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Vitamin C deficiency can lead to pulmonary hypertension: a systematic review of case reports

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Abstract

Background In the early literature, unintentional vitamin C deficiency in humans was associated with heart failure. Experimental vitamin C deficiency in guinea pigs caused enlargement of the heart. The purpose of this study was to collect and analyze case reports on vitamin C and pulmonary hypertension.

Methods We searched Pubmed and Scopus for case studies in which vitamin C deficiency was considered to be the cause of pulmonary hypertension. We selected reports in which pulmonary hypertension was diagnosed by echocardiography or catheterization, for any age, sex, or dosage of vitamin C. We extracted quantitative data for our analysis. We used the mean pulmonary artery pressure (mPAP) as the outcome of primary interest.

Results We identified 32 case reports, 21 of which were published in the last 5 years. Dyspnea was reported in 69%, edema in 53% and fatigue in 28% of the patients. Vitamin C plasma levels, measured in 27 cases, were undetectable in 24 and very low in 3 cases. Diet was poor in 30 cases and 17 cases had neuropsychiatric disorders. Right ventricular enlargement was reported in 24 cases. During periods of vitamin C deficiency, the median mPAP was 48 mmHg (range 29–77 mmHg; $N = 28$). After the start of vitamin C administration, the median mPAP was 20 mmHg (range 12–33 mmHg; $N = 18$). For the latter 18 cases, mPAP was 2.4-fold (median) higher during vitamin C deficiency. Pulmonary vascular resistance (PVR) during vitamin C deficiency was reported for 9 cases, ranging from 4.1 to 41 Wood units. PVR was 9-fold (median; $N = 5$) higher during vitamin C deficiency than during vitamin C administration. In 8 cases, there was direct evidence that the cases were pulmonary artery hypertension (PAH). Probably the majority of the remaining cases were also PAH.

Conclusions The cases analyzed in our study indicate that pulmonary hypertension can be one explanation for the reported heart failure of scurvy patients in the early literature. It would seem sensible to measure plasma vitamin C levels of patients with PH and examine the effects of vitamin C administration.

Keywords Antioxidants, Ascorbic acid, Case report, Heart failure, Oxidative stress, Pulmonary hypertension, Pulmonary vascular resistance, Scurvy, Systematic review

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Background

In the early literature, vitamin C deficiency was associated with exertional dyspnea. James Lind wrote in his 18th century monograph that "the case of scorbutic patients is somewhat singular, that though when at rest they find themselves quite well; yet, upon the least exercise, they are subject to panting and breathlessness" [1, 2]. Lind proposed that the cause of exertional dyspnea might be in the right ventricle: "upon using exercise, the velocity of blood is accelerated through lungs, and much greater quantity, which when at rest, was almost stagnating in the veins, is at once returned into the right cavities of the heart, and from thence into the lungs; the weakened vessels of the lungs not being able so quickly to transmit so great a quantity, causes a laborious breathing and panting" [1, 2].

In another major monograph on scurvy two centuries later, Alfred Hess described that dilatation in the right ventricle was common in patients with scurvy [2, 3]. Erdheim reported right heart enlargement in 21 out of 31 autopsies of infantile scurvy, with a higher degree of enlargement and hypertrophy of both ventricles in the more severe cases [4]. Right heart dilatation was also described in other reports [5–14]. Furthermore, some early reports proposed vitamin C for treating heart failure (HF) [15–17].

Animal studies indicated that vitamin C has effects on the function and structure of the heart and arteries. Experimental vitamin C deficiency in guinea pigs led to enlargement of the heart and degenerative changes in heart valves and myocardium [18–29]. Vitamin C deficiency also caused degenerative changes in the lungs [20–24], such as narrowing of arterioles. In mice, vitamin C deficiency led to alterations in the aorta wall, such as the disruption of elastic laminae and smooth muscle cell proliferation [30]. Vitamin C prevented pulmonary hypertension in broilers, which are especially prone to it due to their high metabolic rates and oxygen requirements [31, 32].

In clinical context, pulmonary hypertension (PH) is defined as mean pulmonary arterial pressure (PAP) over 20 mmHg [33–36]. Elevated PH increases the risk of right heart failure (RHF) and mortality [37, 38]. PH is categorized into 5 groups. Group 1 encompasses pulmonary artery hypertension (PAH), one cause of which is endothelial dysfunction [33, 34, 39, 40]. Pathophysiology of PAH involves impaired production of vasodilators such as nitric oxide (NO) and prostacyclin, along with the over-expression of vasoconstrictors such as thromboxane and endothelin-1. Most current drugs for PAH are focused on these pathways [33, 34, 36]. Furthermore, elevated levels of hypoxia-inducible factor 1α (HIF-1α) seem to play an important role in PAH, such that the accumulation of HIF-1α can lead to pulmonary vasoconstriction and smooth muscle cell proliferation [41]. PAH is also associated with epigenetic changes [42]. Carnitine participates in energy metabolism and has been proposed for treating PAH [43]. Exercise intolerance in PAH may be caused by the degeneration of skeletal muscles [44].

