**Patients and Methods.**

Fourteen subjects with radiologically confirmed interstitial pneumonia and a SARS-CoV-2 RNA positive swab constituted the group of patients with COVID-19 (CoV+, Suppl. Table 1). Four additional patients presenting with similar chest X-ray findings and a negative SARS-CoV-2 RNA swab but requiring hospitalization because of hypoxia were also examined as disease controls (CoV-, Suppl. Table 1). Nine clinically healthy subjects served as controls (HD, Suppl. Table 1). Six CoV+ patients subsequently succumbed after developing acute respiratory distress syndrome (ARDS), and 8 survived. Their laboratory findings are reported in Suppl. Table 2.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board and Ethical Committee of Fondazione IRCCS Policlinico San Matteo.

**Peripheral blood mononuclear cells (PBMC) isolation and Phenotype**

Peripheral blood mononuclear cells (PBMC) were isolated by standard techniques and stored in liquid nitrogen. Cryopreserved PBMC from CoV+, CoV- patients and controls were thawed, washed and rested for 30 min in complete medium RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS; HyClone, GE Healthcare, South Logan, Utah, USA), 2 mM L-glutamine and antibiotic antimycotic solution (100 U/ml penicillin, 0.1 μg/ml streptomycin, 0.25 μg/ml amphotericin B (Sigma-Aldrich, St. Louis, MO, USA). Subsequently, PBMC were washed and stained for phenotypic analysis using the fluorochrome conjugated antibodies detailed in Suppl. Table 3. For the analysis of FcεRIγ expression cells were treated with Foxp3/Transcription Factor Staining Buffer Set (eBioscience, ThermoFisher Scientific, MA, USA) and successively stained with anti- FcεRIγ FITC antibody (Merck Millipore, Burlington, MA, USA) in permeabilization buffer. Data acquisition was performed with FACS Celesta (BD Biosciences). Gating strategy for NK cell analysis is shown in Suppl. Fig.3

**NK functional assay**

Cell function was evaluated after stimulation for 18 hours with 100 U/ml IL2 (Miltenyi Biotec, Bergisch Gladbach, DE) and 10 ng/ml IL12 (PeproTech, London, UK). PBMC were then incubated in the presence of MHC class I-non expressing K562 cells (E:T ratio of 5:1), brefeldin A (GolgiPlug) and CD107a (BD Biosciences) for 5 hours. The cells were then membrane stained with following antibodies: anti-CD3, -CD56 (details were listed in Suppl.Table 3). After fixation and permeabilization (Fixation/Permeabilization Solution Kit, BD Biosciences), cells were stained with anti-IFN-γ, details were listed in Suppl.Table 3). Analysis was performed with FACS Celesta (BD Biosciences).

**ADCC assay**

Antibody-dependent cell-mediated cytotoxicity was performed using SW480 colon cancers cells as target in the presence or absence of Cetuximab (10 μg/ml). Unstimulated PBMCs rested overnight in complete medium were incubated for 5 hours with SW480 colon cancer cells at E:T ratio of 5:1 in the presence of brefeldin A (GolgiPlug) and CD107a (BD Biosciences). IFNγ secretion from NK cells was detected by intracellular staining and analysed with FACS Celesta (BD Biosciences).

**Statistical Analysis**

Statistical analysis and graphical presentations were performed using GraphPad Software 8.01 (GraphPad Software Inc, La Jolla, CA). For three groups analysis ANOVA followed by Tukey's multiple comparison test or Kruskal Wallis followed by Dunn's multiple comparison test were used as appropriate depending on data distribution. The Mann-Whitney U test was used for two groups comparison.

**Supplementary Table 1.Laboratory findings in healthy donors (HD) and patients with Covid-19+ (Cov+) and – (CoV-)pneumonia.**

[§]*p*-value were calculated by Kruskal-Wallis test followed by Dunn's multiple comparisons test.

