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Original Communication

High-Dose Intravenous Vitamin C Treatment: A 10-Year Prospective Cohort Study

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Abstract

Background: Oxidative stress is increasingly recognized as a key factor in diseases such as cancer, infections, and chronic pain. High-dose intravenous vitamin C (IVC) increases plasma levels more than oral intake and is gaining attention as a potential therapy. However, the effects and tolerability of IVC in routine clinical practice remain poorly understood. **Methods**: This 10-year multicenter observational High-Dose Intravenous Vitamin C Treatment Cohort (HIVITC) study (2012–2022) included 5721 patients who received an average of 7.5 g of IVC per week for vitamin C deficiency. The study assessed underlying diseases (UDs), symptom changes, and adverse events in accordance with Good Clinical Practice (GCP), the guideline for Strengthening the reporting of observational studies in epidemiology (STROBE), and the Declaration of Helsinki. **Results**: The concentration of vitamin C (Vit C) was below an adequate level (<50 µmol/L) in 83% of 1295 patients with laboratory-verified Vit C status. Patients with low plasma Vit C concentrations (≤22.9 µmol/L) reported significantly higher symptom intensity. During the IVC treatment period, the prevalence of Vit C deficiency and hypovitaminosis decreased from 36.6% to 7% in a subgroup of 142 patients. The most common UDs were linked to infections. Significant reductions in sum scores were observed for non-specific symptoms (tiredness/fatigue, sleep disorders, depression, lack of concentration), pain, and the most common disease-specific symptoms by the end of the treatment period ($p < 0.0001$). Safety data showed very good tolerability (99.1%), with only 17 non-serious adverse events reported. **Conclusions**: This study provides a robust body of real-world data (RWD) demonstrating the excellent safety profile of high-dose IVC and the association of this therapy with symptom improvement in the general population with various UDs.

Keywords: high-dose intravenous vitamin C (IVC); vitamin C; oxidative stress; ascorbic acid deficiency; infections; pain; fatigue; headache; sore throat; rhinitis

1. Introduction

Most animals produce vitamin C (Vit C) endogenously and can adjust the synthesis rate according to the level of demand. Humans lost this ability due to loss of function mutations in L-gulono-γ-lactone oxidase, the key enzyme that catalyses the final step in Vit C biosynthesis [1].

The daily demand for Vit C must therefore be covered via nutrition or additional supplementation to maintain physiological amounts throughout the body. The recommended dietary allowance (RDA) of Vit C in the US is 75 mg for women and 90 mg for men, while in Germany it is slightly higher (95 mg for women and 110 mg for men) [2,3]. A deficiency of Vit C is known as scurvy, which presents clinically with symptoms such as haemorrhages in the skin and mucous membranes, musculoskeletal pain, infections, and poor wound healing. Determination of Vit C plasma concentration in patients with scurvy revealed concentrations of <11 µmol/L [4]. Plasma concentrations between 11–23 µmol/L have been characterized as hypovitaminosis C. Early non-specific symptoms include fatigue, pain, irritability and loss of appetite, and have been significantly associated with all-cause mortality [4,5]. A suboptimal or inadequate Vit C status is assumed for plasma concentrations ranging from 23–50 µmol/L, whereas the optimal Vit C plasma concentration for healthy individuals is thought to be around 70 µmol/L [4].

An increased need for Vit C may correlate with increased oxidative stress. This is defined as an imbalance between the production of reactive oxygen species (ROS), caused by a variety of disease states and exogenous factors, and the ability to neutralize them [6]. ROS act as second messengers in redox signalling, but at high concentrations they can damage proteins, nucleic acids, and lipids [7]. To combat cellular damage, excess free radicals are usually neutralized by cellular scavenger molecules or potent antioxidants such as Vit C [8]. Vit C deficiency can promote a vicious cycle of increasing ROS production and decreasing cellular antioxidative capacity, which can subsequently worsen the clinical presentation of underlying diseases (UDs) associated with high ROS burden [6,7].

Low Vit C concentrations have been observed in a plethora of systemic diseases, including cancer, rheumatoid

arthritis, diabetes mellitus, trauma and infections [9,10,11,12,13,14]. Restoration of Vit C concentrations has the potential to alleviate disease symptoms and improve the quality of life of affected patients, providing a rationale for further research into high-dose intravenous vitamin C (IVC) therapy [15,16,17,18,19]. This is especially important for diseases that present with non-specific symptoms such as tiredness, fatigue, sleep disorders, depression and lack of concentration, which are often not targeted by medication. It is important to realize that these non-specific symptoms overlap with those of Vit C deficiency.

In practice, Vit C deficiency is treated not only with oral supplements, but also with intravenous administration. The reasons for this are mostly related to compliance and bioavailability. High pharmacological Vit C blood concentrations can only be achieved by infusion, which quickly compensates for tissue deficiencies compared to oral supplementation [20,21,22]. The main objectives of this observational study were to:

(a) obtain data on the tolerability of intravenous therapy;

(b) identify underlying diseases (UDs) frequently associated with Vit C deficiency;

(c) document symptoms that are rather non-specific and not usually covered by standard therapy.

To the best of our knowledge, this 10-year prospective High-Dose Intravenous Vitamin C Treatment Cohort (HIVITC) study represents the largest dataset on Vit C status in various UDs. In conjunction with an assessment of the tolerability and safety of high-dose IVC treatment in routine clinical practice, this provides a valuable pool of real-world data (RWD) in the general population. The absence of a control group precluded us from drawing causative conclusions regarding the impact of high-dose IVC treatment on the progression of symptoms during the observational period. However, the value of the data generated on clinically diagnosed Vit C deficiency and laboratory-determined Vit C status in the various UDs, as well as the safety data, was not diminished by the lack of a control group.

2. Materials and Methods

2.1 Study Objectives

The aim of the study was to provide an overview of the variety and frequency of diseases associated with clinically and/or laboratory diagnosed Vit C deficiency in everyday practice. It was conducted to document the use of IVC (Pascorbin® 7.5 g, Pascoe Pharmazeutische Präparate GmbH, 35394 Giessen, Hesse, Germany) as a treatment for Vit C deficiency associated with UDs in everyday practice. Symptom progression and possible side effects were monitored during the treatment period to produce a comprehensive risk-benefit analysis.

2.2 Study Design

This prospective, multicentre, observational study was conducted by 93 physicians and natural health practitioners in Germany. The study design, concept, ethical validity and performance were based on the recommendations of the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM, German Federal Institute for Drugs and Medical Devices) and the Paul-Ehrlich-Institute in accordance with German laws and the principles of the Declaration of Helsinki and of Good Clinical Practice. The study was registered on Clinical Trials (NCT02422901) and EU PAS Number (3658). It followed the STROBE guidelines for items to be included in reports on observational studies [23].

2.3 Study Duration

The study was conducted over a period of 10 years. It started on 01 November 2012 and it ended on 31 October 2022.