Vitamin C may influence PAH by several mechanisms. Physiological studies have demonstrated that vitamin C has effects on endothelial function in coronary arteries [45–49]. It participates in the synthesis of type IV collagen, which is required for basement membrane formation and endothelial cell adhesion [50]. Vitamin C participates in the synthesis of NO [50–52], and may increase prostacyclin levels [53–57]. A controlled trial found decreased thromboxane levels in the vitamin C group [58], and another study reported that vitamin C prevented the effects of endothelin-1 [59]. Vitamin C participates in the hydroxylation of specific proline residues of HIF-1α and thereby increases its rate of degradation, leading to decreased HIF-1α levels [60, 61]. Vitamin C participates in the demethylation of DNA and histones and influences over 1000 genes through epigenetic changes [62, 63]. Vitamin C participates in the biosynthesis of carnitine [64, 65], and carnitine administration extended the life span of scorbutic guinea pigs [66]. Finally, in the guinea pig, vitamin C deficiency leads to the degeneration of skeletal muscles [18–21, 67], and in humans, vitamin C administration increased resistance of skeletal muscle to fatigue in COPD patients [68].

Over the last decade, an increasing number of case reports have suggested vitamin C deficiency as a cause of PH. The purpose of our study was to analyze the findings of such reports, to evaluate the timing and effect of vitamin C, and to classify the published PH cases.

Methods

Search for case reports

We included case reports in which vitamin C deficiency was considered the cause of PH. We restricted our analysis to reports in which PH was diagnosed by echocardiography or catheterization. Catheterization is the gold standard method to diagnose PH [33]; however, it is not widely available, and it is invasive. The correlation between the PAP from echocardiography and catheterization is high [69–71]. When both methods were used, we selected the outcomes from catheterization.

We did not restrict our report selection based on age or sex, or dose and route of vitamin C administration. Our searches are described in Supplement 1, which includes data about the patients, their signs and symptoms, findings, diet before diagnosis, vitamin C treatment, and the effects of vitamin C. Supplement 2 (spreadsheet) includes numerical data extracted from the case reports, and

calculations. We were able to contact several authors for further details.

Primary outcome

We used the mean PAP (mPAP) as the outcome of primary interest. PH is diagnosed when mPAP > 20 mmHg [33].

Statistical methods

Many case reports did not publish mPAP. Some reported systolic PAP (sPAP) and we calculated an estimate of the mPAP using the Chemla formula: mPAP = 0.61×sPAP + 2 mmHg [72, 73]. Some further case reports published maximal tricuspid regurgitation velocity (TRV). Assuming right atrial pressure (RAP) = 10 mmHg [71, 74], we calculated an estimate of sPAP using the modified Bernoulli Eq. [69, 71, 74, 75]: $sPAP = 4 \times TRV^2 + RAP$; thereafter we calculated the mPAP as above.

In our main analyses we include all cases, ignoring other vitamins, minerals, and drugs; this is discussed further in the Results section.

Results

Description of the included case reports

We identified 32 case reports which suggested that vitamin C deficiency was the cause of PH [76–105] (Supplements 1 and 2). The oldest reports were published in 1996 [92] and 2003 [99], while 21 have been published since 2019 (Table 1). Over half were from the USA and the remaining cases originated from several other countries.

Twelve cases concerned children aged 1–10 years, 10 cases were in patients aged 11–44, and 10 were about patients aged 45–74 years. The sexes were distributed equally (Table 1). Half of the cases had a neuropsychiatric background such as autism, anxiety, anorexia, or paranoidism. Half of the children had autistic spectrum disorder (ASD).

The health condition that led to the patient being hospitalized lasted for over 3 months in 12 cases, 1–2 months in 7 cases, and 3 weeks or less in 7 cases.

