Immunogenicity and tolerability of COVID-19 vaccination in peritoneal dialysis patients—A prospective observational cohort study

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Abstract

Background: In peritoneal dialysis (PD) patients, information on the immunogenicity and tolerability of SARS-CoV-2 vaccination is still scarce. We compared the immunogenicity and tolerability of SARS-CoV-2 vaccination of PD patients with that of medical personnel.

Methods: In a prospective observational cohort study, PD patients and immunocompetent medical personnel were evaluated for SARS-CoV-2 spike-IgG- and Nucleocapsid-IgG-antibody-levels before, 2 weeks after the first, and 6 weeks after the second SARS-CoV-2 vaccination and vaccine tolerability after the first and second vaccination.

Results: In COVID-19-naïve PD patients (N = 19), lower SARS-CoV-2-spike-IgG-levels were found compared with COVID-19-naïve medical personnel (N = 24) 6 weeks after second vaccination (median 1438 AU/ml [25th–75th percentile 775–5261] versus 4577 [1529–9871]; p = 0.045). This finding resulted in a lower rate of strong vaccine response (spike-IgG ≥ 1000 AU/ml) of COVID-19-naïve PD patients compared with medical personnel (58% versus 92%; p = 0.013), but not for seroconversion rate (spike-IgG ≥ 50 AU/ml: 100% vs. 100%; p > 0.99). After first vaccination,
COVID-naïve PD patients presented with significantly fewer side effects than medical personnel (number of any side effect: 1 [1–2] vs. 4 [1–7]; p = 0.015). A similar pattern with slightly decreased frequencies of side effects was observed for tolerability of second SARS-CoV-2 vaccination in PD patients and medical personnel (number of any side effects: 1 [1–1] vs. 2 [1–5]; p = 0.006).

Conclusions: SARS-CoV-2 vaccination in COVID-19-naïve PD patients appeared to induce a very high rate of seroconversion but a substantially lower rate of patients with a strong response compared with medical personnel. Vaccination appeared to be safe in the PD patients studied.

1 | INTRODUCTION

Dialysis patients are considered an immunocompromised patient group. They are at much higher risk of infection and have higher COVID-19-associated infection and mortality rates than the normal population. The optimal vaccination strategy against SARS-CoV-2 in immunosuppressed patients, such as dialysis patients, is still unclear. Importantly, rates of seroconversion after vaccination are often lower in this patient group than in the normal population.

To date, numerous studies in the normal population and more than 40 studies in hemodialysis patients have evaluated seroconversion rates after SARS-CoV-2 vaccination. However, the immunogenicity and tolerability of SARS-CoV-2 vaccination in peritoneal dialysis patients may differ from that in hemodialysis patients and the normal population.

To date, there is limited information on the immunogenicity and tolerability of the SARS-CoV-2 vaccination in peritoneal dialysis patients. There is a particular lack of studies which include an internal control group. A condensed literature overview including details of studies involving SARS-CoV-2 vaccinated peritoneal dialysis patients is provided in Table S1.

In a prospective observational cohort study, we aimed to compare SARS-CoV-2 antibody-related immunogenicity and tolerability of vaccination in peritoneal dialysis patients with medical personnel.

2 | METHODS

2.1 | Design and setting

In a prospective observational cohort study, all peritoneal dialysis patients treated at renal care centers in Potsdam, Ludwigsfelde, and Rangsdorf, Germany, were eligible to participate between February and August 2021 to measure SARS-CoV-2 antibody levels and to obtain information on the tolerability of SARS-CoV-2 vaccination (Figure 1).

Following prioritization by the National Vaccination Committee, all participants were vaccinated, depending on availability, with either two doses of the ChAdOx1-nCoV-19(AZD1222)/Oxford-AstraZeneca (Vaxzevria⁶) with a dosing interval of 42 to 84 days, two doses of the Pfizer/BioNTech-mRNA-BNT162b2-SARS-CoV-2 vaccine

FIGURE 1  Participant flow chart
(Comirnaty™) or mRNA-1273/Moderna Biotech (Spikevax™) with dosing interval of 21 to 28 days, or a combination of one dose of Vaxzevria® followed by one dose of Comirnaty™ following that of Vaxzevria® with dosing interval of 42 to 84 days, respectively. Peritoneal dialysis patients as well as immunocompetent medical personnel, both COVID-19 naïve or with COVID-19 more than 3 months prior to study entry, were enrolled after providing written informed consent for study participation and were vaccinated as described.

