Supplementary material:

Hospitalized patients with breakthrough COVID-19 six month following Comirnaty vaccination compared to unvaccinated inpatients and to inpatients with breakthrough infection six weeks following vaccination - a multicenter comparative cohort study

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51: Specifications of laboratory methods used in study hospitals

PCR tests for SARS-CoV-2 RNA, that were used in various participating hospitals:

1. Xpert® Xpress SARS-CoV-2, Cepheid (Sunnyvale, CA, USA).
2. Simplexa™ COVID-19 direct kit, DiaSorin Molecular (Cyprus, CA, USA).
3. Allplex™ 2019-nCoV assay, Seegene (Seoul, South Korea).
4. BD SARS-CoV-2, BD Max™, BD Diagnostics (Baltimore, MA, USA).
5. TaqPath COVID-19 RT PCR kit, ThermoFisher (Waltham, MA, USA).
6. COBAS® SARS-CoV-2 test, Roche (Rotkreuz, Switzerland).
7. Artus SARS-CoV-2 Prep&Amp UM Kit, Qiagen (Germantown, MD, USA).

For each test, cycle threshold (Ct) values for each gene target were reported, and the lowest Ct of all targets was chosen as representative of the test. As the different assays test for different gene targets and have distinct performances, Ct values should be considered only as correlates of the viral loads.

SARS-CoV-2 antibody tests used in various participating hospitals:

1. LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin (Saluggia, Italy).
2. SARS-CoV-2 IgG, Abbott (Lake Forest, IL, USA).
3. Access SARS-CoV-2 IgG antibody test, Beckman Coulter (Nyon, Switzerland).
4. ADVIA Centaur XP/XPT SARS-CoV-2 IgG, Siemens (Malvern, PA, USA).

All the above tests are quantitative tests for SARS-CoV-2 IgG. As different hospitals used different commercial assays, and as each of these assays has an arbitrary scale of IgG levels, we have only used the qualitative result of the test (positive/negative) as per the manufacturer instructions.
Table S2: Univariate analysis comparing hospitalized COVID-19 patients with a poor outcome (in-hospital death or mechanical ventilation) and a favorable outcome. Included are patients admitted between June and August 2021 (delta-variant wave).

| Comorbidity                | Favorable outcome | Poor outcome | P value |
|----------------------------|-------------------|--------------|---------|
| N                          | 406               | 99           |         |
| Male gender                | 211               | 52%          | 54.5%   | 0.646   |
| Age, years, median (IQR)   | 69.8 (55-80)      | 76 (70-86)   | <0.001* |
| Vaccinated                 | 271               | 66.7%        | 72      | 0.253   |
| LTCF residence             | 43                | 10.6%        | 23      | 0.001*  |

| Comorbidity                | Favorable outcome | Poor outcome | P value |
|----------------------------|-------------------|--------------|---------|
| None                       | 88                | 23.9%        | 10.9%   | 0.004*  |
| Diabetes mellitus          | 140               | 34.5%        | 49      | 0.006*  |
| Hypertension               | 222               | 54.7%        | 69.7%   | 0.022*  |
| Obesity                    | 78                | 22.2%        | 20      | 0.713   |
| Ischemic heart disease     | 81                | 20%          | 36      | 0.001*  |
| Congestive heart failure   | 42                | 10.3%        | 20      | 0.005*  |
| Chronic renal failure      | 57                | 14%          | 25      | 0.007*  |
| Chronic lung disease       | 64                | 15.8%        | 18      | 0.559   |
| Chronic liver disease      | 8                 | 2%           | 3       | 0.517   |
| Dementia                   | 51                | 12.6%        | 27      | <0.001* |
| Cancer                     | 45                | 11.1%        | 20      | 0.015*  |

| Immunosuppression          | Favorable outcome | Poor outcome | P value |
|----------------------------|-------------------|--------------|---------|
| Any                        | 39                | 9.6%         | 17      | 0.032*  |

Abbreviations: IQR, interquartile range; LTCF, long-term care facility. Significant values are marked with an asterisk.
### Table S3: Univariate analysis comparing hospitalized breakthrough COVID-19 patients with a poor outcome (in-hospital death or mechanical ventilation) and a favorable outcome. Included are fully-vaccinated patients with breakthrough infection during both alpha and delta variant waves.

|                                | Favorable outcome |  | Poor outcome |  | P value |
|--------------------------------|-------------------|---|--------------|---|---------|
| N                              | 397               | 118                                          |
| Male gender                    | 241 (60.7%)       | 73 (61.9%)                                   | 0.821 |
| Age, years, median (IQR)       | 73 (64-82)        | 77 (71-86)                                   | <0.001* |
| Time from vaccination to admission\(^1\) - median (IQR) | 154 (48-177) | 93 (39-169)                                    | 0.026 |
| LTCF residence                 | 70 (17.6%)        | 35 (29.7%)                                   | 0.004* |
| Comorbidity                    |                   |                                            |       |
| None                           | 43 (10.8%)        | 1 (0.8%)                                     | 0.001* |
| Diabetes mellitus              | 172 (43.3%)       | 58 (49.2%)                                   | 0.264 |
| Hypertension                   | 261 (65.7%)       | 91 (77.1%)                                   | 0.020* |
| Obesity                        | 89 (25.2%)        | 32 (30.2%)                                   | 0.308 |
| Ischemic heart disease         | 104 (26.2%)       | 47 (39.8%)                                   | 0.004* |
| Congestive heart failure       | 66 (16.6%)        | 35 (29.7%)                                   | 0.002* |
| Chronic renal failure          | 94 (23.7%)        | 33 (28%)                                     | 0.343 |
| Chronic lung disease           | 76 (19.1%)        | 28 (23.7%)                                   | 0.276 |
| Chronic liver disease          | 12 (3%)           | 4 (3.4%)                                     | 0.840 |
| Dementia                       | 66 (16.6%)        | 33 (28%)                                     | 0.006* |
| Cancer                         | 65 (16.4%)        | 31 (26.3%)                                   | 0.015* |
| Immunosuppression              | Any               | 76 (19.1%)                                   | 0.015* |
| Delta variant                  | 271 (63.8%)       | 72 (61%)                                     | 0.143 |

Abbreviations: IQR, interquartile range; LTCF, long-term care facility. Significant values are marked with an asterisk.
Figure S4: Forest plot displaying a regression analysis comparing breakthrough infections during a delta-predominant late wave (VD cohort) to non-vaccinated patients in the same wave (ND cohort). Vertical bars and whiskers signify odds ratio (VD vs. ND cohort) and 95% confidence intervals (CI). Statistically significant variables are emphasized by a thicker line.
**Figure S5**: Forest plot displaying a regression analysis comparing breakthrough infections during a delta-predominant late wave (VD cohort) to an alpha-predominant earlier wave (VA cohort). Vertical bars and whiskers signify odds ratio (VD vs. VA cohort) and 95% confidence intervals (CI). Statistically significant variables are emphasized by a thicker line.

- **Male sex**, OR=0.6 (95%CI 0.4-0.9), p=0.023
- **Age**, OR=1 (95%CI 1-1), p=0.164
- **Immunosuppression**, OR=0.3 (95%CI 0.2-0.5), p<0.001
- **Congestive heart failure**, OR=0.6 (95%CI 0.3-0.9), p=0.022
- **Chronic renal failure**, OR=0.7 (95%CI 0.4-1), p=0.067
- **Obesity**, OR=0.7 (95%CI 0.4-1), p=0.067
- **Poor outcome**, OR=0.8 (95%CI 0.5-1.4), p=0.481