Dyspnea was reported in 69%, edema in 53% and fatigue in 28% of the patients (Table 2). Chest pain was reported in 4 patients. Common symptoms included petechiae and ecchymoses, and pains in muscles and joints. Pathological changes in the gums were reported only in 56% of the cases. Of the remaining cases, 7 were thorough reports and we consider it likely that gum changes would have been reported if observed [76, 87, 90, 91, 98, 100, 103]. Corkscrew hairs are pathognomonic to scurvy but were reported for only 6 patients. Possibly physicians are more consistent in reporting dyspnea in patients with PH than on searching and reporting corkscrew hairs. Thus, the percentages should not be considered as the definite assessment of prevalence.

For 9 of the 12 children, the reported heart rates and respiratory rates were above the reference range [106] (Fig. S1 in Supplement 1). Only 1 child had levels within the reference range [104]. Over all ages, low systolic blood pressure < 100 mmHg was reported in 10 out of 22 cases (Fig. S1). Of the 20 cases that reported the level of blood O_2 saturation, 6 reported low saturation (< 90% or "hypoxia"), and oxygen administration was reported in 7 cases. B-type natriuretic peptide (BNP or NT-proBNP) was reported in 12 cases, and all were elevated. The majority of cases that published the hemoglobin level reported anemia with Hb < 100 (11/16 cases).

For 30 cases diet was reported to be poor. The patients consumed a narrow selection of foods, avoiding fruit and vegetables. Two cases did not comment on diet, one was a brief report [88], and another had Crohn's disease and underwent liver transplantation [105].

Vitamin C plasma level was measured in 27 cases. In 24 cases the level was undetectable with a local assay. The level was measurable but very low in 3 cases: 3 μM [84], 6 μM [76], and 11 μM [92].

The dose of vitamin C was reported for 19 cases. In 9 cases the dose was between 0.15 and 0.84 g/day, in 8 cases it was 1 g/day, and in 2 cases 2 g/day. At the start of the treatment, vitamin C was administered orally in 13 cases, and intravenously in 11 cases. Vitamin C was administered without other micronutrients in 17 cases, while in 14 cases other vitamins or trace elements were administered together with vitamin C.

Cardiac findings in the case reports

In 31 cases, echocardiogram was used to diagnose PH, followed by catheterization in 14 cases to confirm the diagnosis and to differentiate between pre- and post-capillary PH. In 1 case the diagnosis was based solely on catheterization. To exclude other diagnoses and to determine the etiology of PH, chest CT (20 cases), ventilation/perfusion scan (7 cases), pulmonary function test (5 cases), and cardiac MRI (1 case) were performed (see Supplements 1 and 2). From ECGs, 7 cases suggested right ventricle (RV) hypertrophy: 5 had right axis deviation and 3 had right bundle branch block.

Of the 32 case reports, 26 reported cardiac features of PH: RV enlargement in 24 cases and septal flattening in 14 cases. Pericardial effusion was reported in 4 cases [79, 90, 99, 103]. The P2 sound is common in PH [33, 107] and was reported in 6 cases.

The mPAP levels were published or could be calculated for 28 cases. At the time of the PH diagnosis, the median mPAP was 48 mmHg (range 29–77

Table 1 Characteristics of the patients in the case reports and the findings

Study [ref]	Country	Age (y)	Sex	Neuro-psychiatric disorders	mPAP		Ratio (mPAP pre/post)	Benefit on cardiac outcomes (days)[a]
					diagnosis (mmHg)	repeat (mmHg)		
Vitamin C alone (16 cases)[b]								
Abbas (2016) [76]	USA	50	F	Anxiety	[c]			28
Abe (2021) [77]	USA	7	M	ASD	46	22	2.1	38
Azar (2023) [79]	USA	35	F	Anxiety	41			21
Conte (2021) [81]	USA	48	F	Anxiety	35			
Ferreira (2020) [84]	Brazil	51	M	Paranoid	39			
Ghulam Ali (2018) [87]	Italy	66	M		61	19	3.2	14
Gilmore (2021) [88]	USA	22	M	ASD	32	12	2.8	42
Kurnick (2023) [91]	USA	25	F		45	24	2.0	
Mehta (1996) [92]	USA	40	F	Anorexia	36			19
Mertens (2011) [93]	USA	74	F	Food delusions	51			150
Nagamatsu (2009) [94]	USA	73	F		48	23	2.1	90
Petersen (2019) [97]	USA	5	M	ASD	[c]			14
Shah (2021) [101]	USA	35	F	Anxiety	54	19	2.9	14
Singh (2017) [102]	USA	48	F		41			30
Tan (2021) [103]	Malaysia	7	M	ASD	48	14	3.4	10
Valencia (2022) [105]	USA	19	M		76	33	2.3	
Vitamin C with other vitamins or minerals (15 cases)								
Benhamed (2019) [80]	France	40	M		63	19	3.3	2
Dean (2018) [82]	USA	6	M		43	14	3.2	2
Duvall (2013) [83]	USA	9	M	ASD	45			9
Frank (2019) [85]	USA	17	M		51	22	2.3	30
Gayen (2020) [86]	USA	60	M		41	20	2.1	150
Ichiyanagi (2019) [89]	Japan	3	M	ASD	77	19	4.1	1
Kupari (2012) [90]	Finland	40	F		48	15	3.2	7
Nariai (2022) [95]	Japan	2	F		54	21	2.5	2
Penn (2019) [96]	USA	48	F		41	26	1.6	42
Quinn (2022) [98]	USA	6	M	ASD	42	21	2.0	9
Ratanachu (2003a) [99]	Thailand	2	M		[c]			7
Ratanachu (2003b) [99]	Thailand	3	M		[c]			7
Sakamornchai (2022a) [100]	Thailand	6	M	ASD	57			60
Sakamornchai (2022b) [100]	Thailand	5	M	ASD	57			1
Ueki (2022) [104]	Japan	11	M	ASD	29	23	1.2	105
Vitamin C was not administered (1 case)								
Azar (2019) [78]	USA	73	F		50			Died