Exclusion criteria for SARS-CoV-2 antibody measurement were lack of written informed consent or age <18 years. The study was approved by the Ethics Committee of the “Landesärztekammer Brandenburg,” Germany (S9/(bB)/2021). This manuscript adheres to the “Strengthening the Reporting of Observational Studies in Epidemiology” guidelines.4

2.2 Definitions

History of COVID-19 was defined as previous PCR-positive COVID-19. A positive response to SARS-CoV-2 vaccine (“seroconversion”) was defined as SARS-CoV-2 spike IgG level ≥50 AU/ml, a moderate vaccine response as level ≥500 AU/ml, and a strong response ≥1000 AU/ml, the latter corresponding to the 25th percentile of SARS-CoV-2 spike IgG levels in the current study population 6 weeks after the second vaccination. Furthermore, SARS-CoV-2-spike-IgG-levels ≥1000 AU/ml of the assay used in the present study correspond to an ACE2-receptor-binding-inhibition capacity >30%,3 a cut-off value that is consistent with the titer of this assay considered acceptable by the FDA for neutralizing SARS-CoV-2.6,7 Patients with seroconversion were referred to as responders and those without seroconversion as non-responders.

2.3 Endpoints

Primary endpoint was SARS-CoV-2 spike IgG levels 6 weeks after second dose of vaccine. Secondary endpoints were the proportion of patients or medical personnel with positive, moderate, or strong SARS-CoV-2 spike IgG response 6 weeks after second dose of vaccine, spike IgG and IgM levels before and after both vaccinations, the proportion of patients with local, systemic, or severe vaccination side effects, the latter defined as medication intake or medical presentation within the first week after SARS-CoV-2 first and second vaccination, and, the number of any side effects in affected participants.

2.4 SARS-CoV-2-antibody measurement

Participant serum was collected immediately before a first SARS-CoV-2 vaccination, at 2 weeks after receiving a first, and at 6 weeks after a second vaccine dose. Participants were tested for SARS-CoV-2 IgG and IgM antibody levels from serum directed against the spike protein (SARS-CoV-2 spike IgG: positive, if >50 AU/ml, SARS-CoV-2 IgM: positive, if >1.0) and IgG antibodies directed against the Nucleocapsid protein (Index positive, i.e., previous contact with SARS-CoV-2, if ≥1.4 Index).5 All samples were run on Abbott ARCHITECT™ i2000SR instrument (Abbott Park, IL). The FDA EUA approved SARS-CoV-2 IgG (List 6R86), AdviseDx SARS-CoV-2 IgM (List 6R87), and SARS-CoV-2 IgG II Quant (List 6S60) assays were used, both automated Chemiluminescent Microparticle Immunoassays (CMIA). Assay results are reported as an index value of the ratio of specimen to calibrator Relative Light Units (RLU) signal. The SARS-CoV-2 IgG II Quant-assay is an automated CMIA used for quantitative detection of IgG antibodies directed against the receptor-binding-domain of the SARS-CoV-2 spike protein and results are reported in AU/ml. Assay linearity was shown between 21.0 and 40,000 AU/ml. The laboratory investigators were blinded to the sample sources and clinical outcomes. Researchers who obtained clinical data were blinded to antibody measurements.

2.5 SARS-CoV-2-vaccination tolerability questionnaire

All vaccinated peritoneal dialysis patients at the above dialysis centers were offered to participate in the evaluation of the tolerability of SARS-CoV-2 vaccination. Patients who agreed were interviewed in person at each medical presentation about their COVID-19 status, and, during the first week after vaccination, about the occurrence of local and systemic side effects and medication intake or medical presentation after the first and second vaccine doses. Vaccine side effects and reactions were assessed following the pivotal study by Polack et al.8 Patients completed questionnaires independently or with the assistance of nursing staff to obtain information on the occurrence and duration of local and systemic side effects or the need to take medications or present to a physician to treat vaccination side effects. Medical personnel also completed these questionnaires as described above.