2.4 Study Setting

All relevant information including study protocols, the ethical and scientific basis of the study, the allocation procedure, and the case report form (CRF) or electronic CRF (eCRF) were provided to interested physicians and natural health practitioners before the start of the study. Data was collected at the start of observation (visit 1) and after the treatment period (end of observation, visit 2) in patients with an acute UD. In patients with chronic UDs, therapists could record data at the start of observation (visit 1), during treatment (visit 2), and after the treatment period (end of observation, visit 3). Varying numbers of high-dose IVC infusions were applied by the respective physician and natural health practitioners during the treatment period.

2.5 Variables Studied

The study was conducted to document the use of Pascorbin® 7.5 g (Pascoe Pharmazeutische Präparate GmbH, 35394 Giessen, Hesse, Germany) as a treatment for Vit C deficiency associated with UDs in everyday practice. Moreover, it provides an overview of the variety and frequency of UDs, classifying them according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10 coding) [24]. Symptom progression during the IVC treatment period was monitored by analysing changes in non-specific symptoms (tiredness/fatigue, sleep disorders, depression, lack of concentration) and three individual disease-specific symptoms. Symptom intensity was evaluated by the attending therapist on a four-point rating scale (0 = not present, 1 = mild, 2 = moderate, 3 = severe). Non-specific and disease-specific symptoms were each analysed cumulatively in a sum score, which ranged from 0 to 12 points, and 0 to 9 points, respectively. Disease-specific symptoms were classified according to Medical Dictionary for Regulatory Activities (Med-

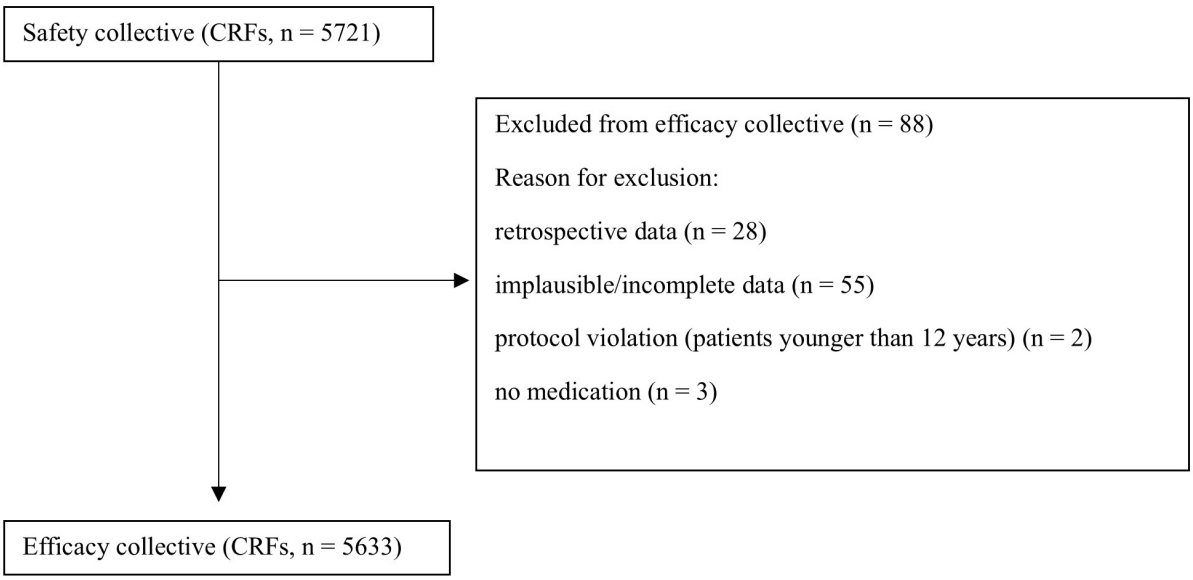


Fig. 1. Flow-chart of participant allocation.

DRA) coding (version 15.1 and higher). Additionally, the progression of symptom pain was documented by the therapist using a numeric rating scale (NRS) from 0 = no pain to 10 = extreme pain (https://europeanpainfederation.eu/measuring-pain-in-the-clinic/). For the evaluation of symptoms, only data from patients who displayed the symptom and had at least two assessments were included. The therapists documented the subjective efficacy rating by using the following scales as defined in our observational plan: 1 = high efficacy (complete regression of symptoms), 2 = good efficacy (symptoms much improved), 3 = moderate efficacy (symptoms slightly improved), 4 = no efficacy (symptoms unchanged), 5 = no efficacy (symptoms worsened). The safety and overall tolerability were assessed by the therapist as very good tolerability (no side effects), or poor tolerability (occurrence of side effects).

2.6 Eligibility Criteria for the HIVITC Study and Sample Size

Inclusion criteria for this study were: clinically and/or laboratory determined Vit C deficiency that indicated treatment with IVC (Pascorbin® 7.5 g, Pascoe Pharmazeutische Präparate GmbH, 35394 Giessen, Hesse, Germany); patient aged $\geq$12 years; and statement of consent provided by the patient. Exclusion criteria were: oxalate urolithiasis; iron storage diseases; patients recently received Red Blood Cell (RBC) transfusion; patient aged $<$12 years; pregnancy and lactation; or hypersensitivity to an ingredient (for more information, see **Supplementary Table 1** and the Summary of Product Characteristics (SmPC) of the administered drug (Pascorbin® 7.5 g, Pascoe Pharmazeutische Präparate GmbH, 35394 Giessen, Hesse, Germany). Complete and correct datasets for 5633 patients were obtained from 93 physicians and natural health practitioners. Safety information for high-dose IVC treatment was available for 88 additional Case Report Forms (CRFs), resulting in data from a total of 5721 patients for the safety assessment (Fig. 1).

2.7 Description of Statistical Methods

Descriptive statistical summaries are provided for the total population, as well as stratified by current medication for the UDs and by duration of treatment. Numeric data are described by the following statistical parameters: valid N, missing N, mean, standard deviation, minimum and maximum. Categorical data is presented by means of (absolute and relative) frequency distributions. The calculation of percentages was based on the number of patients with valid data per parameter, i.e., excluding patients with missing values. A *t*-test (two-sided) was used to analyse differences in symptom intensity (mean sum score and NRS) between groups with lower ($\leq$22.9 µmol/L) and higher ($\geq$23 µmol/L) Vit C plasma concentrations. The homogeneity of variances was assessed by the Levene test. The significance level was defined as $\alpha = 0.05$. The Statistical Package for Social Sciences (SPSS) version 24.0 Software (IBM, Armonk, New York, United States) was used for all statistical analyses performed at Pascoe pharmazeutische Präparate GmbH.

The investigated parameters were also compared between the different subgroups by means of appropriate statistical tests on an exploratory basis (two-sided with nominal significance level $\alpha = 0.05$). Additionally, 95% confidence intervals (CI) are provided for quantitative variables. All analyses were performed with the statistical analysis software (SAS) package , version 9.4 (SAS, Cary, North Carolina, United States), by an independent statistician (Gesellschaft für Therapieforschung mbH, Full-service CRO | GKM Gesellschaft für Therapieforschung mbH, Munich, Germany).