This table summarizes the data collected in Supplements 1 and 2

ASD Autism spectrum disorder

[a] Many studies reported only a late repeat echocardiograph. Late benefit does not indicate that the effect of vitamin C necessarily was slow. For example, Mertens (2011) [93] stated that a repeat echocardiography was carried out after 5 months, but there is no information about the cardiac status before the 5-month time point. See a survival curve of the effect of vitamin C on cardiac outcomes in Fig. S2

[b] Vitamin C alone indicates that no other vitamins or minerals were administered. Many patients in this group were administered drugs for PAH. However, no PAH drugs were administered for the patients reported in Abbas (2016) [76], Abe (2021) [77], Ferreira (2020) [84], Gilmore (2021) [88], Mehta (1996) [92], and Shah (2021) [101]

[c] Four case reports stated that PH was demonstrated, but no mPAP estimate is available. They are not shown in Fig. 1

mmHg) (Fig. 1). After vitamin C administration, mPAP was available for 18 cases, with a median of 20 mmHg (range 12–33 mmHg). For the latter 18 cases, mPAP was 2.4 fold (median; range 1.2–4.1) higher during periods of scurvy than during vitamin C administration.

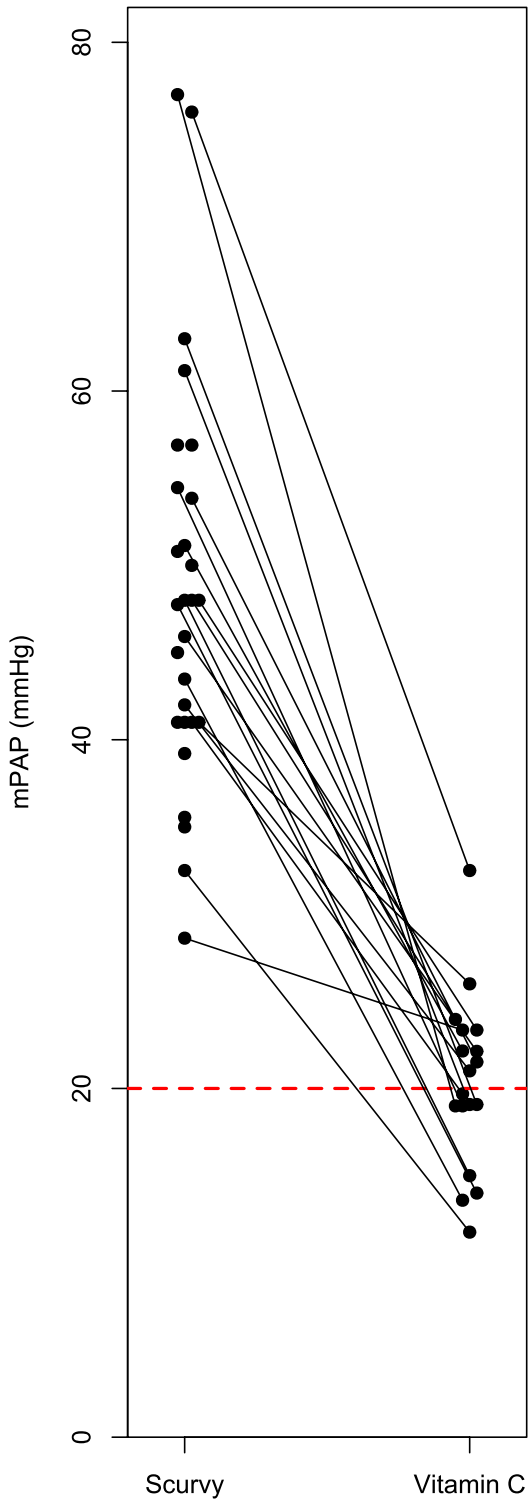

Fig. 1 Mean pulmonary artery pressure (mPAP) during scurvy and after vitamin C administration. mPAP was available at baseline for 28 patients, but 1 patient died before vitamin C was given [78]. The median mPAP level was 47 mmHg during scurvy. mPAP level after vitamin C administration was available for 18 cases, with the median mPAP 20 mmHg. The lines indicate the patients with both values. The mPAP level during scurvy was 2.4 fold (median; range 1.2–4.1) higher than the level during vitamin C administration. The red dash line indicates 20 mmHg, which is the limit for concluding PH [33]

The post-treatment mPAP level and the route of vitamin C administration was available for 16 cases. With oral administration, the median mPAP was 19 mmHg (range 12–26 mmHg; 8 cases), compared with intravenous administration with a median mPAP of 22 mmHg (range 13–33 mmHg; 8 cases).

Nine cases reported pulmonary vascular resistance (PVR) at the time of PH diagnosis, ranging from 4.1 to 41 Wood units (WU); PVR > 2 WU indicates pre-capillary PH [33] (Fig. 2). One of these 9 patients died before vitamin C was administered [78]. Five cases published the PVR level after vitamin C administration. During periods of scurvy PVR was 9-fold (median; range 2.2–22) higher.

