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Breakthrough infections in MPN-COVID vaccinated patients

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The first wave of COVID-19 in patients with myeloproliferative neoplasms (MPN) including polycythemia vera (PV), essential thrombocytopenia (ET), prefibrotic myelofibrosis (pre-PMF) and overt myelofibrosis (MF), was characterized by severe illness, high hospitalization rate, and excess of mortality [1, 2]. Deaths accounted for 28.5% of patients [1], an estimate 3-4-fold higher than in general population [3], and progressively decreased thereafter [4]. This improvement was likely related to better critical care management, less virulence of circulating variants of concern (VOCs), younger patient’s age and vaccinations. The effectiveness of vaccines to protect against disease severity, hospitalization and death has been consistently demonstrated in the general population; [5] conversely, very limited information has been provided so far in rare diseases such as MPNs [6, 7] in which vaccines elicit poor neutralizing antibody titers, particularly in MF on ruxolitinib active treatment [8, 9].

We investigated 3 cohorts of COVID-MPN patients, observed since the beginning of the SARS-CoV2, from February 2020 to June 2022. In the European MPN-COVID registry, promoted by the LeukemiaNet (ELN) (clinicaltrials.gov: NCT04385160), 863 MPN patients with COVID-19 have been enrolled and in 649 of them, information on the vaccination status was provided. Diagnosis of covid-19 required a positive real-time reverse transcriptase polymerase chain reaction from nasal swab and symptoms highly suggestive for sars-cov-2 infection. according to the most prevalent circulating vocs in europe at that time, 4 waves were identified: 1st, February to June 2020 (wild-type original variant) 2nd, July 2020–June 2021 (alpha/beta/gamma); 3rd, July 2021–December 2021 (delta); and wave 4th, January to June 2022 (Omicron). The severity of COVID-19 was categorized as asymptomatic, mild, moderate or severe/critical according to the NIH COVID-19 Treatment Guidelines [10].

Vaccine doses (COVID-19 mRNA vaccine—Pfizer/BioNTech in 71%) were 1–2 and 3–4 in 77 and 23%, respectively. Only 3 patients (1%) received 4 vaccine shots.

Adverse events (AE) attributed to vaccines (fever, headache) occurred in 8 patients (2.8%). No patient reported serious adverse events including thrombosis.

Overall, 18 reinfections were diagnosed; of these, 4 occurred during Delta and 14 during Omicron variants period (Table 1). Eight (6.1%) were recorded in unvaccinated and 10 (3.5%) in vaccinated patients (p = 0.22). Therefore, a statistically significant benefit of vaccination in individuals with prior COVID-19 was not apparent; however, these findings were based on a small number of reinfections and need confirmation by prolonging the follow-up in longitudinal studies to assess the durability of the protection in comparable groups [11].

Of note, among patients who developed reinfections, 9/10 (90%) and 5/8 (63%) occurred during Omicron period in vaccinated and unvaccinated groups, respectively. The time interval between the first SARS-Cov-2 infection and the reinfection was double in vaccinated than in unvaccinated patients (14.3 vs. 7.5 months, respectively, p = 0.016), suggesting that booster or repeat vaccination is important and the immunity wanes with time. Time from last vaccine shot to reinfection was 3.1 months.

Severity of reinfection was mild in the great majority of both unvaccinated and vaccinated patients (88 and 67%, respectively, p = 0.72).

Overall, compared with the normal population, partial and fully hybrid vaccination in our MPN patient cohorts conferred a 10-fold lower protection (3.5%) than that reported in Italy (0.4%) [12] and in 2 US cohorts in New York city (0.4%) [13] and California (0.3%) [13]. Notably, this poor result was limited to myelofibrosis and to exposure to ruxolitinib in which the rate of reinfections was not different from that registered in severely immunocompromised patients [14].