2.6 Search, study selection, and data extraction of condensed literature overview

To identify studies regarding immunogenicity or tolerability of SARS-CoV-2 vaccines, we used the databases PubMed, Scopus, and Web of Science, independently of the publication type and status and without any limits imposed on the time periods covered. Furthermore, we regularly screened medical journals that were relevant for the subject matter of our review article, and conference abstracts; we also searched pre-publication platform medRxiv for non-peer-review studies. Reference lists of identified publications were screened for relevance.

Inclusion criteria: Patient population: dialysis patients; intervention: full SARS-CoV-2 vaccination; reported endpoints: vaccine immunogenicity/efficacy and tolerability. Study design: no restrictions.
Search terms: #1 dialysis, #2 COVID-19, #3 SARS-CoV-2, #4 vaccination, #5 vaccine and combinations (#1–5: no filter).

Effective date of search: 12 August 2021.

Results: PubMed, Scopus, and Web of Science: N = 92; medRxiv: N = 196. Then, double publications were excluded and extracted data on peritoneal dialysis patients was summarized in Table S1 including information on reference, vaccine type, number of patients and controls, inclusion/exclusion of individuals with peritoneal dialysis and prior COVID-19, SARS-CoV-2 antibody assay and cut-off used, vaccine response rate and SARS-CoV-2 antibody levels, and side effects.

2.7 | Statistical analysis

For evaluation of the study endpoints, study size was determined by the availability of serum sampling or SARS-CoV-2 tolerability questionnaire before 20 July 2021 to gather early potentially important clinical information for this patient population. For evaluation of tolerability of SARS-CoV-2 vaccines, study size was determined by individuals asked to participate in this study. No formal power analysis was performed. Values are presented as median (25th–75th percentile). According to study hypothesis, two-group comparisons were performed regarding the SARS-CoV-2 spike IgG-related immunogenicity and vaccination tolerability (COVID-19 naïve peritoneal dialysis patients versus medical personnel). Mann–Whitney U test, χ² test, or Fisher’s exact test were used where appropriate. Alpha was set at 0.05 (two-tailed). SPSS version 26.0 (IBM Corp., Armonk, NY, USA) was used.

3 | RESULTS

3.1 | Patient characteristics

Of 43 peritoneal dialysis patients at three dialysis centers, 32 patients with two doses of SARS-CoV-2 vaccination were enrolled, of those 16 males. Of 32 patients enrolled, in nine patients, a serum sample was missing, and two patients died before second vaccination. Thus, data from 21 patients with SARS-CoV-2 antibody measurements until 20 July 2021 were analyzed, of those two patients with prior COVID-19 (Figure 1). Thirty patients returned questionnaires on vaccination tolerability.

Of these 19 COVID-19 naïve patients with SARS-CoV-2 antibody measurements, 13 received two doses of Comirnaty®, 4 two doses of Vaxzevria®, 1 one dose of Vaxzevria® followed by one dose of Comirnaty®, and 1 two doses of Spikevax®.

Patients represented a typical peritoneal dialysis patient cohort, comprising 37% with type 2 diabetes and 90% with arterial hypertension. Median patient age was 77 years (25th–75th percentile 63–80), Charlson Comorbidity Index 6.0 points (4.0–6.3) and peritoneal dialysis vintage 16 months (12–33). Primary kidney disease was mainly diabetic/hypertensive nephropathy and IgA nephropathy (42%, 26%). Patient characteristics for total cohort and separated by status of seroconversion are provided in Tables S2–S4. There were no significant differences between non-responders and responders.

3.2 | Medical personnel characteristics

After second vaccination, 31 medical personnel, aged 45 (37–56), were enrolled, of those eight males. Of COVID-19 naïve medical personnel with available IgG spike levels (N = 24), 10 received two doses of Vaxzevria®, 4 two doses of Comirnaty®, and 10 one dose of Vaxzevria® followed by one dose of Comirnaty®. In addition, three medical personnel had prior COVID-19.

3.3 | SARS-CoV-2 spike IgG/IgM and Nucleocapsid IgG

No case of COVID-19 was reported in any peritoneal dialysis patients or medical personnel since vaccination program started at study sites. In COVID-19 naïve participants, no individual Nucleocapsid IgG result had a positive Index indicating no previously undetected COVID-19 in any patient or medical personnel, respectively. Interval between second SARS-CoV-2 vaccinations and sampling was 42 days (42–55) for patients, and 43 days (42–46) for medical personnel, respectively. SARS-CoV-2 spike IgG and IgM levels and Nucleocapsid IgG levels of participants before, 2 weeks after first and 6 weeks after second vaccination are shown in Table 1. SARS-CoV-2 spike IgG levels before and after first vaccination are shown in Figure 2A.B.