Of the 19 patients for whom a time point of observed benefit from vitamin C on symptoms or signs was reported, 12 described that there was substantial benefit within 4 days. In this calculation, we have made the interpretation that "rapidly" [76], "in a few days" [79, 99], and "progressively" [77] indicate within 4 days.

A time point for demonstrated benefit on cardiac outcomes was reported in 28 cases. These time points are not based on regular daily follow-up; instead, repeat echocardiography was usually carried out after a fixed time period such as after 1 week or 1 month depending on local routines. Therefore, the recorded time of improvement in the cardiac outcomes is biased upwards. Nevertheless, it is useful to examine the rate of benefit. In 8 cases cardiac improvement was demonstrated in the first week, and in 7 other cases in the second week (Fig. S2). Thus, benefit in cardiac outcomes within 2 weeks was shown in half of the patients (15/28).

Eight cases reported mPAP for more than 1 repeat examination after the start of vitamin C administration. In most cases there was a substantial decline in the mPAP level within a few days or weeks (Fig. 3).

Tricuspid annular plane systolic excursion (TAPSE) is a measure for RV function, with normal level ≥ 18 mm [33, 108]. In 4 patients, TAPSE rapidly increased to normal levels after vitamin C administration (Fig. 3). In one patient, TAPSE was 9.5 mm during scurvy, but 23 mm 4 months earlier (Fig. S3), but follow-up TAPSE after vitamin C administration was not reported [91].

Table 2 Distribution of symptoms and signs in patients with scurvy-induced pulmonary hypertension

Symptom	Cases
Dyspnea	22
Edema	17
Fatigue	9
Chest pain	4
Gum pathology	18
Petechiae and ecchymoses	17
Pains in muscles and joints	19
Corkscrew hairs	6

The frequencies should not be compared as definite evidence of different prevalence of the symptoms, since physicians may record and report, for example, dyspnea more consistently than corkscrew hairs. This table is based on Supplements 1 and 2

Normal left ventricles (LV) are quite rounded, and the LV eccentricity index is a measure of RV overload, such that 1.0 indicates normal RV volume and pressure load, whereas RV pressure overload is indicated by an eccentricity index ≥ 1.2 at the end of both diastole and systole [33, 109]. In 3 cases, an elevated LV eccentricity index rapidly decreased after vitamin C administration (Fig. 4).

After the start of vitamin C, the size of the right heart, and the diameter of vena cava inferior substantially decreased in one patient (Fig. S4A [90]), and in another patient, the RV systolic to diastolic duration ratio decreased, and the RV fractional area change increased (Fig. S4B [98]).