Table 1. Demographics of 5633 patients and classification of the vitamin C level in a subgroup of 1295 patients.

Characteristic	N	%
Age, mean (range in years), [n][a]	51 (12–96) [5633]	100
12–17 years	65	1.2
18–64 years	4295	76.3
≥65 years	1266	22.5
Not reported	7	0.1
Sex	5633	100
Female	3245	57.7
Male	2380	42.3
Not reported	8	0.1
Height, mean (range in cm), [n]	174 (102 to 202) [5583]	
Weight, mean (range in kg), [n]	76.5 (26 to 200) [5579]	
Vitamin C (Vit C) deficiency associated with underlying disease UD	5628	99.9
Patients with additional medication to high-dose intravenous vitamin C (IVC) treatment		
Yes	2982	52.9
No	2648	47
No data available	3	0.1
Patients with concomitant diseases		
Yes	1750	31.1
No	3883	68.9
Total number of concomitant diseases [n]	3230	
Most frequently mentioned International Statistical Classification of Diseases and Related Health Problems (ICD-10) groups [n][b]		
Endocrine, nutritional, and metabolic diseases	976	30.2
Diseases of the circulatory system	904	28
Diseases of the musculoskeletal system and connective tissue	198	6.1
Patients with medication of concomitant diseases		
Yes	1509	26.8
No	4124	73.2
Total number of medications for concomitant diseases [n]	3128	
Most frequently mentioned medications [n][c]		
Beta-receptor blockers, calcium channel blockers and inhibitors of the renin-angiotensin-aldosterone system	558	17.8
Thyroid drugs	413	13.2
Antihypertonics	267	8.5
Patients with laboratory-determined Vit C blood concentration at start of observation (visit 1)		
Yes	1295	23
No	4338	77
Classification of Vit C blood concentration [n]*,[a]		
Saturating (≥70 µmol/L)	71	5.5
Adequate (50–69.9 µmol/L)	147	11.4
Inadequate (23–49.9 µmol/L)	345	26.6
Hypovitaminosis (11–22.9 µmol/L)	182	14.1
Deficiency (0–10.9 µmol/L)	550	42.5

[a] The column percentage sums may not add up to 100 because of rounding.

[b] Percentages refer to the total number of concomitant diseases.

[c] Percentages refer to the total number of medications for concomitant diseases.

* The vitamin C (Vit C) blood concentrations were classified according to internationally accepted reference ranges [4,6].

3. Results

3.1 Descriptive Data

Correctly completed CRFs in paper or electronic form were received for 5633 patients (Fig. 1). Overall, 42.3% of patients were male and 57.7% were female. Gender was not reported in 8 cases. At the beginning of the documentation, the average age of patients was 51 years (12 to 96 years). The majority of patients (76.3%) were aged between 18 and

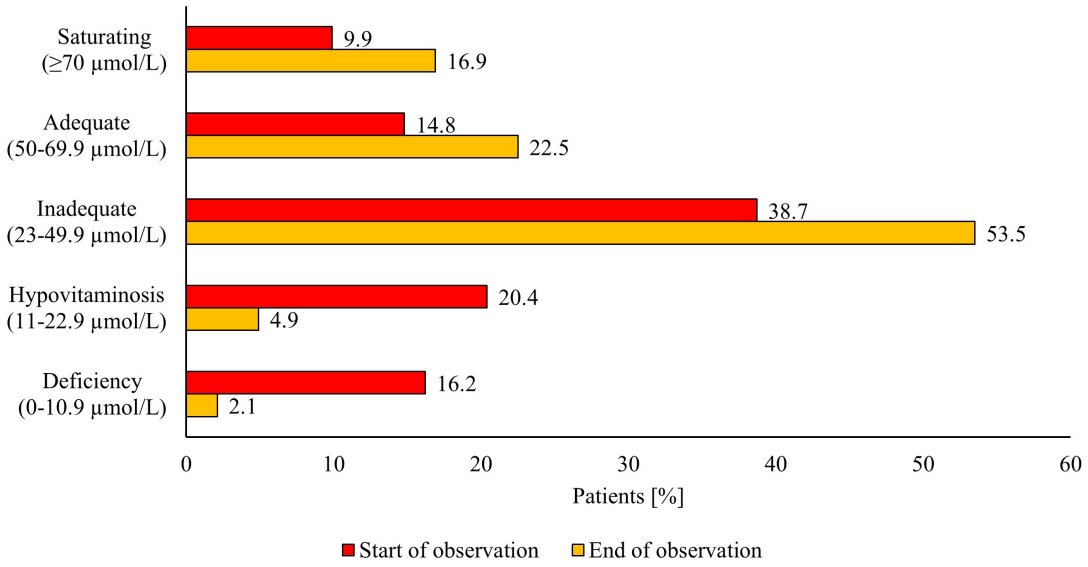


Fig. 2. Laboratory-determined Vit C blood plasma concentrations in a subgroup of patients at the start and end of observation (n = 142). The respective blood values were grouped according to the Vit C status classification, from saturating concentration to deficiency. The relative distribution of patients is shown.

64 years, 22.5% were aged 65 years or older, and 1.2% were aged 12–17 years. Age was not reported in 7 cases (0.1%) (Table 1, Ref. [4,6]).

A total of 3230 concomitant diseases were reported for 1750 of the 5633 patients. Endocrine, nutritional, and metabolic diseases were the most frequently mentioned diseases, followed by diseases of the circulatory system, musculoskeletal system, and connective tissue. Concomitant diseases were treated in 1509 patients, and a total of 3128 concomitant medications were documented. The medications used most often were beta-receptor blockers, calcium channel blockers, and inhibitors of the renin-angiotensin-aldosterone system, followed by thyroid drugs and antihypertonics (Table 1).

All patients were clinically diagnosed with Vit C deficiency by their treating physician or natural health practitioner. In 99.9% of these patients (n = 5628), the deficiency was associated with an UD. Approximately half the patients (52.9%) received medication to treat the UD (MUD), in addition to treatment with high-dose IVC. The other half (47%) received only high-dose IVC for treatment of the UD. No data were available for three patients (Table 1).

3.2 Vit C Laboratory Values

Routine laboratory diagnostics were used to determine the blood Vit C concentration in 23% of patients (1295 out of 5633 participants) at the start of the observation period (treatment with IVC at a dose of ~7.5 g/week) (Table 1). Of these, 83% had Vit C values below the adequate concentration (<50 µmol/L). A direct comparison of blood Vit C concentration between the start and end of the observation period was available for 142 patients. At the start, 36.6% were in the range of deficiency or hypovitaminosis (n = 52), while 38.7% showed inadequate plasma concentrations. At the end of the observation period, the incidence of deficiency and hypovitaminosis decreased to 7% of patients. Half the patients with deficiency or hypovitaminosis (0–22.9 µmol/L) entered the category of inadequate Vit C concentration (50%; 26 of 52). An adequate or saturating concentration was reached by 38.5% of patients (20 of 52), while 11.5% of patients (6 of 52) remained in the range of deficiency or hypovitaminosis (Fig. 2).

