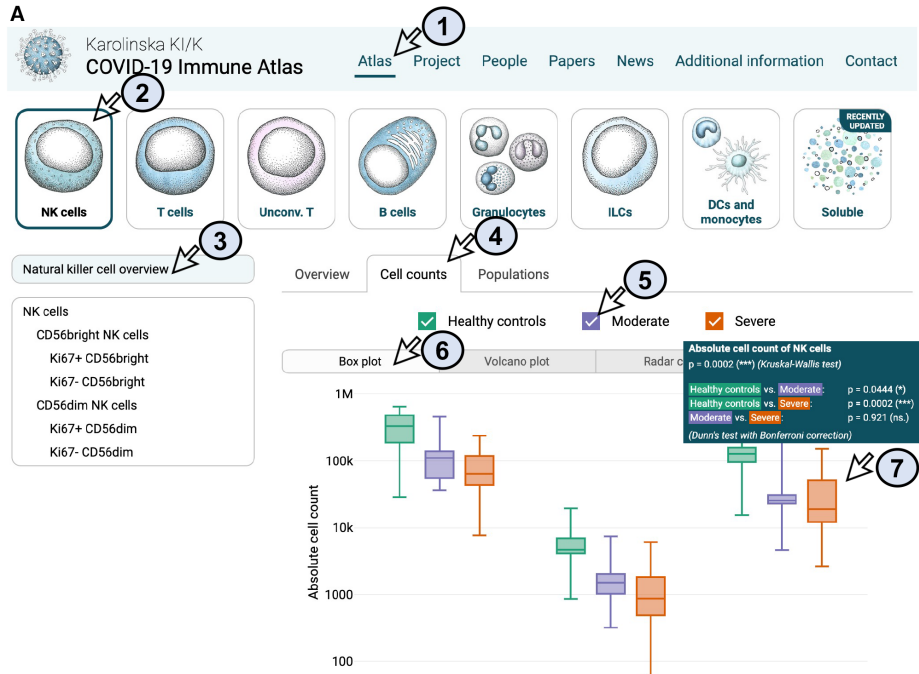
## 2.6 | Construction of web application

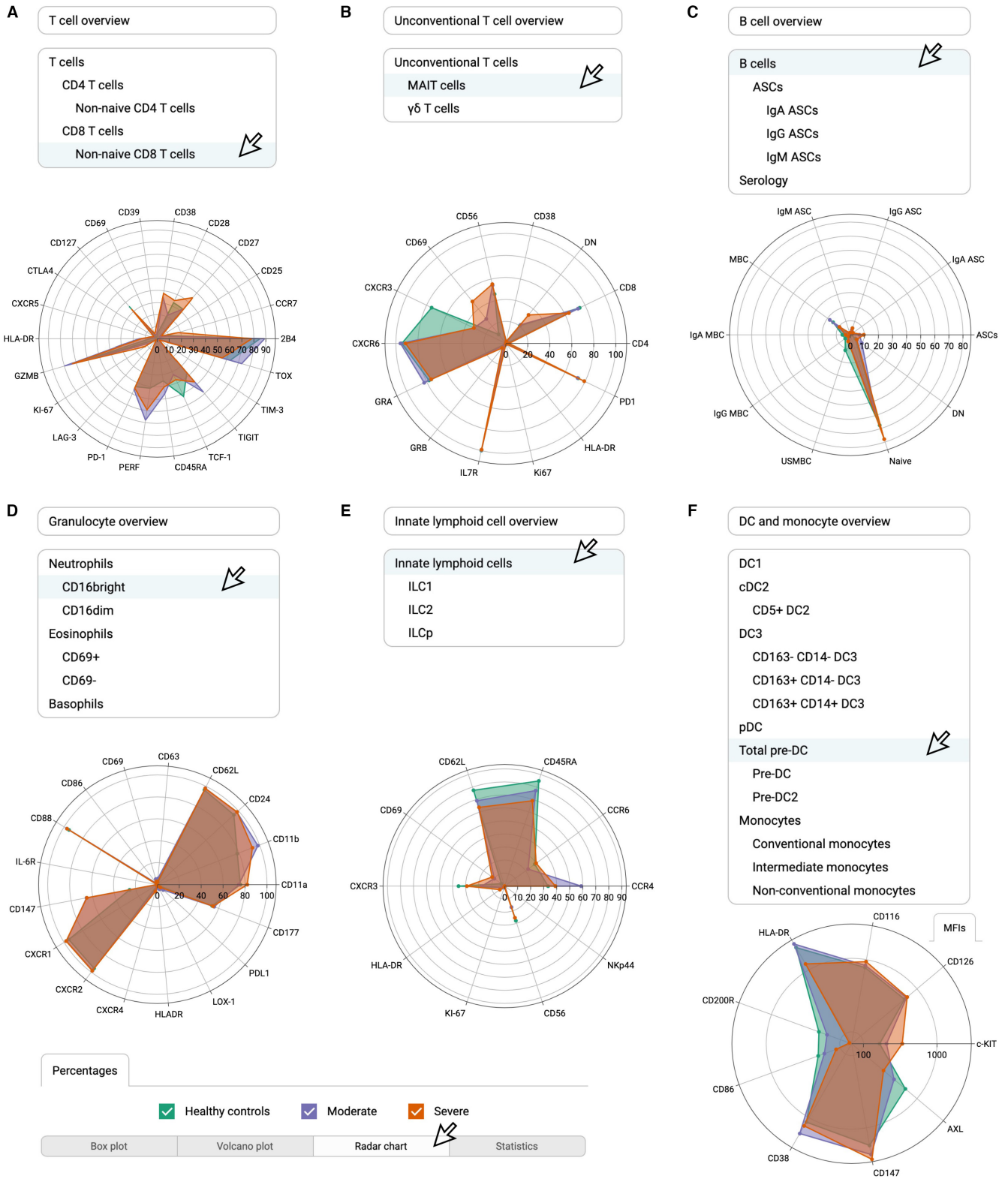
The web application was developed specifically for online presentation of the present Immune Atlas data. To ensure correct and verifiable statistics, all statistical calculations and testing were performed beforehand in R (R Core Team, 2021), using built-in statistical functions with default settings. P-values and other relevant summarized statistics were then exported as a large data file, readable by the application. This strategy also ensured data privacy, as no raw data is exposed to the internet. To simplify maintenance and thereby facilitate the Immune Atlas' long-term availability, the web application was developed as a fully client-side JavaScript-based application. The Plotly JavaScript library (Plotly Technologies Inc. Collaborative data science. Montréal, QC, 2015) is used extensively for data visualization.