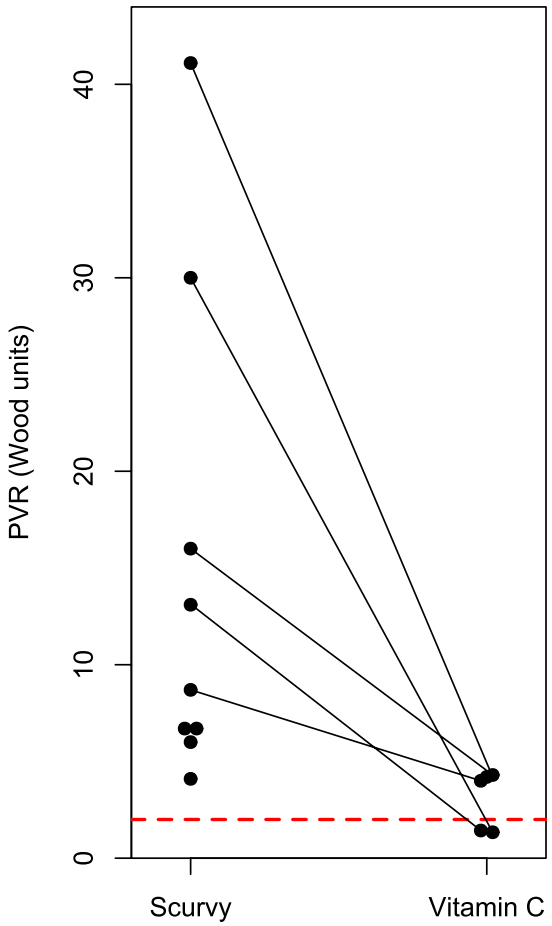

Fig. 2 Pulmonary vascular resistance (PVR) during scurvy and after vitamin C administration. PVR was available at the baseline for 9 cases, but 1 case died before vitamin C [78]. Follow-up PVR level was available for 5 cases with the lines showing the paired values. During scurvy, the PVR level was 9 times (median) as high as during vitamin C administration. The red dash line indicates 2 Wood units, which is the limit for concluding PAH [33]. See extracted data in Supplement 2

Classification of the included cases

Authors of the reports proposed that 10 cases were PAH. According to current recommendation group 1 PAH classification is based on three criteria: mPAP > 20 mmHg, pulmonary wedge pressure < 15 mmHg and PVR > 2 WU [33]. Only 5 of the 10 proposed PAH cases demonstrated these criteria [78, 79, 82, 86, 96]. However, we noted 3 further cases satisfying the criteria [89–91]. Thereby, 8 of the 32 patients were PAH cases.

Thus, 24 cases were not demonstrated to have PAH. Nevertheless, some or all of them might be cases of PAH, but firm conclusions cannot be drawn in the absence of definitive data. On the other hand, of these remaining 24 cases with unclear PH classification, chronic pulmonary thromboembolism was excluded in 21 cases by CT and/or ventilation-perfusion scans, and lower limb deep vein thrombosis in 4 cases by Doppler ultrasound, thereby excluding group 4 PH [33]. None of these 24 case reports indicated interstitial lung diseases or COPD, making group 3 PH unlikely [33]. In addition, none of the 24 case reports indicated substantial long-term LV dysfunction before the PH episode, and in 23 of the 24 cases echocardiography would have shown LV dysfunction if it existed, thereby excluding group 2 PH [33]. Finally, in most cases the recovery from PH was rapid and such a response to vitamin C is inconsistent with the chronic conditions behind PH groups 2, 3 and 4. Only Valencia et al. reported wedge pressure 30 mmHg and PVR 6.7 WU in a patient after liver transplant [105], probably explained by left-sided heart disease [33].