In both groups, SARS-CoV-2 spike IgG levels were low after first vaccination (Table 1, Figure 2B). In peritoneal patients, SARS-CoV-2 spike IgG levels increased 21-fold from first to second vaccination, and in medical personnel, 32-fold.

For the primary endpoint, 6 weeks after second vaccination, significantly lower SARS-CoV-2 spike IgG levels were found in COVID-19 naïve peritoneal dialysis patients compared to that of medical personnel (median 1438 AU/ml [25th–75th percentile 775–5261] versus 4577 [1529–9871]; p = 0.045), Figure 2C.

This finding resulted in a lower rate of strong-vaccine-response (spike IgG ≥ 1000 AU/ml) of COVID-19 naïve peritoneal dialysis patients compared to medical personnel (58% versus 92%; p = 0.013), but not for seroconversion rate (spike IgG > 50 AU/ml: 100% vs. 100%; p > 0.99), Figure 3.

SARS-CoV-2 spike IgG levels in vaccinated peritoneal dialysis patients with prior COVID-19 were 912 and 110,551 AU/ml, and in medical personnel with prior COVID-19, median IgG spike level was 8840 AU/ml (5771–27,958).

3.4 | SARS-CoV-2-vaccine tolerability

Questionnaires on SARS-CoV-2-vaccine tolerability were available from 28 COVID-naïve peritoneal dialysis patients (Figure 1).
After first vaccination, COVID-naïve peritoneal dialysis patients presented with significantly fewer side effects than medical personnel (number of any side effect: 1 [1–2] vs. 4 [1–7]; p = 0.015/local side effects: 36% vs. 86%; p = 0.001/systemic side effects: 11% vs. 72%; p < 0.001/use of medication or medical presentation: 7% vs. 55%; p < 0.001), Figure 4.

A similar pattern with slightly decreased frequencies of side effects was observed for tolerability of second SARS-CoV-2 vaccination in peritoneal dialysis patients and medical personnel (number of any side effect: 1 [1–1] vs. 2 [1–5]; p = 0.006/local side effects: 30% vs. 65%; p = 0.013/systemic reactions: 9% vs. 62%; p < 0.001/use of medication or medical presentation: 0% vs. 42%; p = 0.001), Figure 4. Detailed information on tolerability of SARS-CoV-2 vaccination is provided in Table 2.

### 4 | DISCUSSION AND CONCLUSIONS

In a prospective observational cohort study of 43 peritoneal dialysis patients and 31 medical personnel, we demonstrated lower SARS-CoV-2 spike IgG levels in COVID-19-naïve peritoneal dialysis patients compared with medical personnel 6 weeks after the second dose of vaccine. In addition, SARS-CoV-2 vaccination in peritoneal dialysis patients and medical personnel resulted in a similar seroconversion rate but less frequently in a strong response (spike-IgG-levels ≥1000 AU/ml) in patients compared with medical personnel. Peritoneal dialysis patients had 3.2-fold lower SARS-CoV-2 spike IgG levels 6 weeks after the second vaccination compared with medical staff. Overall, the SARS-CoV-2 vaccination resulted in a lower proportion of and fewer side effects in peritoneal dialysis patients compared with medical personnel. The safety profile of SARS-CoV-2 vaccination in peritoneal dialysis patients was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, muscle aches, and headache.

Compared with the normal population, patients receiving hemodialysis or peritoneal dialysis are considered immunocompromised patient populations. Both groups of dialysis patient have a similar rate of non-responders after Hepatitis B vaccination of up to 40–50%, and peritoneal dialysis patients have an even more rapid decline in anti-HBs titers than hemodialysis patients. In this sense, lower spike IgG levels were observed in hemodialysis patients than in healthy controls after SARS-CoV-2 vaccination. Similar to hemodialysis patients who fail to respond to two doses of SARS-CoV-2 vaccination (up to 20%), peritoneal dialysis patients may also experience an inadequate response. For example, approximately 12% of all dialysis patients in the United Kingdom and 7% in Germany receive peritoneal dialysis. However, to date, only one research letter reported the immunogenicity of SARS-CoV-2 vaccination in peritoneal dialysis patients and healthy controls. Yanay et al. examined the spike-IgG levels and associated seroconversion rates after two vaccinations in 33 patients and 132 controls. SARS-CoV-2 vaccination resulted in a seroconversion rate of 90% in patients and 100% in healthy controls. However, the proportion of patients with moderate or strong response and the tolerability of vaccination were not described. Coherent information of the immunogenicity and tolerability of SARS-CoV-2 vaccination from one study of peritoneal dialysis patients and an internal control group is needed to weigh potential benefits and harms of such vaccination in this patient population.