## 3 | IMMUNE ATLAS IMMUNOPHENOTYPING

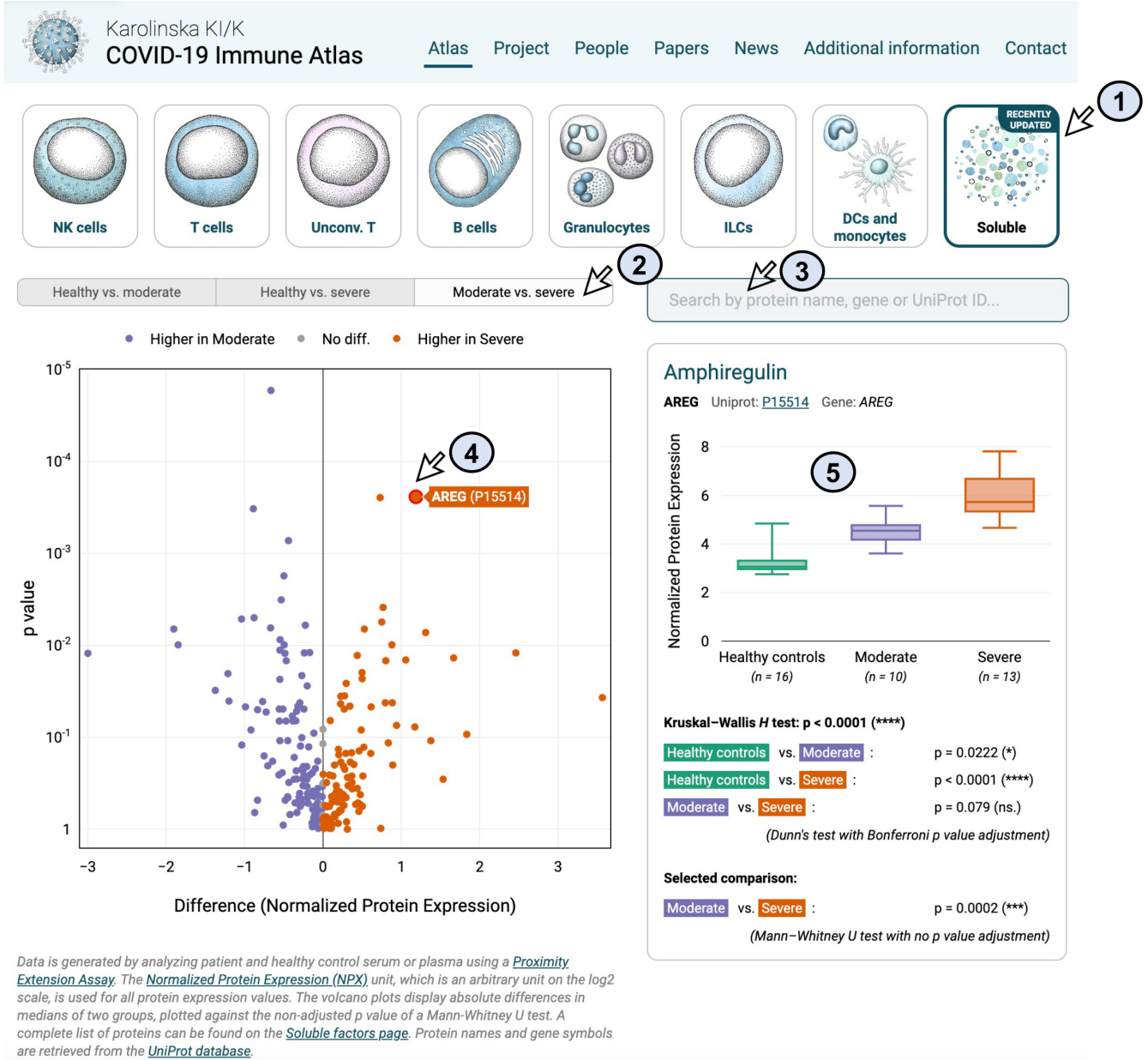
The Immune Atlas primarily allows interactive exploration of immune cell immunophenotyping results from all immune cell subset analysed, as illustrated for one