**INFECTIONS IN VACCINATED PATIENTS WITH PREVIOUS COVID-19 (HYBRID VACCINATION)**

Of 418 patients with prior COVID-19, 287 were vaccinated and 131, at the moment of the present analysis, were not. Almost all vaccinated cases (98%) had prior COVID-19 during the first and second pandemic wave. In unvaccinated cases, prior COVID-19 occurred frequently during the last 2 waves, including Delta and Omicron VOCs (26%) (Table 1). Of note, unvaccinated cases experienced the first episode of COVID-19 less severe than vaccinated ones (i.e., asymptomatic in 7.3% vs. 2.6%, respectively, p = 0.003) and were younger (median age 59 years vs. 62 years, respectively, p = 0.016). The proportion of PV, ET, pre-PMF was similar in the two groups while the proportion of MF patients was lower in the vaccinated than unvaccinated group (19% vs 28%) (p = 0.024). No difference of driver mutations frequency and splenomegaly among the MPN phenotypes was found.

**BREAKTHROUGH INFECTIONS IN VACCINATED PATIENTS WITHOUT PREVIOUS COVID-19 INFECTION**

Breakthrough infections were reported in vaccinated patients (ET = 89, PV = 75, MF = 54 and pre-PMF = 13) who had no previous history of COVID-19. Of these, 26 (11%) were hospitalized and their characteristics, compared with home-treated cases, are reported in Table 2. Hospitalized patients were more likely to be older (median age 76 years), males (69%), afflicted with MF (39%), and to have had prior exposure to ruxolitinib (42%: 7 MF and 4 PV). Of note, baseline values at COVID-19 diagnosis of C-reactive protein (CRP) and neutrophil to lymphocyte ratio (NLR) were significantly higher in hospitalized than in home-managed cases (CRP = 33.1 mg/dl vs. 2.0 and NLR = 5.9 vs. 3.3, p < 0.001). Although some infections occurred in the second wave, corresponding to Alpha/Beta/Gamma VOCs, the majority of breakthrough episodes occurred during Delta and Omicron variant periods (41% and 53%, respectively), and illness severity was mild.

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Table 1. Characteristics of patients with previous COVID-19 infection according to vaccination status.