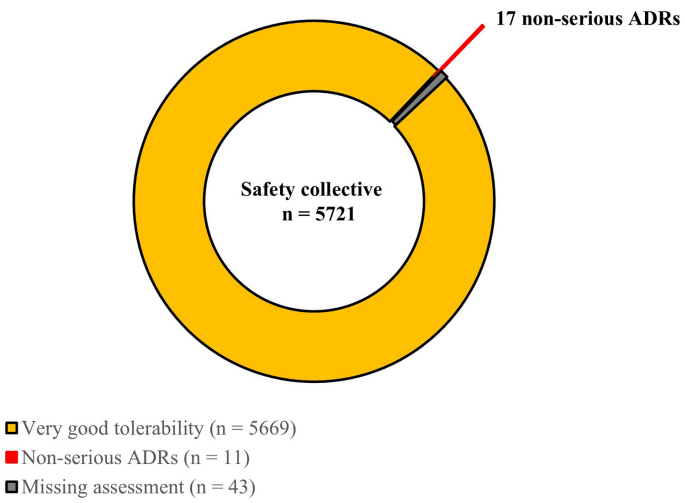
3.3 Treatment Duration and Dosage

Because of the nature of this observational study, the duration of treatment and application rate was an estimation only (min. documented 2 visits and max. documented 3 visits). The mean duration of treatment was 6.9 weeks, with a clear difference between cases with acute UD (mean: 1.7 weeks) and chronic UD (mean: 18.4 weeks). On average, patients received one infusion of high-dose Vit C (7.5 g) per week (ratio of average number of infusions to average duration of therapy).

3.4 Global Assessment of Efficacy and Tolerability

At the end of the observation period, the global treatment efficacy of high-dose IVC (7.5 g) was subjectively assessed by the respective therapist and patient in a total of 5623 cases (99.8%) via a five-point-rating scale. In the large majority of patients, the subjective efficacy was assessed as good (30.6%, n = 1719) or very good (62.7%, n = 3525).

Tolerability data were analysed in 5721 patients and rated as very good in the large majority (99.1%, n = 5669). A total of 17 non-serious adverse drug reactions (ADRs) were documented in 11 patients. Two of these patients



Preferred Term (PT)-Level of ADRs
Diarrhea
Urinary tract infection
Osteitis
Pulpitis dental
General physical health deterioration
Neuritis
Vertigo
Blood glucose increased
Blood glucose false positive
Dizziness
Lymphadenopathy
Skin reaction
Tiredness
Feeling cold
Rash
Tachycardia
Insomnia

Fig. 3. Global assessment of intravenous vitamin C (IVC) treatment tolerability. Data on tolerability were analysed in 5721 patients. Two of the 11 patients with non-serious ADRs reported very good tolerability and were thus included in the 5669 patients. The 17 non-serious adverse drug reactions (ADRs) are listed according to the preferred term (PT) level.

(0.03%) reported very good tolerability, although an ADR occurred during treatment (Fig. 3). Non-serious ADRs occurred in 5 patients without concomitant disease, and in 6 patients receiving medications for concomitant disease. Information on tolerability was missing for 43 patients (0.75%). No serious side effects occurred.

3.5 Non-Specific Symptoms

All participants were asked to document the occurrence and intensity of four non-specific symptoms (tiredness/fatigue, sleep disorders, depression, lack of concentration). These were documented and analysed for 5420 patients. Changes in the mean score for the severity of non-specific symptoms, and the mean sum score change between the start and end of observation (treatment period with IVC at a dose of ~7.5 g/week), were significant for the total population and for all subgroups analyzed (with/without MUD, different treatment durations) (Table 2, **Supplementary Table 2**).

Further analysis of the data revealed that the non-specific symptoms of tiredness/fatigue, sleep disorders, depression and lack of concentration at the end of observation were no longer present in 66.3%, 68.9%, 67.5% and 77.7% of patients, respectively (Fig. 4A).

3.6 Assessment of Symptom Pain

The occurrence and intensity of pain were documented according to a numeric rating scale. Data on the progression of pain from the start to end of observation (treatment period with IVC at a dose of ~7.5 g/week) were available for 3928 patients, with improvement detected in ~95% of patients. In the few remaining patients, the symptoms either did not change (3%), or continued to deteriorate (~2%). The mean sum score for the total population and for all subgroups analyzed (with/without MUD, different treatment durations) improved significantly between the start and end of observation. The mean sum score for the total population improved by 3.7 points (Table 2, **Supplementary Table 3**).

3.7 Disease-Specific Symptoms

The physicians and natural health practitioners documented the occurrence and intensity of up to three individual disease-specific symptoms. Data were available for 5248 patients (93.2% of 5633) and 12,304 specific symptoms. The change from the start to the end of observation (treatment period with IVC at a dose of ~7.5 g/week) was determined. MedDRA coding resulted in 448 various preferred terms (PTs). Sore throat, headache, and rhinitis were the most frequent disease-specific symptoms showing significant improvement in the mean score for symptom severity during the treatment period (Table 2). Moreover, the mean sum score change between the start and the end of observation was significant for all specific symptoms in the total population, as well as all subgroups (Table 2, **Supplementary Table 4**). After the treatment period, the most frequent disease-specific symptoms of sore throat, headache and rhinitis were completely absent in 94.8%, 77.0% and 87.8% of patients, respectively (Fig. 4B).

Table 2. Intensity and mean score change of non-specific symptoms, pain and disease-specific symptoms in the total population from the start to the end of the IVC treatment period.

Symptoms	Patients (n) (Start/End/ Difference) [%]	Mean sum score (SD) [95% CI]		Difference [a] (SD) [95% CI]	*p*-value*
		Start of observation	End of observation		
Non-specific symptoms[b]					
Tiredness/Fatigue [%]	4544/4547/4544 [83.84]	1.9 (0.82) [1.91 to 1.96]	0.4 (0.64) [0.39 to 0.43]	–1.5 (0.84) [–1.55 to –1.50]	<0.0001
Sleep disorders [%]	3643/3644/3642 [67.20]	1.8 (0.86) [1.81 to 1.87]	0.4 (0.66) [0.37 to 0.42]	–1.4 (0.91) [–1.47 to –1.41]	<0.0001
Depression [%]	2424/2426/2424 [44.72]	1.8 (0.83) [1.72 to 1.79]	0.4 (0.64) [0.37 to 0.42]	–1.4 (0.90) [–1.39 to –1.32]	<0.0001
Lack of concentration [%]	3605/3608/3605 [66.51]	1.7 (0.78) [1.64 to 1.69]	0.3 (0.55) [0.25 to 0.29]	–1.4 (0.82) [–1.42 to –1.37]	<0.0001
Mean sum score of all non-specific symptoms [%][c]	5109/5102/5101 [94.11]	5.1 (3.26) [4.97 to 5.15]	1.0 (1.73) [0.98 to 1.07]	–4.0 (2.96) [–4.12 to –3.96]	<0.0001
Pain [%][b,c]	3928/3933/3928 [72.47]	4.7 (2.94) [4.65 to 4.83]	1.1 (1.77) [1.01 to 1.12]	–3.7 (2.73) [–3.76 to –3.59]	<0.0001
Disease-specific symptoms[d]					
Sore throat [%]	863/863/863 [16.44]	1.9 (0.74) [1.83 to 1.93]	0.1 (0.27) [0.04 to 0.08]	–1.8 (0.75) [–1.87 to –1.77]	<0.0001
Headache [%]	756/757/756 [14.41]	2.2 (0.75) [2.10 to 2.20]	0.3 (0.56) [0.24 to 0.32]	–1.9 (0.84) [–1.93 to –1.81]	<0.0001
Rhinitis [%][c]	748/748/748 [14.25]	1.8 (0.76) [1.70 to 1.81]	0.1 (0.37) [0.11 to 0.16]	–1.6 (0.74) [–1.67 to –1.57]	<0.0001
Mean sum score of all disease-specific symptoms [%][c]	5246/5248/5246 [99.96]	4.9 (2.26) [4.87 to 4.99]	0.9 (1.37) [0.84 to 0.91]	–4.1 (2.27) [–4.12 to –3.99]	<0.0001