**FIGURE 2** Interactive exploration of immune cell counting and immunophenotyping results. A, From the head menu “Atlas” (1), by selecting the immune cell population of interest (here “NK cells”) (2), and the corresponding level of detail (here total or specific subsets of NK cells) (3), analytic results (4), and group comparisons (5) are available. Several graphical representations can be chosen (here “Box plot”) (6), where interactive statistics appear when pointing at the comparison of interest (7). B, When selecting a specific cell subset (1), “Percentages” and mean fluorescence intensity (“MFI”) from the flow cytometry analysis are available (2), for the groups of interest (here “Healthy controls” vs “Severe” COVID-19 patients) (3), and can be visualized (here “Volcano plots”) (4), with interactive statistics (5). C, Other graphical representations are available such as “Radar chart” displaying all investigated markers for the selected cell subset (left) as well as related statistics (right)





**FIGURE 3** Overview of the immune cell subsets and corresponding immunophenotyping results. Radar charts display immunophenotyping profiles related to each immune cell subset for the following immune cell populations: (A) T cells, (B) unconventional T cells, (C) B cells, (D) granulocytes, (E) ILCs, (F) DC and monocytes. Here, three patient groups are compared (tool bar at the bottom left; percentages for all cells except for DC and monocytes where MFI are displayed)



**FIGURE 4** Interactive exploration of results from analysis of soluble factors. By selecting “Soluble factor” from the head menu (1), results from proteomic analyses are available for exploration. Comparisons of interest can be selected (2), where results are displayed as volcano plots and the search for a specific protein can be performed (3), or selected directly from the plot (4). In both cases, the corresponding details on results and statistics are interactively displayed in the right panel (5)

particular cell type (NK cells) in [Figure 2](#). It also allows interactive exploration of soluble factors from serum. We summarize here information displayed in the Immune Atlas on the different subgroups of innate lymphoid (NK cells, ILCs, unconventional T cells), adaptive lymphoid (T cells, B cells), and myeloid (granulocytes, monocytes, DCs) cells being accessible for assessment and analyses in the Immune Atlas. Key aspects of results are also briefly mentioned. An example overview of immunophenotyping results from immune cell subsets analysed is shown in [Figure 3](#).