| Characteristic                        | Total pts with previous infection \( N = 418 \) | UNVACCINATED \( N = 131 \) | VACCINATED \( N = 287 \) | \( p \) |
|---------------------------------------|-----------------------------------------------|-----------------------------|--------------------------|------|
| Male gender                           | 189/418 (45.2%)                               | 51/131 (38.9%)              | 138/287 (48.1%)          | 0.081|
| Age                                   | 61.3 (53.0–71.7)                              | 59.3 (47.9–71.9)            | 61.8 (54.6–71.7)         | 0.016|
| > 70                                   | 124/417 (29.7%)                               | 36/131 (27.5%)              | 88/286 (30.8%)           | 0.50 |
| BMI                                    | 24.0 (21.3–26.5)                              | 24.4 (21.7–26.1)            | 23.9 (21.3–26.5)         | 0.89 |
| MPN diagnosis                         |                                               |                             |                          |      |
| ET                                    | 156/418 (37.3%)                               | 41/131 (31.3%)              | 115/287 (40.1%)          | 0.085|
| PV                                    | 133/418 (31.8%)                               | 41/131 (31.3%)              | 92/287 (32.1%)           | 0.88 |
| MF                                    | 90/418 (21.5%)                                | 37/131 (28.2%)              | 53/287 (18.3%)           | 0.024|
| Early/pre-PMF                         | 39/418 (9.3%)                                 | 12/131 (9.2%)               | 27/287 (9.4%)            | 0.94 |
| Previous thrombosis                   | 81/415 (19.5%)                                | 24/129 (18.6%)              | 57/286 (19.9%)           | 0.75 |
| Mutational status                     |                                               |                             |                          |      |
| JAK2 V617F                            | 303/408 (74.3%)                               | 93/127 (73.2%)              | 210/281 (74.7%)          | 0.75 |
| CALR                                  | 64/231 (27.7%)                                | 19/89 (21.3%)               | 45/142 (31.7%)           | 0.087|
| MPL                                   | 10/220 (4.5%)                                 | 5/88 (5.7%)                 | 5/132 (3.8%)             | 0.53 |
| JAK2 EXON12                           | 1/126 (0.8%)                                  | 1/55 (1.8%)                 | 0/71 (0.0%)              | 0.44 |
| Spleen palpable                       |                                               |                             |                          |      |
| No                                    | 270/386 (69.9%)                               | 88/125 (70.4%)              | 182/261 (69.7%)          |      |
| Yes                                   | 111/386 (28.8%)                               | 35/125 (28.0%)              | 76/261 (29.1%)           | 0.87 |
| Previously splenectomized             | 5/386 (1.3%)                                  | 2/125 (1.6%)                | 3/261 (1.1%)             |      |
| Size below costal margin (cm)         | 4.0 (2.0–6.0)                                 | 4.5 (2.0–6.5)               | 3.0 (2.0–6.0)            | 0.30 |
| MPN treatment post-COVID              |                                               |                             |                          |      |
| Phlebotomy                            | 76/410 (18.5%)                                | 24/130 (18.5%)              | 52/280 (18.6%)           | 0.98 |
| Cytoreduction                         | 289/418 (69.1%)                               | 83/131 (63.4%)              | 206/287 (71.8%)          | 0.084|
| HU                                    | 196/412 (47.6%)                               | 54/130 (41.5%)              | 142/282 (50.4%)          | 0.096|
| Anagrelide                            | 13/412 (3.2%)                                 | 1/130 (0.8%)                | 12/282 (4.3%)            | 0.071|
| Interferon                            | 12/412 (2.9%)                                 | 3/130 (2.3%)                | 9/282 (3.2%)             | 0.76 |
| Ruxolitinib                           | 63/412 (15.3%)                                | 20/130 (15.4%)              | 43/282 (15.2%)           | 0.97 |
| Antiplatelets post-COVID              | 250/410 (61.0%)                               | 75/129 (58.1%)              | 175/281 (62.3%)          | 0.43 |
| ASA                                   | 233/412 (56.6%)                               | 73/130 (56.2%)              | 160/282 (56.7%)          | 0.91 |
| Anticoagulants                        | 95/409 (23.2%)                                | 32/128 (25.0%)              | 63/281 (22.4%)           | 0.57 |
| Characteristics of COVID-19           |                                               |                             |                          |      |
| Wave                                  |                                               |                             |                          |      |
| 1 (Wild-type)                         | 94/418 (22.5%)                                | 14/131 (10.7%)              | 80/287 (27.9%)           | <0.001|
| 2 (Alpha, Beta, Gamma)                | 284/418 (67.9%)                               | 83/131 (63.4%)              | 201/287 (70.0%)          | 0.175|
| 3 (Delta)                             | 19/418 (4.5%)                                 | 17/131 (13.0%)              | 2/287 (0.7%)             | <0.001|
| 4 (Omicron)                           | 21/418 (5.0%)                                 | 17/131 (13.0%)              | 4/287 (1.4%)             | <0.001|
| COVID-19 severity*                    |                                               |                             |                          |      |
| Asymptomatic infection                | 16/389 (4.1%)                                 | 9/123 (7.3%)                | 7/266 (2.6%)             | 0.003|
| Mild Illness                          | 286/389 (73.5%)                               | 84/123 (68.3%)              | 202/266 (75.9%)          | 0.11 |
| Moderate Illness                      | 25/389 (6.4%)                                 | 7/123 (5.7%)                | 18/266 (6.8%)            | 0.69 |
| Severe/critical Illness               | 62/389 (15.9%)                                | 23/123 (18.7%)              | 39/266 (14.7%)           | 0.31 |
| Vaccine information                   |                                               |                             |                          |      |
| Months since prior infection          | –                                             | –                           | 5.9 (4.3–11.2)           | –    |
| No administered doses                 |                                               |                             |                          |      |
| Only 1 dose                           | –                                             | –                           | 109/287 (38.0%)          | –    |
| 2 doses                               | –                                             | –                           | 112/287 (39.0%)          | –    |
| 3–4 doses                             | –                                             | –                           | 66/287 (23.0%)           | –    |
in the great majority (86%), even though a moderate to severe infection accounted for more than half of hospitalized patients. Five deaths were registered: 3 and 2 in hospitalized and home managed cases, respectively (12% vs. 1%, \( p = 0.011 \)). The number of vaccine doses was the same in the 2 groups, and patients fully vaccinated (3–4 shots) were 42% and 41%, respectively. Mild adverse events (AE) attributed to vaccination were seen in only 3 patients (1.3%).