Abbreviations: SD, standard deviation; 95% CI, 95% confidence interval.

[a] The difference was calculated as the symptom intensity at the end of observation minus the symptom intensity at the start of observation. Negative values indicate a reduction in symptom intensity.

[b] Percentages refer to a total of 5420 patients with non-specific symptoms.

[c] Calculations may differ because of rounding.

[d] Percentages refer to a total of 5248 patients with disease-specific symptoms.

*one-sample *t*-test for the differences between baseline and final visit.

Non-specific and disease-specific symptom intensity was evaluated on a 4-point ranking scale (0 = not present, 1 = mild, 2 = moderate, 3 = severe). Accordingly, the calculated sum score ranged from 0 to 12 points and from 0 to 9 points, respectively. Symptom pain was evaluated on a 10-point numeric rating scale.

Further categorization of all PTs resulted in 24 different system organ classes (SOCs), including (1) respiratory thoracic and mediastinal disorders, (2) general disorders and administration site conditions, and (3) nervous system disorders (**Supplementary Table 5**). The most common symptoms in the top three SOCs, besides the most frequently mentioned disease-specific symptoms, were cough (n = 743), asthenia (n = 559), hypokinesia (n = 207) and malaise (n = 185).

3.8 Symptom Intensity is Significantly Increased in Patients With Low Vit C Plasma Concentration

Patients with laboratory-determined Vit C concentrations at the start of observation were pooled into two groups: those with hypovitaminosis or deficiency ($\leq$22.9 µmol/L), and those with inadequate, adequate or saturating Vit C plasma concentrations ($\geq$23 µmol/L). Differences in the intensity of non-specific symptoms, disease-specific symptoms, and pain were then compared between the two groups. The symptom intensity of non-specific and disease-specific symptoms (mean sum score) was significantly higher ($p < 0.001$) in the lower Vit C group compared to the higher Vit C group (6.9 vs. 3.8, and 6.4 vs. 4.2, respectively) (Fig. 5A,B). Similarly, the level of pain (NRS) was significantly higher ($p < 0.001$) in patients with low Vit C blood concentrations (6.7 vs. 4.1) (Fig. 5C).

3.9 Classification of Underlying Disease (UD)

Coding for an UD according to ICD-10 resulted in a broad spectrum of different ICD-10 groups. UDs were most frequently mentioned in ICD-10 groups J00–J99 (diseases of the respiratory system) and A00–B99 (certain infectious and parasitic diseases). ICD-10 coding of the UD was not possible in 16 patients (0.3%) (Fig. 6, **Supplementary Table 6**).