| | **HD** | **CoV+** | **CoV-** | | |
|---|---|---|---|---|---|
| | n=9 | n=14 | n=4 | **P-value** | **P-value** |
| | Mean±SD | Mean±SD | Mean±SD | HD-CoV+ | HD-CoV- |
| **Males** (n) | 6 | 11 | 3 | | |
| **Females** (n) | 3 | 3 | 1 | | |
| **Age** | 49.7±9.9 | 67.8±18.7 | 52.2±23.5 | ns | ns |
| **ALT** U/ml* | 32.4±7.4 | 37.8±27.7 | 52±58.8 | ns | ns |
| **AST** U/ml* | 29.7±8.1 | 46.2±20.0 | 38.7±26.0 | ns | ns |
| **PLT** x$10^3$/µl | 223±47.29 | 231.2±127.7 | 325.5± 110.4 | ns | ns |
| **CD3+ T cells** c/µl° | 1978±611.9 | 891.1±295.8 | 649.3±103.5 | *p=0.0007*[§] | *p=0.001*[§] |
| **CD4+ T cells** c/µl° | 797.3±280.9 | 350.3±156.6 | 279±206.7 | *p=0.001*[§] | *p=0.01*[§] |
| **CD8+ T cells** c/µl° | 500±122.5 | 226.6±133.4 | 101.7±33.8 | *p=0.02*[§] | *p=0.004*[§] |
| **B cells**c/µl° | na | 50.91±25.15 | 73.5±26.2 | - | - |
| **NK cells**c/µl° | na | 161.1±145.8 | 117±24.0 | - | - |
| **Monocyte cells** c/µl° | 487.5±124.6 | 648.9±457.5 | 640±280 | ns | ns |
| **LDH** mU/ml | na | 362.5±163 | 277.5± 63.3 | - | - |
| **CRP** mg/dl | na | 9.1±9.5 | 9.7± 8.9 | - | - |
| **I.N.R.** (%) | 0.9±0.14 | 1.5±0.9 | 1.0± 0.03 | ns | ns |
| **Creatinine** mg/dl | na | 1.38±1.23 | 0.74±0.15 | - | - |

*Normal values ≤ 40 U/ml;°c/µl=cells/µl; na: not available; NK: Natural Killer; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; PLT: Platelet; LDH: Lactate Dehydrogenase; CRP: C-reactive Protein.

**Supplementary Table 2. Laboratory findings of patients infected with SARS-CoV-2stratified according to outcome.**

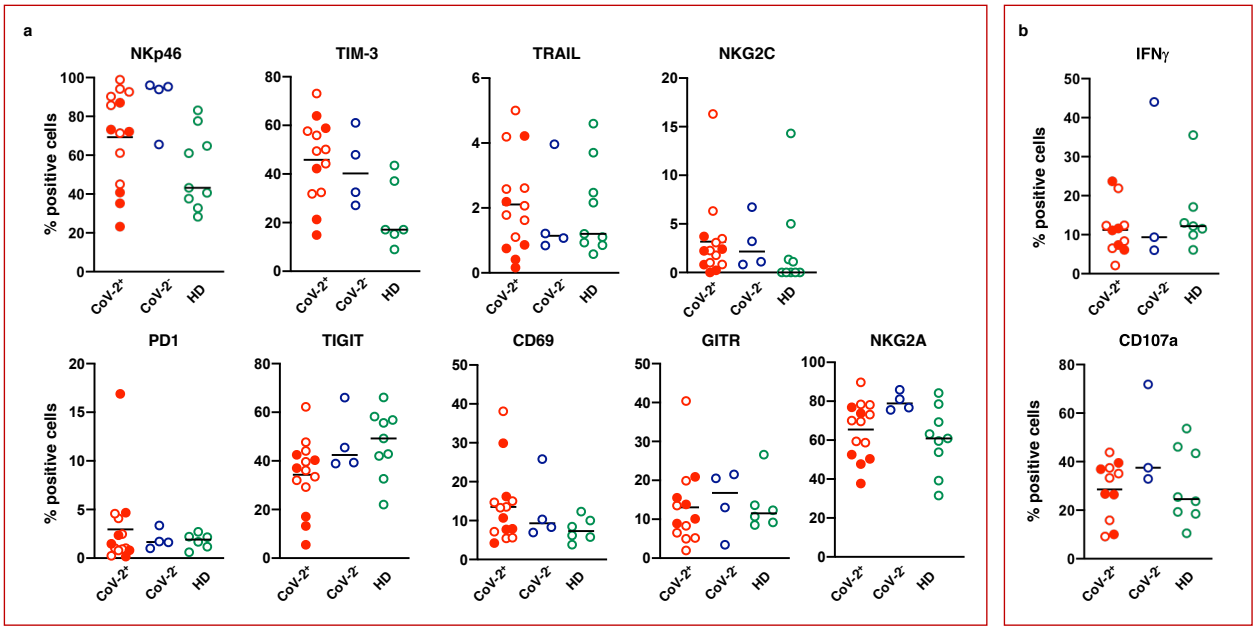
| | **Survived** | **Dead** | |
|---|---|---|---|
| | n=8<br>Mean±SD | n=6<br>Mean±SD | **p-Value** |
| **Males** (n) | 6 | 5 | |
| **Females**(n) | 2 | 1 | |
| **Age** | 58.75±17.88 | 81. 7±7.5 | ns |
| **ALT** U/ml* | 44.43±30.22 | 20.7±12.2 | ns |
| **AST** U/ml* | 40.86±15.89 | 53.7±23.9 | ns |
| **PLT** x$10^3$/µl | 259.4±141.4 | 164.2±92.3 | ns |
| **CD3+ T cells** c/µl° | 859.6±345.8 | 933±237.4 | ns |
| **CD4+ T cells** c/µl° | 324.6±111.7 | 405.2±99.5 | ns |
| **CD8+ T cells** c/µl° | 236±148.6 | 197±112.6 | ns |
| **B cells**c/µl° | 56.14±24.82 | 58.2±43.34 | ns |
| **NK cells**c/µl° | 153±115.7 | 167.2±181.9 | ns |
| **Monocyte** c/µl° | 705.5±348.1 | 573.3±602.2 | ns |
| **LDH** mU/ml | 320.3±73.98 | 475±238.9 | P=0.051 |
| **C-RP** mg/dl | 4.9±5.5 | 17.1±10.9 | *p=0.02*[§] |
| **I.N.R.** (%) | 1.4±0.9 | 1.5±0.9 | ns |
| **Creatinine** mg/dl | 1.95±1.32 | 1.55±1.06 | ns |