Compared with the normal population of the 2 US cohorts of patients experiencing COVID-19 after vaccination [13], the proportion of hospitalization in our patients is markedly higher (11% vs 4.4% and 1.8%). This difference was not attributable to the number of vaccine shots in home-managed and in hospitalized patients and the two groups did not differ regarding the time between the last shot of vaccination and the onset of infection, likely excluding that hospitalization could be attributed to the waning of vaccine protection. This possibility is particularly relevant with Delta and Omicron variants which are able, at least partially, to evade vaccine-induced immunity [11].

In a multivariable logistic model fitted to predict hospitalization, we found that this risk was age-related and substantially higher in males on ruxolitinib (Fig. 1S, panel A). Interestingly, these two factors were also related to a progressive increase of NLR inflammatory biomarker (Fig. 1S, panel B), suggesting a connection between sex, aging and inflammation.

In conclusion, we have provided quantitative estimates of SARS-CoV2 infections in vaccinated patients with MPN revealing a higher rate of severe disease than in the normal population. Compared to unvaccinated, a trend for a lower reinfection rate was found in patients with hybrid vaccination. In COVID-naïve patients, the proportion of hospitalization is markedly higher (11% vs 4.4% and 1.8%). This difference was not attributable to the number of vaccine shots in home-managed and in hospitalized patients and the two groups did not differ regarding the time between the last shot of vaccination and the onset of infection, likely excluding that hospitalization could be attributed to the waning of vaccine protection. This possibility is particularly relevant with Delta and Omicron variants which are able, at least partially, to evade vaccine-induced immunity [11].
Table 2. Characteristics of vaccine breakthrough infections according to the severity of Covid-19.