Therefore, information on the strength of immunogenicity and tolerability of SARS-CoV-2 vaccination in peritoneal dialysis patients was not available and needed before the present study.

The findings of the present study are novel with respect to the graded magnitude of the SARS-CoV-2 IgG spike levels in response to COVID-19 vaccination in peritoneal dialysis patients compared with normal population. While seroconversion rates (spike IgG level >50 AU/ml) were similar in both groups in the present study, peritoneal dialysis patients showed lower immunogenicity as they were less likely to reach a higher spike IgG cut-off value (>1000 AU/ml) compared with medical personnel. This cut-off value was considered a likely indication of better protection against COVID-19. In our study, a threefold higher spike IgG level was found in medical personnel compared with patients, whereas this ratio was 1.5 times higher in a recent report. SARS-CoV-2 spike IgG levels of peritoneal dialysis patients observed in the present study appeared to be similar or higher compared with that recently reported in hemodialysis patients; however in these studies, immunogenicity of vaccines in normal population and tolerability of vaccination in peritoneal dialysis patients or normal population was not reported. The results of the present study can be explained, at least in part, by the shorter time between the first and second vaccinations, the different spike IgG assays, and the SARS-CoV-2 vaccines used compared with the recent report.

### TABLE 1 SARS-CoV-2 antibody levels in study participants before and after 1st or 2nd SARS-CoV-2-vaccination

|                  | COVID-19 naïve Peritoneal dialysis patients | COVID-19 naïve Medical personnel |
|------------------|--------------------------------------------|----------------------------------|
|                  | Before 1st vaccination                      | Before 1st vaccination |
|                  | 2 weeks after 1st vaccination               | 2 weeks after 1st vaccination |
|                  | 6 weeks after 2nd vaccination               | 6 weeks after 2nd vaccination |
| **spike IgG, AU/ml** | 0.4 (0.0–3.3)                              | 0.3 (0.0–6.2)                   |
| **spike IgM, Index** | 0.0 (0.0–0.1)                              | 0.0 (0.0–0.1)                   |
| **IgG Nucleocapsid, Index** | 0.0 (0.0–0.1) | 0.0 (0.0–0.1) |

|                  | Before 1st vaccination                      | Before 1st vaccination |
|                  | 2 weeks after 1st vaccination               | 2 weeks after 1st vaccination |
|                  | 6 weeks after 2nd vaccination               |
|                  | 6 weeks after 2nd vaccination               |
| **spike IgG, AU/ml** | 1437 (775–5261)                             | 4577 (1529–9871)          |
| **spike IgM, Index** | 0.1 (0.0–0.2)                              | 0.3 (0.2–1.2)              |
| **IgG Nucleocapsid, Index** | 0.0 (0.0–0.1) | 0.1 (0.1–0.4) |
Spike IgG levels were low after the first vaccination in both study groups, highlighting the need for an additional SARS-CoV-2 booster vaccination. Finally, as expected, immunosuppressed peritoneal dialysis patients experienced fewer and less severe side effects to vaccination than immunocompetent medical personnel. However, in the present study, fewer local (1st vaccination: 36% vs. 80%; 2nd vaccination: 30% vs. 60%) but slightly more frequent systemic side effects (1st vaccination: 11% vs. 6%; 2nd vaccination: 9% vs. 7%) were observed compared with a recent study reporting the tolerability of SARS-CoV-2 vaccination in 20 peritoneal dialysis patients. This finding might be partly explained by different types of vaccines used in both studies, with a mix of vectored and mRNA vaccines in the present study and only mRNA vaccines in the previous study. Further comparison with the previous study is not possible because characteristics of peritoneal dialysis patients were not reported in detail.
The results of the present study may have several implications. Vaccine breakthroughs observed in the normal population can also be expected in dialysis patients. This may also be true for peritoneal dialysis patients, who are similarly likely to fail to respond to hepatitis B vaccination as hemodialysis patients.9 The results of the present study demonstrate effective and safe immunization against COVID-19 in peritoneal dialysis patients and support the notion that COVID-19-naive peritoneal dialysis patients should be prioritized for spike IgG antibody profiling and, potentially, additional SARS-CoV-2 booster vaccinations.22,23 The results of the present study may help to dispel patients’ doubts and reduce their reluctance to receive SARS-CoV-2 vaccination. Finally, our data underscore the urgent need for similar studies to evaluate the immunogenicity and tolerability of SARS-CoV-2 vaccine in at-risk populations to inform future vaccination strategies.