### 3.1 | Natural killer cells

Data are presented on the major CD56<sup>dim</sup> and CD56<sup>bright</sup> NK cell subsets.<sup>10</sup> Within these subsets, expression of differentiation markers such as NKG2A, CD62L, KIRs, NKG2C, and CD57 as well as cytotoxic effector molecules were evaluated.<sup>11–13</sup> NK cell activation in COVID-19 was studied by measuring upregulation of CD25, CD38, CXCR6, HLA-DR, and CD69. Further subset analysis was performed by subdividing CD56<sup>dim</sup> and CD56<sup>bright</sup> NK cells into proliferating (Ki-67<sup>+</sup>) and non-proliferating

(Ki-67<sup>-</sup>) cells and staining for the above markers within those subsets. A specific analysis was performed on the response of educated and non-educated NK cells as defined by self- versus non-self KIR and/or NKG2A expression. Main findings of this analysis include a general activation of both CD56<sup>dim</sup> and CD56<sup>bright</sup> NK cells in COVID-19 regardless of disease severity, but a specific appearance of NKG2C<sup>+</sup>CD57<sup>+</sup>KIR<sup>+</sup> adaptive NK cells in patients with severe manifestation of disease.<sup>10,14,15</sup>

### 3.2 | Innate lymphoid cells

Data are presented on the non-NK ILCs (Lineage<sup>-</sup>CD127<sup>+</sup>), dividing the analysis further within the ILC1 (CD117<sup>-</sup>CRTH2<sup>-</sup>CXCR3<sup>+</sup>), ILC2 (CD117<sup>+/-</sup>CRTH2<sup>+</sup>), and ILC precursor (ILCp; CRTH2<sup>-</sup>CD117<sup>+</sup>) subsets. Within each subset, activation markers (CD69, HLA-DR, Ki-67), differentiation and activation markers (CD45RA, CD62L), and chemokine receptors (CCR4, CCR6, CXCR3) were assessed. As compared to healthy controls, ILCs were depleted from the circulation of COVID-19 patients regardless of disease severity,<sup>5</sup> which was also reported by others.<sup>16</sup> An in-depth analysis of the ILC compartment revealed further disturbances particularly confined to the ILC2 subset which showed increased expression of tissue residency/activation marker CD69 and reduced expression of the chemokine receptors CCR6 and CXCR3 in COVID-19 patients. Severely ill COVID-19 patients had lower ILC2 numbers than moderately ill patients, and ILC2 frequencies were inversely correlated to markers of disease severity including those related to coagulation (D-dimer) and organ/muscle damage (myoglobin, troponin, and lactate dehydrogenase) in COVID-19.<sup>5</sup>

### 3.3 | Unconventional T cells

Data are presented on three unconventional T cell populations including MAIT cells,  $\gamma\delta$  T cells, and iNKT cells. Subsequent analyses were focused on MAIT cells and  $\gamma\delta$  T cells, where activation markers like CD69, CD38, Ki-67, and HLA-DR were assessed. Furthermore, expression of inhibitory check-point receptor PD-1, effector molecules granzyme A and B, and chemokine receptors CXCR3 and CXCR6 were studied. The first major finding was a severe depletion of MAIT cells from the circulation of COVID-19 patients, which was more pronounced than the decline in circulating conventional T cells or  $\gamma\delta$  T cells.<sup>4</sup> The second major finding was the association between high activation of residual MAIT cells (CD69 expression) and severe outcomes.<sup>4</sup> These findings were subsequently confirmed and extended by others,<sup>17</sup> and high MAIT cell activation

was shown to be an independent predictor of death in COVID-19 patients.<sup>14,18</sup>

### 3.4 | T cells

Data are presented on memory (non-CD45RA<sup>hi</sup>CCR7<sup>hi</sup>) CD4<sup>+</sup> and CD8<sup>+</sup> T cells. Subsequent analysis defined the expression levels of activation markers (CD25, CD38, CD69, HLA-DR, Ki-67), differentiation and effector molecules (CCR7, CD127, CD27, CD28, CD45RA, granzyme B, perforin), inhibitory checkpoint molecules (2B4, CD349, CTLA-4, Lag-3, PD-1, Tim-3), and transcription factors (Tox, Tcf-1). Similar to other studies,<sup>19</sup> our findings showed a reduction of the absolute numbers and relative frequencies of CD4<sup>+</sup> and CD8<sup>+</sup> T cells in the circulation of moderate and, in particular, severe COVID-19 patients.<sup>3</sup> Of all assessed markers, the activation profile (CD38, HLA-DR, PD-1, Ki-67) of memory CD4<sup>+</sup> and CD8<sup>+</sup> T cells was higher in both moderate and severe COVID-19 patients compared to healthy controls.