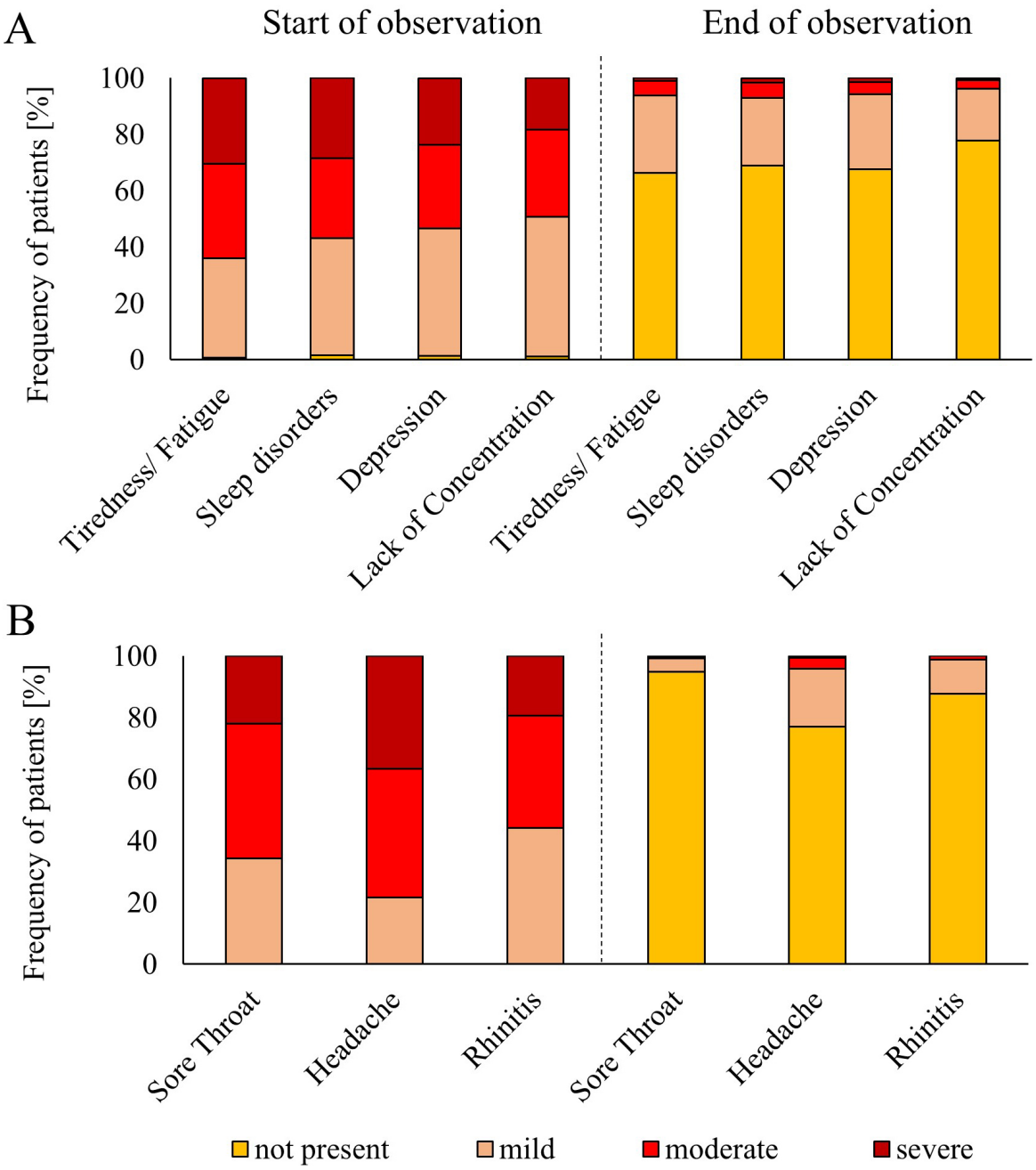


Fig. 4. Symptom intensity at the start and end of observation (treatment period with IVC at a dose of ~7.5 g/week). (A) Intensity of non-specific symptoms. The percentage of valid patient data is shown. 100% represents 4544 patients with tiredness/fatigue, 3642 patients with sleep disorders, 2424 patients with depression, and 3605 patients with lack of concentration. (B) Intensity of the most frequently mentioned disease-specific symptoms. The percentage of valid patient data is shown. 100% represents 863 patients with sore throat, 756 patients with headache, and 748 patients with rhinitis.

4. Discussion

The main goals of this 10-year HIVITC study were to collect data on the tolerability and safety of administering high-dose IVC in routine practice, and to identify diseases that frequently accompany Vit C deficiency, as well as those that it may contribute to or exacerbate. However, the observational nature of the study and the absence of a control group precluded causal associations between the observed symptom improvements and IVC treatment. Nevertheless, the results suggest that this therapy may have potential benefits for symptoms such as tiredness/fatigue, sleep disorders, depression, and lack of concentration. Unlike disease-specific symptoms, these symptoms are not usually addressed by standard medication.

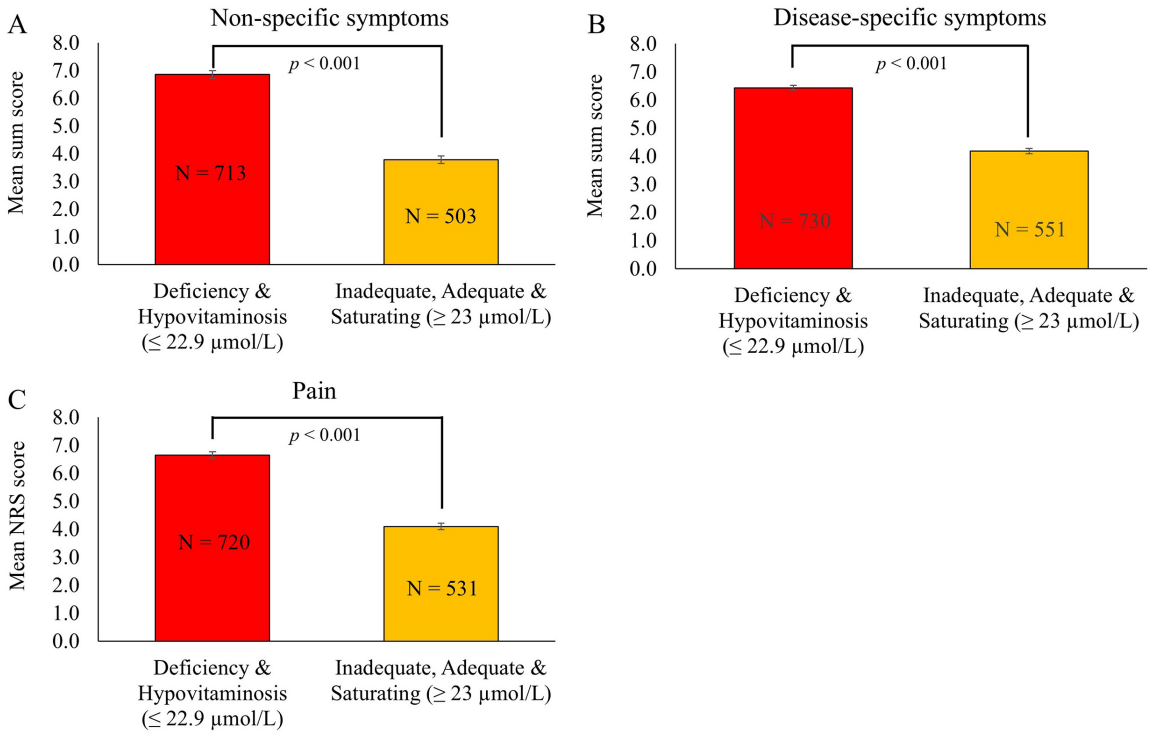


Fig. 5. Symptom intensity and Vit C plasma concentration. Patients with Vit C deficiency or hypovitaminosis (≤22.9 µmol/L), and those with inadequate, adequate or saturating (≥23 µmol/L) Vit C concentrations were pooled into two groups. The mean sum scores for (A) non-specific symptoms, (B) disease-specific symptoms, and (C) mean NRS score for pain were compared between the two groups. N = total number of patients in each group/symptom class. Error bars represent the standard error. Significant differences in all symptoms were observed between the groups ($p < 0.001$, *t*-test).

4.1 Safety and Tolerability

In the underlying study, high-dose IVC (7.5 g) was administered on average once per week for 7 weeks, with a mean of 1.7 weeks for acute UD and 18.4 weeks for chronic UD.

The treatment was reported to be very well tolerated by 99.1% of included patients. However, 17 non-serious ADRs were reported in 11 patients, which did not negatively impact the benefit-risk assessment. The safety data from this study suggests that IVC treatment was safe when used alongside medications for concomitant diseases in various patient subgroups. These results are consistent with several clinical studies which reported good safety data for up to 100 g doses of IVC in healthy controls and oncology patients [14,19,20,25,26]. IVC may therefore have potential applications for the treatment of various medical conditions and as an adjuvant therapy. Further evaluation is needed to assess how Vit C treatment affects the benefit-risk ratio in high-risk groups with known contraindications and medical conditions requiring special precautions [27].

4.2 Vit C Deficiency and UD

The prerequisite for starting high-dose IVC therapy was a diagnosis of Vit C deficiency by the treating physician or natural health practitioner. Laboratory data on Vit C concentrations were available for 1295 patients (23% of cases), indicating that Vit C deficiency is predominantly diagnosed symptomatically in Germany. Laboratory testing at visit 1 showed that 42.5% of patients had Vit C deficiency, and a further 40.7% had hypovitaminosis or inadequate Vit C status.

Data on Vit C blood concentrations at the end of the observation period were available for 142 patients, most of whom had chronic diseases (93.7%). Despite an overall improvement in Vit C levels in patients with hypovitaminosis or deficiency (0–22.9 µmol/L), the majority remained within the inadequate concentration range. This may be due to chronic conditions, which are often associated with increased oxidative stress and potentially increased Vit C requirements. Therefore, Vit C supply should be closely monitored, and regular supplementation may be necessary for certain patients.