[§]p-Value were calculated by Mann-Whitney Test.

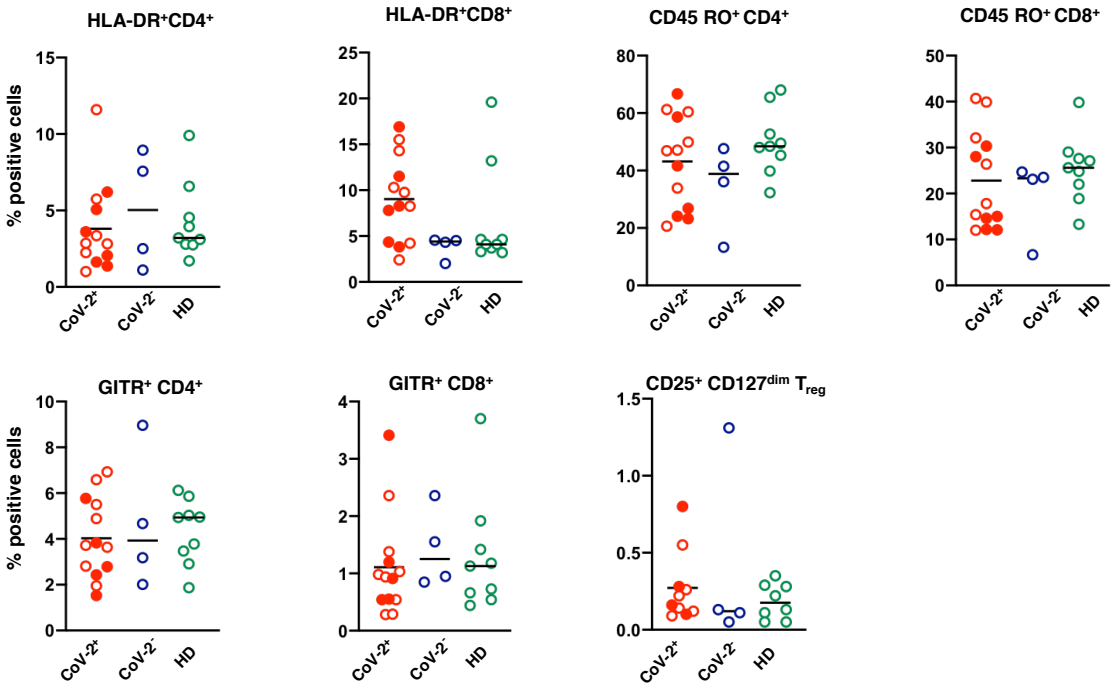
* Normal values ≤ 40 U/ml;°c/µl=cells/µl; ALT: Alanin Aminotransferase; AST: Aspartate Aminotransferase; PLT: Platelet; LDH: lactate Dehydrogenase; C-RP: C-reactive Protein.