### 3.5 | B cells

Data are presented on several B cell subsets with the primary focus on antibody-secreting cells (ASCs). ASCs were identified as CD19<sup>+</sup>CD20<sup>-</sup>IgD<sup>-</sup> cells expressing high levels of surface CD38 and CD27. Immunoglobulin expression (IgA, IgG, and IgM) and the proliferation status (Ki67 expression) were also assessed. Non-ASC B cell subsets (memory, unswitched memory, naïve, and double-negative B cells) were analysed by surface expression of CD27 and IgD. In addition to flow cytometry, SARS-CoV-2 S1 and N specific IgG antibody levels (OD ratios) and neutralizing antibody titers were measured. A significant expansion of ASCs was observed in COVID-19 patients, marked by higher Ki-67 expression than in healthy controls, and dominated by the IgG-expressing ASC subset.<sup>7</sup> ASC expansion during acute COVID-19 was confirmed by other independent studies.<sup>20,21</sup> Seroconversion was detected in most COVID-19 patients. However, higher SARS-CoV-2-specific antibody levels were observed in severely ill patients compared to moderately ill patients. The data indicate a robust B cell response to SARS-CoV-2 in hospitalized COVID-19 patients.

### 3.6 | Granulocytes

Data are presented on neutrophils, eosinophils, and basophils that were identified after the exclusion of potential contamination by non-granulocytes using lineage



exclusion markers (CD3, CD14, CD19, CD56, CD304). Subsequent analysis focused on the quantification of absolute counts, frequencies, and expression levels of key surface receptors on the major neutrophil subsets CD16<sup>bright</sup> and CD16<sup>dim</sup>, on CD69<sup>+</sup> and CD69<sup>-</sup> eosinophils, and on basophils. The frequencies of CD16<sup>dim</sup> neutrophil and CD69<sup>+</sup> eosinophil populations were significantly increased in COVID-19 patients.<sup>8</sup> Moreover, there were differences in several surface receptors in both CD56<sup>bright</sup> and CD16<sup>dim</sup> neutrophils between moderately/severely ill COVID-19 patients and healthy controls. These included, for example, CD11b, CD63, CD147 and CXCR4. The expression of CD15, CD62L and CD147 was significantly different in CD69<sup>+</sup> eosinophils from the moderately/severely ill COVID-19 patients compared to controls. The expression of CD11a and CD66b was different between CD69<sup>+</sup> eosinophils in moderately and severely ill COVID-19 patients. CD11b, CD63, PD-L1 (CD274), and CXCR4 expression on basophils could differentiate an uninfected individual from both moderately and severely ill COVID-19 patients. Basophils from moderately ill COVID-19 patients showed higher expression of CD62L and CD177 than the basophils from severely ill COVID-19 patients.

### 3.7 | DCs and monocytes

Data are presented on major subsets of circulating mononuclear phagocytes including late DC progenitors. Dendritic cells, namely pDC, DC1, CD5<sup>+</sup> DC2, and subsets of the newly discovered DC3, circulating DC progenitors (pre-DC and pre-DC2), and monocyte subsets (classical CD14<sup>+</sup>CD16<sup>-</sup>, intermediate CD14<sup>+</sup>CD16<sup>+</sup>, and nonclassical CD14<sup>low</sup>CD16<sup>++</sup>) were assessed with respect to frequencies, absolute numbers, and surface receptor expression.<sup>6</sup> A general decrease in circulating DCs was observed in response to SARS-CoV-2. DC1s were associated with an interferon imprint and a decreased expression of IL-6R. The co-inhibitory molecule CD200R was detected in lower levels in pre-DCs, DC2s, and DC3 subsets of severely sick patients. Moreover, maturation and developmental phenotype was affected across several DC lineages with lower levels of HLA-DR and CD86, and higher frequencies of pre-DC2 among total pre-DCs in severe COVID-19. While all monocyte subsets had increased CD38 levels unrelated to disease severity, intermediate monocytes showed higher levels of CCR2 in severe manifestations of the disease. In addition, an immature phenotype together with increased expression of CD163 was found in all monocyte subsets in severe COVID-19, in line with other reports. Through unsupervised clustering analyses, it was revealed that mononuclear phagocytes, alone, could identify a cluster with non-survivors.