The most frequently reported UDs associated with the clinical diagnosis of Vit C deficiency were acute and recurrent viral infections of the respiratory system (ICD-10 group J00–J99), and infections with different herpesviruses (Epstein-Barr virus, *Herpes zoster*) (ICD-10 group A00–B99). Additionally, these patients suffered from several other UDs in different ICD-10 groups, including emotional

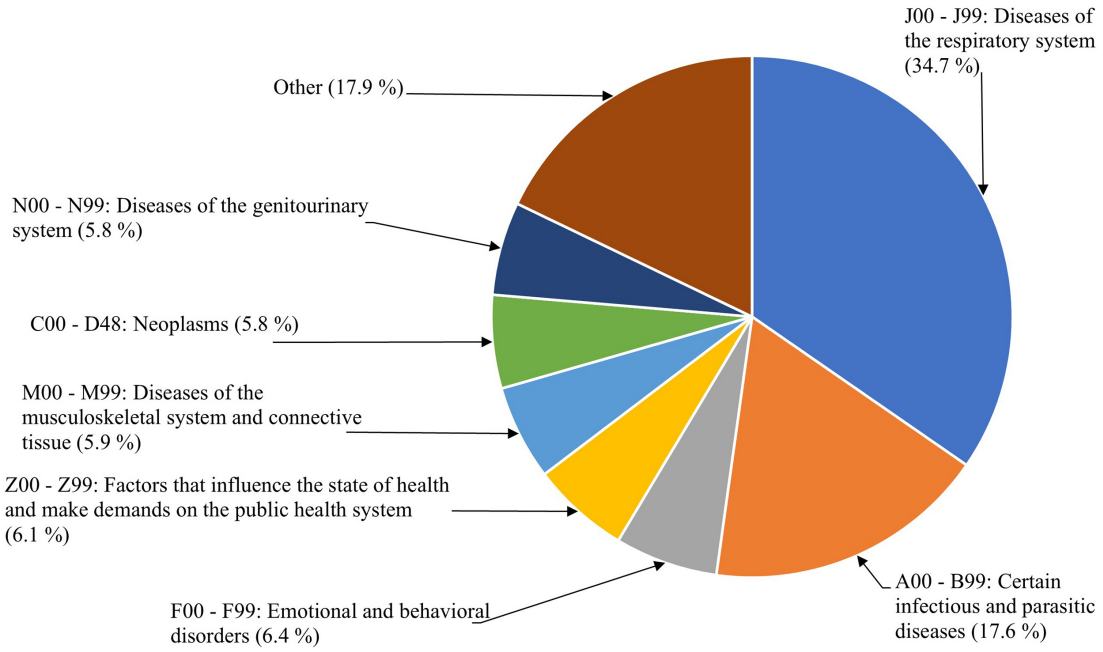


Fig. 6. Percentage distribution of UDs according to ICD-10 groups. A total of 5628 UDs were reported and classified into the respective ICD-10 group. The most frequent UDs were classified into the ICD-10 groups "diseases of the respiratory system" (34.7%, n = 1951) and "certain infectious and parasitic diseases" (17.6%, n = 989). Five other ICD-10 groups shown in the figure include reported UDs with n $\geq$325. ICD-10 groups containing n $<$325 UDs and UDs not applicable to ICD-10 are included in "other". For further information, see **Supplementary Table 6**.

and behavioural disorders (6.4%), musculoskeletal diseases (5.9%), and neoplasms (5.8%). The association of Vit C deficiency with various diseases is well documented in the literature, especially for infectious diseases such as COVID-19, as well as for neoplasia and rheumatoid diseases [12,13,14,17]. However, patients in our observational study were also taking several medications for concomitant diseases, and no information on dietary intake or supplement use was collected. These factors may be potential confounders that contribute to reduced Vit C blood concentrations, independent of any UD.

4.3 Non-Specific Symptoms and Pain

Since the non-specific symptoms examined in this study (tiredness/fatigue, sleep disorders, depression, and lack of concentration) overlap with those of Vit C deficiency, the observed alleviation of symptoms may be interpreted as a consequence of treating the deficiency. These non-specific symptoms occur in many diseases and can lead to significant suffering, particularly in chronic conditions such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), fibromyalgia, autoimmune diseases, and cancer [14,28,29,30]. It is generally agreed that increased oxidative stress contributes to many diseases. However, effective therapies that target non-specific symptoms to improve patient quality of life remain scarce.

Several studies in the literature have investigated the effect of IVC on symptoms such as fatigue, sleep disorders, depression, and lack of concentration. The efficacy of treating fatigue with high-dose IVC was summarized in a recent review [31]. In 7 out of 9 clinical studies with a total of 720 participants, a significant improvement in fatigue was observed with IVC, regardless of the UD severity. Most trials examined the treatment of fatigue in the context of cancer therapy, whereas others included patients with infections, allergies, post-operative recovery, and apparently healthy individuals.

There is also growing evidence for the therapeutic efficacy of IVC in preventing and reducing pain in complex regional pain syndrome (CRPS), post-herpetic neuralgia, infection-related pain, post-surgery, and cancer patients [32]. For infection-related pain, particularly during *herpes zoster* infection, a multicentre prospective cohort study reported notable pain relief from treatment with high-dose IVC alone. In addition, peri- or post-operative application of IVC significantly reduced post-operative pain and the need for analgesics such as opioids after surgery. Observational studies in cancer patients have also shown a significant reduction in pain with high-dose IVC as an adjunct therapy [32]. Data from the present study showed that patients with Vit C plasma concentrations in the hypovitaminosis and deficiency range ($\leq$22.9 µmol/L) experienced a significantly higher intensity of non-specific symptoms and pain at the start of observation. This, together with the potential association between high-dose IVC treatment and improvement in the aforementioned symptoms

and pain, suggests that IVC is an effective and safe therapeutic intervention. Two main effects of Vit C are currently under consideration as possible mechanisms of action: firstly, the antioxidant and anti-inflammatory effects of Vit C protect against tissue damage, and secondly, Vit C functions as an enzymatic co-factor for the synthesis of pain-reducing neurotransmitters and peptides such as serotonin, dopamine, noradrenaline and endorphins. In the absence of adequate levels of Vit C, these functions cannot be fully performed, suggesting that pain is a symptom of Vit C deficiency [16,32].

4.4 Specific Symptoms

Sore throat, headache and rhinitis were the most common symptoms of acute and/or recurrent infections, sinusitis, bronchitis or pollinosis, and other allergies, reported as UDs (ICD-10 group J00–J99; A00–B99). The main causes for developing the reported symptoms are viral infection, predominantly rhinoviral, but also some bacterial infections [33]. For acute infections such as the common cold, the evidence is mainly from oral Vit C supplementation, which shows highly variable efficacy in the treatment of symptoms [34].