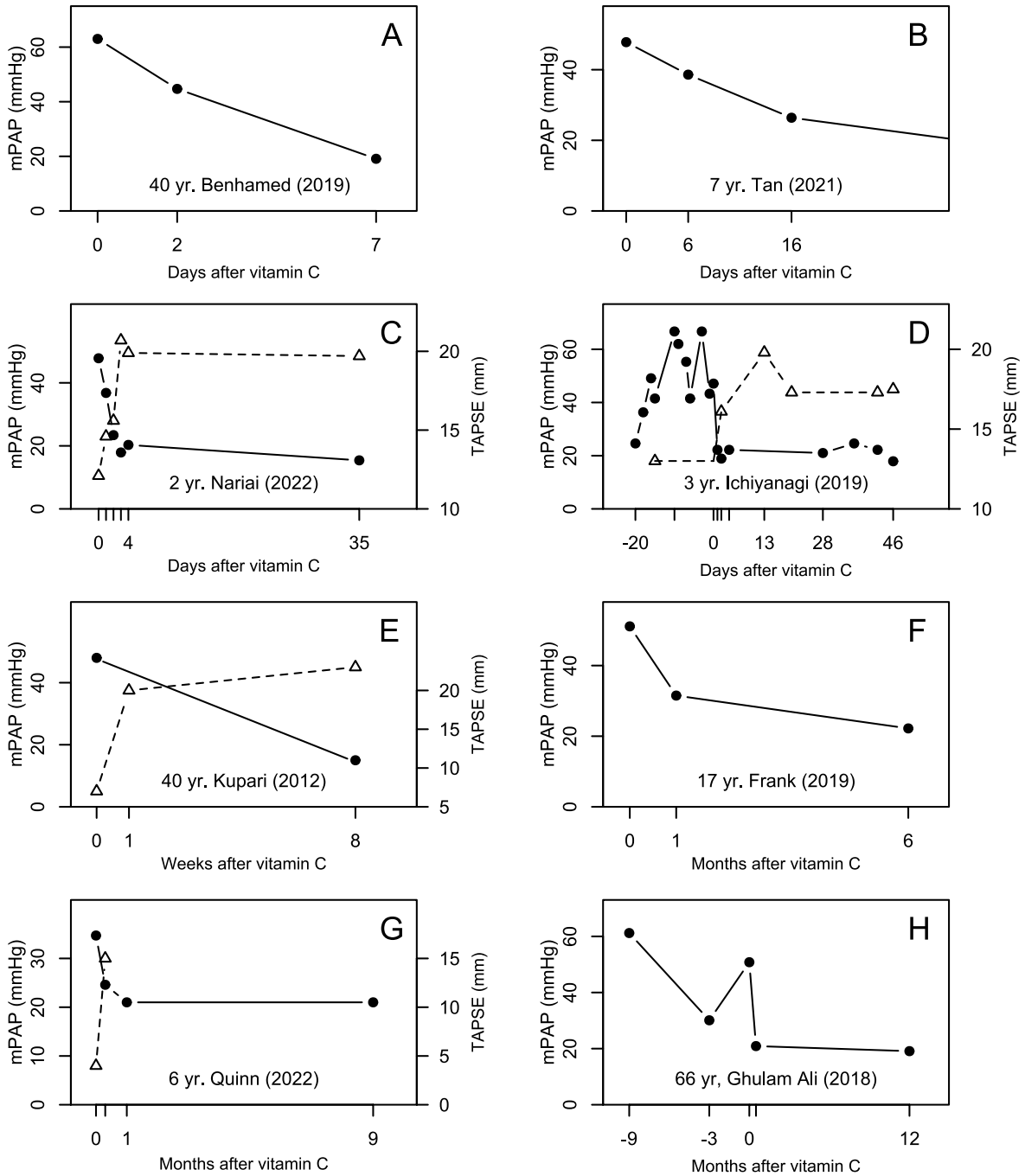

Fig. 3 Evolution of mPAP and TAPSE over time. mPAP is shown with filled circles on the left-hand side, and the TAPSE with open triangles on the right-hand side. Each point indicates one observation, and the lines are added to help visualize the change over time. Normal TAPSE ≥ 18 mm [33]. Note that the time scale of the horizontal axis is not constant. Time points ≤ 0 indicate the period during scurvy. Vitamin C administration was started soon after the time point 0. Data are for: (**A**) a 40-year-old male in France [80], (**B**) a 7-year-old boy in Malaysia [103], (**C**) a 2-year-old girl in Japan [95], (**D**) a 3-year-old boy in Japan [89], (**E**) a 40-year-old female in Finland [90], (**F**) a 17-year-old male in the USA [85], (**G**) a 6-year-old boy in the USA [98], (**H**) a 66-year-old male in Italy [87]. See extraction of data in Supplementary files 1 and 2. TAPSE, tricuspid annular plane systolic excursion