| Characteristic                                      | Total pts without previous infection | HOME-TREATED  | HOSPITALIZED  | p     |
|-----------------------------------------------------|-------------------------------------|---------------|---------------|-------|
|                                                     | N = 231                             | N = 205       | N = 26        |       |
| Male gender                                         | 105/231 (45.5%)                     | 87/205 (42.4%)| 18/26 (69.2%) | 0.010 |
| Age at COVID diagnosis                              | 60.4 (49.8–73.2)                    | 57.4 (49.2–71.5)| 75.5 (67.3–84.3)| <0.001|
| >70                                                 | 71/231 (30.7%)                      | 55/205 (26.8%)| 16/26 (61.5%) | <0.001|
| MPN diagnosis                                       |                                     |               |               |       |
| ET                                                  | 89/231 (38.5%)                      | 80/205 (39.0%)| 9/26 (34.6%)  | 0.66  |
| PV                                                  | 75/231 (32.5%)                      | 68/205 (33.2%)| 7/26 (26.9%)  | 0.52  |
| MF                                                  | 54/231 (23.4%)                      | 44/205 (21.5%)| 10/26 (38.3%) | 0.054 |
| Early/pre-PMF                                       | 13/231 (5.6%)                       | 13/205 (6.3%) | 0/26 (0.0%)   | 0.19  |
| Previous thrombosis                                 | 36/231 (15.6%)                      | 30/205 (14.6%)| 6/26 (23.1%)  | 0.26  |
| Mutational status                                   |                                     |               |               |       |
| JAK2 V617F                                          | 166/227 (73.1%)                     | 147/203 (72.4%)| 19/24 (79.2%) | 0.48  |
| CALR                                                | 34/136 (25.0%)                      | 32/126 (25.4%)| 2/10 (20.0%)  | 0.70  |
| MPL                                                 | 7/131 (5.3%)                        | 6/123 (4.9%)  | 1/8 (12.5%)   | 0.36  |
| JAK2 EXON12                                         | 0/70 (0.0%)                         | 0/65 (0.0%)   | 0/5 (0.0%)    |       |
| Spleen palpable                                     |                                     |               |               |       |
| No                                                  | 152/218 (69.7%)                     | 136/193 (70.5%)| 16/25 (64.0%) | 0.60  |
| Yes                                                 | 64/218 (29.4%)                      | 55/193 (28.5%)| 9/25 (36.0%)  |       |
| Previously splenectomized                           | 2/218 (0.9%)                        | 2/193 (1.0%)  | 0/25 (0.0%)   |       |
| Size below costal margin (cm)                       | 5.0 (2.0–7.0)                       | 4.5 (2.0–7.0) | 6.0 (4.0–20.0) | 0.11  |
| MPN-treatment before COVID                          |                                     |               |               |       |
| Phlebotomy                                          | 38/230 (16.5%)                      | 36/204 (17.6%)| 2/26 (7.7%)   | 0.20  |
| Cytoreduction pre-COVID                             | 167/230 (72.6%)                     | 144/204 (70.6%)| 23/26 (88.5%)| 0.054 |
| Type:                                               |                                     |               |               |       |
| HU                                                  | 93/231 (40.3%)                      | 83/205 (40.5%)| 10/26 (38.5%) | 0.84  |
| Anagrelide                                          | 19/231 (8.2%)                       | 19/205 (9.3%) | 0/26 (0.0%)   | 0.11  |
| Interferon                                          | 5/231 (2.2%)                        | 5/205 (2.4%)  | 0/26 (0.0%)   | 0.42  |
| Ruxolitinib                                         | 40/231 (17.3%)                      | 29/205 (14.1%)| 11/26 (42.3%) | <0.001|
| Other                                               | 11/231 (4.8%)                       | 9/205 (4.4%)  | 2/26 (7.7%)   | 0.36  |
| Characteristics of Covid-19                         |                                     |               |               |       |
| Wave                                                |                                     |               |               |       |
| 2 (Alpha, Beta, Gamma)                              | 14/231 (6.1%)                       | 11/205 (5.4%) | 3/26 (11.5%)  | 0.20  |
| 3 (Delta)                                           | 94/231 (40.7%)                      | 79/205 (38.5%)| 15/26 (57.7%) | 0.061 |
| 4 (Omicron)                                         | 123/231 (53.2%)                     | 115/205 (56.1%)| 8/26 (30.8%) | 0.015 |
| COVID-19 severity*                                  |                                     |               |               |       |
| Asymptomatic infection                              | 11/220 (5.0%)                       | 11/197 (5.6%) | 0/23 (0.0%)   | 0.61  |
| Mild Illness                                        | 190/220 (86.4%)                     | 180/197 (91.4%)| 10/23 (43.5%) | <0.001|
| Moderate Illness                                    | 6/220 (2.7%)                        | 4/197 (2.0%)  | 2/23 (8.7%)   | 0.12  |
| Severe/critical Illness                             | 13/220 (5.9%)                       | 2/197 (1.0%)  | 11/23 (47.8%) | <0.001|
| Respiratory support                                 | 19/231 (8.2%)                       | 3/205 (1.5%)  | 16/26 (61.5%) | <0.001|
| ICU                                                 | 5/230 (2.2%)                        | 1/204 (0.5%)  | 4/26 (15.4%)  | <0.001|
| Saturation                                          | 98.0 (96.0–99.0)                    | 98.0 (97.0–99.0)| 92.0 (88.0–94.0)| <0.001|
| Lab values at COVID diagnosis                       |                                     |               |               |       |
| Hb                                                  | 12.9 (11.3–14.0)                    | 13.0 (11.5–14.1)| 11.5 (9.0–13.1)| 0.002 |
| HCT                                                | 40.0 (36.0–44.0)                     | 40.5 (36.7–44.5)| 37.5 (27.3–40.1)| 0.004 |
| RDW                                                | 16.5 (14.3–18.7)                     | 16.0 (13.9–18.1)| 18.3 (15.4–18.9)| 0.093 |
| WBC                                                | 7.5 (5.5–10.5)                       | 7.5 (5.7–10.2)| 8.1 (4.8–11.3)| 0.93  |
| Neutrophils                                         | 68.9 (56.9–76.0)                     | 67.1 (56.3–75.0)| 75.3 (63.0–82.8)| 0.028 |
| Lymphocytes                                         | 18.2 (10.9–26.8)                     | 19.8 (12.0–28.2)| 13.1 (7.4–18.5)| 0.005 |
| Neutrophils/lymphocytes ratio                       | 3.6 (2.1–6.0)                       | 3.3 (2.0–5.3)  | 5.9 (3.6–10.2) | <0.001|
| PLT                                                | 401.0 (226.0–608.5)                   | 430.0 (274.0–622.0)| 199.0 (119.0–294.0)| <0.001|
| LDH                                                | 243.0 (200.0–470.0)                   | 236.5 (191.0–447.0)| 415.0 (269.0–573.0)| 0.022 |
| CRP                                                | 8.9 (1.4–32.9)                       | 2.0 (0.9–16.0) | 33.1 (17.0–123.0) | <0.001|
| Fibrin                                             | 402.0 (339.0–579.0)                   | 339.0 (309.0–480.0)| 432.0 (360.0–726.0) | 0.12  |
| D-dimer                                            | 510.0 (270.0–759.0)                   | 331.5 (185.0–568.5)| 650.0 (440.0–910.0) | 0.015 |
MPN patients, current original vaccine shots have shown a limited protection against delta and omicron VOCs. While waiting for the results of the new boosters targeting the newest strains of the omicron variants, we suggest a prompt identification of the MPN subgroup at high risk of hospitalization, in which early treatment with the recent monoclonal antibodies against the spike protein of the SARS-CoV-2 virus, anti-inflammatory and antiviral drugs can be suggested.