## 4 | ADDITIONAL INFORMATION IN THE IMMUNE ATLAS

All personnel involved in the Immune Atlas project, including scientists, physicians, physician scientists, and support personnel are listed on the home page ([www.covid19cellatlas.com](http://www.covid19cellatlas.com)). Likewise listed, are papers published containing original data, on which the Immune Atlas was built. Additional data may be continuously added to the Immune Atlas. The Karolinska KI/K COVID-19 Immune Atlas is licensed under the [Creative Commons Attribution-ShareAlike 3.0 International License](https://creativecommons.org/licenses/by-sa/4.0/) for all copyrightable parts of the database (see Home page for details). Use of Immune Atlas data for research and educational purposes is encouraged. The Immune Atlas web page contains information on how to properly cite the Atlas' content if data or other relevant information is to be used in scientific and/or other related contexts. As noted in the Atlas, other parts of this website, including photographs, drawings, design, and code, are copyrighted, and cannot be distributed or reused without permission.

## 5 | FURTHER DEVELOPMENT OF THE IMMUNE ATLAS

There are several possibilities of further developing the Immune Atlas. Development could follow several lines, including the addition of deeper datasets concerning the patients included in the study, with additional longitudinal immunological and related analyses. Inclusion of additional larger patient cohorts is another option. The latter could also include different but related patient cohorts, such as those infected with more recent SARS-CoV-2 variants-of-concern, being re-infected, being anti-SARS-CoV-2 vaccinated, or being infected following vaccination. Furthermore, possibilities exist with respect to the creation of interactive tools allowing comparative analysis within different datasets in the Immune Atlas.

## 6 | CONCLUSION

The Karolinska KI/K COVID-19 Immune Atlas project was conceptualized with the aim of rapidly providing a simple curated dataset encompassing the immune response towards SARS-CoV-2 infection in human beings. It was built as an open resource for broad research and educational purposes to be used by scientists, students, and other interested parties at a timepoint when only limited data existed to freely explore the nature of the immune response towards human SARS-CoV-2 infection in an on-line setting. The data are still unique with the sense

of displaying immunological reactions in a representative previously non-SARS-CoV-2 virus (or corresponding vaccine) exposed population. It is noteworthy that the COVID-19 pandemic has stimulated many different types of related open resources, all aiming at organizing, grouping, and/or presenting various forms of available data and resources in relation to COVID-19. These initiatives are very much welcomed by the scientific and educational community. One local example is the Swedish COVID-19 Data Portal that provides information, guidelines, tools, and services to support researchers in utilizing Swedish and European infrastructures for data sharing; in particular, the [European COVID-19 Data Portal](#). Several other examples exist. In this respect, the recent initiative by several scientific journals, including the *Scandinavian Journal of Immunology*, to publish Resource Articles will promote the use of newly developed open online resources for research and educational purposes.

### AUTHOR CONTRIBUTIONS

H.G.L., M.C., E.H.A., K.J.M., K.S., and N.B. conceptualized the Immune Atlas project and its corresponding web page. The project was endorsed by the Karolinska KI/K COVID-19 Resource Group. O.R., L.I.E., S.A., and K.S. coordinated clinical sample collection. P.C., J.R.M., M.C., and M.A. coordinated clinical sample processing. H.G.L., M.C., B.S., P.C., J.R.M., M.A., M.B., B.J.C., A.C., M.D., I.F., M.F.T., M.G., J.B.G., S.G.R., L.H., J.K., E.K., E.G., K., M.L., J.M., C.M., A.N.T., L.M.P.M., T.P., A.P.P., A.P., E.R., O.R.B., J.K.S., J.T.S., T.S., M.S., R.V., D.W., and N.B. coordinated specific immunological analyses and related processes. E.H.A. and K.J.M. constructed the Karolinska KI/K COVID-19 Immune Atlas web page. H.G.L., N.K.B. wrote the manuscript with input from M.C., E.H.A., K.J.M., and K.S. All authors read and approved the manuscript. Karolinska KI/K COVID-19 Immune Atlas contact persons are N.K.B. (science/research), H.G.L. (science/research), K.S. (science/clinic), and E.H.A. (science/web).

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### DATA AVAILABILITY STATEMENT

The data that support the findings described in the present Resource Article are openly available in the Immune Atlas at ([www.covid19cellatlas.com](http://www.covid19cellatlas.com)), reference number.<sup>22</sup>

### ETHICAL APPROVAL

The present project was approved by the Swedish Ethical Review Authority in 2020 (2020-01558). All COVID-19 patients and healthy controls provided informed consent to the study. All data are presented at group aggregate levels.

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