**Supplementary Table 3**. List of Antibodies used for flow cytometry analysis.

| Name | Supplier | Cat no. |
|---|---|---|
| Anti-human CD3 APC-Cy7 | BD Biosciences San Diego, CA, USA | 557832 |
| Anti-human CD3 BV421 | BD Biosciences San Diego, CA, USA | 562426 |
| Anti-human CD3-BV510 | BD Biosciences San Diego, CA, USA | 563109 |
| Anti-human CD4 BB700 | BD Biosciences San Diego, CA, USA | 745981 |
| Anti-human CD8 BV510 | BD Biosciences San Diego, CA, USA | 563919 |
| Anti-human CD14BV605 | BD Biosciences San Diego, CA, USA | 564054 |
| Anti-human CD16 BV786 | BD Biosciences San Diego, CA, USA | 563690 |
| Anti-human CD25 PE | BD Biosciences San Diego, CA, USA | 555432 |
| Anti-human CD45RO BB515 | BD Biosciences San Diego, CA, USA | 564529 |
| Anti-human CD56BB700 | BD Biosciences San Diego, CA, USA | 566573 |
| Anti-human CD57 BV421 | BD Biosciences San Diego, CA, USA | 563896 |
| Anti-human CD69 APC | BD Biosciences San Diego, CA, USA | 560712 |
| Anti-human CD107a BV786 | BD Biosciences San Diego, CA, USA | 563869 |
| Anti-human CD127 BV650 | BD Biosciences San Diego, CA, USA | 563225 |
| Anti-human CD226 BB515 | BD Biosciences San Diego, CA, USA | 565152 |
| Anti-human CD253PE | BioLegend San Diego, CA, USA | 308206 |
| Anti-human CD328APC | BioLegend San Diego, CA, USA | 339206 |
| Anti-human CXCR6 BV421 | BD Biosciences San Diego, CA, USA | 566008 |
| Anti-human GITR BV421 | BD Biosciences San Diego, CA, USA | 566423 |
| Anti-human HLA-DR BV605 | BD Biosciences San Diego, CA, USA | 562844 |
| Anti-human IFN-γAPC | BD Biosciences San Diego, CA, USA | 554702 |
| Anti-human IFN-γPE | BD Biosciences San Diego, CA, USA | 554701 |
| Anti-human NKp30 BV786 | BD Biosciences San Diego, CA, USA | 743172 |
| Anti-human NKp46 BV421 | BD Biosciences San Diego, CA, USA | 564065 |
| Anti-human NKG2A APC | BeckmanCoulter, Fullerton, CA | A60797 |
| Anti-human NKG2C PE | R&D System, Minneapolis, MIN, USA | FAB138P |
| Anti-human NKG2D PE-CF594 | BD Biosciences San Diego, CA, USA | 562498 |
| Anti-human PD1 BV605 | BD Biosciences San Diego, CA, USA | 563245 |
| Anti-human TCRγδ PE | BD Biosciences San Diego, CA, USA | 561994 |
| Anti-human TIGIT BV50 | BD Biosciences San Diego, CA, USA | 747840 |
| Anti-human TIM3 BB515 | BD Biosciences San Diego, CA, USA | 565568 |
| Anti-human FcεRIγ FITC | Merck Millipore, Burlington, MA, USA | FCABS400F |




**Supplementary figure 1. Phenotype and function of peripheral NK cells in COVID-19 patients. a)** Frequencies of circulating NKp46, TIM-3, TRAIL, NKG2C (upper panel), PD1, TIGIT, CD69, GITR, and NKG2A (lower panel) expressing NK cells in COVID-19 positive and negative patients with pneumonia and HD. **b)** IFN-γ production (upper panel) and degranulation (lower panel) of IL-2 + IL-12 stimulated NK cells of patients and HD. Middle bars represent median values. The One Way Anova test was used to compare data.




**Supplementary figure 2. T cell chracterization in COVID-19 patients.** Expression of HLA-DR, CD45RO and GITR in CD4+ and CD8+ T cell subsets and frequency of $T_{reg}$ cells in COVID-19 positive and negative patients or healthy donors. Full red symbols indicate patients who subsequently died. Middle bars represent median values. The One Way Anova test was used to compare data.