| Vaccine information | Total pts without previous infection | HOME-TREATED N = 205 | HOSPITALIZED N = 26 | p |
|---------------------|-------------------------------------|----------------------|-------------------|---|
| Months from last vaccine dose to infection | 4.0 (1.4–6.6) | 4.0 (1.5–6.7) | 2.6 (1.2–6.0) | 0.37 |
| N° administered doses | | | | |
| Only 1 dose | 22/231 (9.5%) | 19/205 (9.3%) | 3/26 (11.5%) | 0.90 |
| 2 doses | 115/231 (49.8%) | 103/205 (50.2%) | 12/26 (46.2%) | |
| 3–4 doses | 94/231 (40.7%) | 83/205 (40.5%) | 11/26 (42.3%) | |
| Vaccine type | | | |
| Pfizer/BioNTech | 179/231 (77.5%) | 164/205 (80.0%) | 15/26 (57.7%) | 0.010 |
| Moderna | 28/231 (12.1%) | 22/205 (10.7%) | 6/26 (23.1%) | 0.069 |
| AstraZeneca | 18/231 (7.8%) | 14/205 (6.8%) | 4/26 (15.4%) | 0.13 |
| Johnson&Johnson | 5/231 (2.2%) | 4/205 (2.0%) | 1/26 (3.8%) | 0.45 |
| UNK | 1/231 (0.4%) | 1/205 (0.5%) | 0/26 (0.0%) | |

Outcome

Death | 5/231 (2.2%) | 2/205 (1.0%) | 3/26 (11.5%) | 0.011 |

*According to the NIH COVID-19 Treatment Guidelines.
Data availability

Aggregated data available by request. Patient-level data will not be shared.

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Author contributions

TB conceived and designed the study, supervised the analysis and wrote the paper. AMV, SK revised the study and contributed to manuscript writing. AC and AG performed statistical analysis. VDS, MAS, ER, EME, FL, MGK, BC, PG, MB, MM, AAL, LF, MB, RD, GB, GCT, AP, HKAA, MMMCAC, FP, CH, MAF, SQ, SK, EMM, JIK, EBC, FIHH, KOC, MG, VGG, AMS, JCHB, ELA, GC, MSS, RK, BXC, MG, BNE, AA, EC, AKDN, DC, CB, SB, OB, FC, SC, NCG, LB, AR collected data. All authors revised and approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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