The present study has several strengths and limitations. The use of vaccinated COVID-19-naive medical personnel as controls in the present study facilitated interpretation of the immunogenicity and tolerability of SARS-CoV-2-vaccination in peritoneal dialysis patients. However, the generalizability of the study results is limited by the relatively small number of participants. Distribution of age, gender and type of SARS-CoV-2 vaccine was different in peritoneal dialysis patients compared to medical personnel, a fact which complicates the interpretation of the findings of the study. Sampling for SARS-CoV-2 spike IgG measurement was missed in several patients due to sporadic sampling during routine medical presentation of peritoneal dialysis patients.
patients. We were unable to determine cell-related immunity parameters but measured the kinetics of SARS-CoV-2 spike IgG levels before, 2 weeks after first, and 6 weeks after the second vaccination. Finally, measurement of Nucleocapsid-19 IgG level improved assessment of current COVID-19 status, which is essential for interpretation of vaccine-derived SARS-CoV-2 spike IgG levels.

In summary, SARS-CoV-2 vaccination in COVID-19-naive peritoneal dialysis patients appeared to induce a very high rate of seroconversion but a substantially lower rate of patients with a strong response compared with medical personnel. Vaccination appeared to be safe in the peritoneal dialysis patients studied. We conclude that the humoral response of peritoneal dialysis patients to SARS-CoV-2 vaccination requires special attention and possibly further booster vaccination for adequate protection against COVID-19, if confirmed in larger studies.

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|                         | 1st vaccination | 2nd vaccination |
|-------------------------|-----------------|-----------------|
|                         | SARS-CoV-2 naïve | SARS-CoV-2 naïve |
|                         | PD patients     | Medical personnel |
|                         | (N = 28)        | (N = 28)        |
| Local reactions         |                 |                 |
| Pain at injection site  | 10              | 23              | <0.001 | 7       | 23              | 0.013 |
| Arm swelling            | 1               | 0               | >0.99  | 1       | 0               | >0.99 |
| Systemic reactions      |                 |                 |
| Headache                | 2               | 17              | <0.001 | 0       | 12              | <0.001 |
| Chills                  | 1               | 7               | 0.025  | 0       | 3               | 0.23  |
| Fever                   | 0               | 7               | 0.004  | 0       | 3               | 0.23  |
| Fatigue                 | 3               | 13              | 0.003  | 1       | 9               | 0.010 |
| Muscle pain             | 1               | 8               | <0.001 | 0       | 5               | 0.050 |
| Joint pain              | 2               | 13              | 0.040  | 0       | 9               | 0.002 |
| Dizziness               | 1               | 6               | 0.10   | 0       | 2               | 0.49  |
| Nausea and emesis       | 0               | 4               | 0.051  | 1       | 2               | >0.99 |
| Other complaints        | 0               | 3               | 0.11   | 0       | 2               | 0.49  |
| Use of medication or medical presentation | | |
| Intake of drugs against side effects | 2 | 14 | <0.001 | 0 | 9 | 0.002 |
| Medical present. Due to side effects | 0 | 3 | 0.11 | 0 | 1 | >0.99 |
| ECG or lab. Values due to side effects | 0 | 0 | >0.99 | 0 | 0 | >0.99 |
| Emergency room presentation due to side effects | 0 | 0 | >0.99 | 0 | 0 | >0.99 |
| Hospital admission due to side effects | 0 | 0 | >0.99 | 0 | 0 | >0.99 |
| Sick leave due to side effects | 0 | 1 | 0.49 | 0 | 0 | >0.99 |
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