Infections have often been associated with Vit C deficiency, especially in pneumonia and COVID-19 [26,35]. A recent study compared the blood concentrations of four vitamins between a cohort of COVID-19 patients with different severities and a control group of uninfected individuals. The survival analysis showed that plasma ascorbate below 11.4 µM was associated with longer hospitalization and a higher risk of death [13]. In line with these findings, our study demonstrated a significantly higher intensity of disease-specific symptoms in patients with low Vit C plasma concentrations ($\leq$22.9 µmol/L) at the start of observation. These data suggest that high-dose IVC treatment aimed at restoring Vit C levels in affected patients may be beneficial. Two meta-analyses of Vit C treatment in COVID-19 patients were published in 2022. One study found that Vit C significantly reduced the severity and mortality of COVID-19 patients, with no significant effect on the length of hospital stay [36]. The other found that Vit C treatment was associated with reduced mortality and led to an increased length of ICU stay [37]. Both meta-analyses included RCTs and retrospective studies conducted mainly with IVC. However, there was a large overlap in the studies analyzed by both meta-analyses. In contrast, the LOVIT-COVID trial reported low efficacy for high-dose IVC in the treatment of COVID-19 patients in terms of organ support-free days and survival to hospital discharge [38]. These conflicting results indicate that more preclinical and clinical research is needed to understand the mechanisms behind the observed beneficial effects of high-dose IVC in critically ill patients. Further research is also needed to determine when high-dose IVC treatment may be potentially harmful.

Vit C is an important immunomodulator that supports infection control processes and reduces excessive inflammation [15,39]. The beneficial effects of Vit C on disease progression may be achieved by modulating pro-inflammatory mediators such as interleukins (IL 1, 6, 8) and TNFα, by attenuating NF-κB activation (through reduction of ROS), and by up-regulating interferon levels, which are the key host defence proteins for combating infections [17]. Similar to pro-inflammatory cytokines, histamines can activate immune responses, leading to typical allergic symptoms such as rhinitis [40]. Interim subgroup analysis of the data from this study revealed a significant improvement in allergic symptoms when high-dose IVC was applied [18]. The beneficial effect of Vit C in allergies is likely due to its histamine-reducing effect, as observed in patients with infections and acute allergies [41].

4.5 Strengths and Weaknesses

The main strength of this study is the large volume of data collected. Except for medication contraindications, patient enrolment was not significantly restricted by the inclusion and exclusion criteria. There has recently been increasing interest in real-world data (RWD) generated by observational studies. The less controlled study design enabled data on the safety and efficacy of drugs to be collected in a large population with multiple comorbidities, in contrast to controlled clinical trials involving rigorously selected patients. Hence, the large number of participants represents a strong pool of data and a valuable complement to controlled clinical trials for monitoring the safety and efficacy of drugs following development and marketing. The European Medicines Agency (EMA) recently drafted the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M14 guideline on the use of RWD in pharmaco-epidemiological studies to assess the safety of medicines, highlighting the importance of observational studies with RWD [42].

Nevertheless, the absence of a control arm in this study significantly limits the ability to draw causal conclusions. Although improvements in non-specific symptoms such as fatigue and pain during the IVC treatment period align with findings from other studies, the lack of a control group means there is no direct evidence that such improvements were caused by IVC treatment.

The most frequently reported disease-specific symptoms (sore throat, headache, and rhinitis) are typical of the common cold and of acute or recurrent infections, which are generally self-limiting conditions. Patients in this observational study may have benefited from IVC treatment, consistent with the results from a meta-analysis of randomized, double-blind trials showing that Vit C significantly reduced the severity of common cold symptoms compared to controls [43]. However, due to the absence of a control group, the observed trend towards improvement cannot be attributed directly to IVC treatment.

Moreover, a potential placebo effect from study participation cannot be excluded. However, this has minimal impact with respect to the safety and tolerability assessment of IVC treatment, which was the main aim of our observational study.

Another limitation of the study is the lack of data on dietary intake, since malnutrition may also contribute to Vit C deficiency. Moreover, the non-interventional study design did not allow strict control over blood sample handling, with sample management relying on the diligence of the respective physicians or natural health practitioners and adherence to GLP.

5. Conclusions

To the best of our knowledge, this observational HIV-ITC study represents the largest dataset on high-dose IVC treatment in routine clinical practice. It provides comprehensive population data that confirms the very good safety profile of high-dose IVC treatment, even in combination with other remedies used to treat comorbidities. More than half of the diseases associated with Vit C deficiency affect the immune system, particularly the upper respiratory tract. The current study showed that patients with low Vit C plasma concentration had a significantly higher symptom burden. The results also suggest positive associations between high-dose IVC treatment and improvements in non-specific and disease-specific symptoms, as well as pain. This is in line with currently published trials using IVC as therapy. In summary, the results of this observational HIV-ITC study show that treatment of Vit C deficiency can impact the intensity of symptoms in various underlying diseases. Further large-scale, controlled studies are needed to confirm a causal link between high-dose IVC treatment and the observed improvement in symptoms. In addition, dietary assessments, such as Vit C intake, should be included to rule out potential confounders unrelated to underlying diseases and that may contribute to reduced Vit C blood concentrations.

Availability of Data and Materials

Full data supporting the reported results can be found on Clinical Trials (NCT02422901) upon publication or requested from the corresponding author.

Author Contributions

Conceptualization, CV, IT, BK and HM; Data curation, CV, IT, FS, BK and HM; Formal analysis, BK and FS; Methodology, CV, IT, BK and HM; Project administration, CV, IT, BK and HM; Validation, BK; Writing — original draft, FS and CV; Writing — review & editing, FS, CV, IT, BK and HM. All authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki. The submitted study was designed as an observational study/post-marketing surveillance study. Post-marketing surveillance studies are a sub-category of non-interventional trials as defined in § 4 (23) sentence 3 of the German Medicines Act (AMG). In these studies, the treatment, including diagnosis and monitoring, does not follow a pre-defined study protocol, but is exclusively based on medical practice according to the Summary of Product Characteristics (SmPC). According to Directive 2001/20/EC/EU Regulation 536/2014, an ethics vote is mandatory for clinical trials. However, according to Article 1 of Directive 2001/20/EC/EU Regulation 536/2014, these guidelines do not apply to this non-interventional trial. As a result, we are not subject to the requirement for an ethics vote under this guideline study. Pursuant to Section 67 (6) of the German Medicines Act (AMG), the person conducting the observational study is obliged to notify the relevant authorities (including the higher federal authority (BfArM)) and to provide information. We have fulfilled the pre-study notification requirements according to § 67 (6) of German Medicines Act (AMG). Informed consent was obtained from all subjects involved in the study. Parental consent was obtained for children.

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Conflicts of Interest

Fabian Stahl, Claudia Vollbracht, Inga Trompetter, Bianka Krick and Holger Michels are employed at Pascoe pharmazeutische Präparate GmbH (Giessen, Germany). The authors have no other potential conflicts of interest relating to this work. GKM Gesellschaft für Therapieforschung mbH, a full-service CRO, based in Munich, Germany, was commissioned by Pascoe pharmazeutische Präparate GmbH to carry out the statistical analysis of the data. The CRO was not involved in data collection, interpretation of the results, preparation of the manuscript or any other aspect of the study.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used Deepl Write in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/IJVNR48070.

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