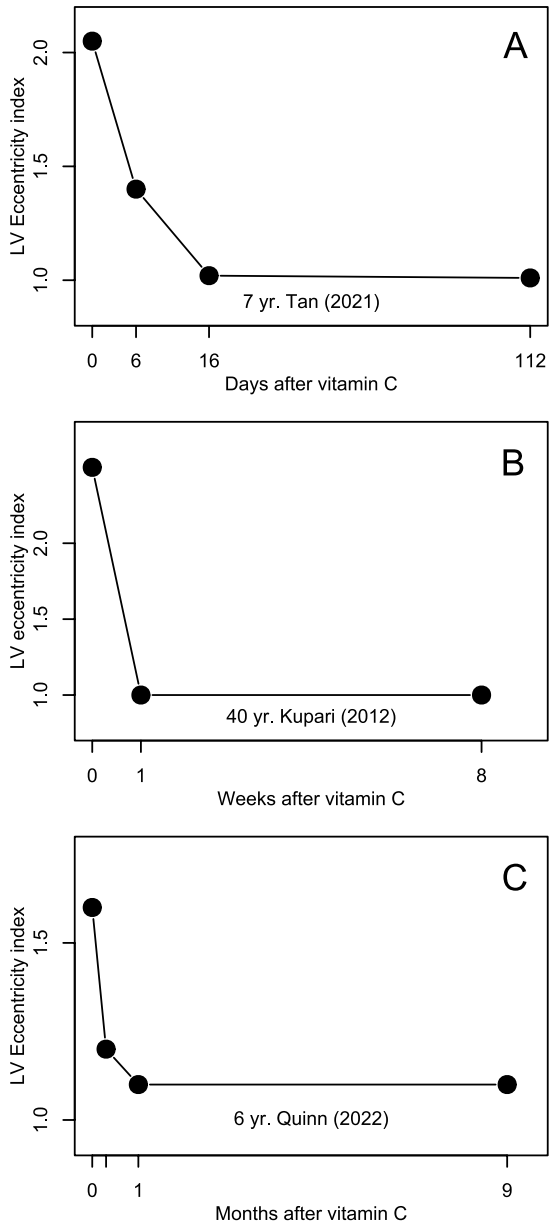

Fig. 4 Effect of vitamin C on LV eccentricity index in pulmonary hypertension patients. Normal LV eccentricity index is 1.0 [33, 109]. Each point indicates an observation, and the lines are added to help visualize the change over time. Time point 0 indicates the start of vitamin C administration. Data are from (**A**) Tan [103], (**B**) Kupari [90], and (**C**) Quinn [98]

Effect of vitamin C on laboratory endpoints

In a few cases, laboratory assays were reported after vitamin C administration. Ueki et al. reported a 80–90% decrease in BNP, CRP and D-dimer levels [104]. Dean et al. reported normalization of the BNP level [82]. Hb level doubled in 2 cases during vitamin C administration [90, 104].

Specificity of the effects of vitamin C

There are no control patients in our analysis and some of the changes over time may have been caused by factors other than vitamin C. Evidently, even with its potential limitations, hospital food is better than the food eaten at home for most of the included patients, but none of the cases improved just by being taken to hospital.

Hospital stay usually includes a number of medical treatments, but the other treatments did not lead to sufficient improvement in the included cases. Within hospitals, several patients were administered standard PAH drugs such as prostacyclins [90, 96, 102, 105], phosphodiesterase 5 inhibitors [78, 79, 82, 89, 90, 96, 98, 102, 103, 105], endothelin receptor antagonist [87, 103, 105], inhaled NO [82, 98, 103], calcium channel blockers [93, 94, 100], phosphodiesterase 3 inhibitors [82, 91, 95, 105], and nonspecified pulmonary vasodilator [100].

None of them led to substantial clinical improvement. Furthermore, when sildenafil and tadalafil [82, 89, 90, 96, 102], bosentan [87], and nifedipine [93] were discontinued after discharge, the patients remained cured of PH by taking vitamin C alone. Finally, no standard PAH drugs were administered for 13 cases.

Another potential confounding factor is the administration of other vitamins and minerals. Thiamine (vitamin B_1) deficiency can cause PH and RHF [5, 110–112], however, the level was normal in 9 of the 15 cases for whom plasma thiamine level was measured, and the few low levels were mostly marginally low. Thiamine was administered to 7 cases. Thus, no proportion of clinical improvement in 24 cases can be attributed to thiamine. Vitamin D was administered to 4 cases. A few cases were administered iron or multivitamins. However, 17 cases were administered vitamin C alone (Table 1).

A further approach to estimate the possible contribution of the other vitamins and minerals was to compare the post-treatment mPAP levels in those who received vitamin C alone vs. those who received other vitamins or minerals together with vitamin C. In 9 cases receiving vitamin C alone, the median post-treatment mPAP was 19 mmHg (range 12–33 mmHg). In 9 cases receiving other vitamins or minerals, the median post-treatment mPAP was 21 mmHg (13–26 mmHg).

In 7 cases, no PAH drugs and no other vitamins or minerals were administered and the improvements in those patients gives the most specific evidence that it was vitamin C that caused the decrease in mPAP levels [76, 77, 84, 88, 92, 97, 101].

Vitamin C was undetectable in 24 cases and very low in 3 cases. Evidently, such extremely low levels are

rapidly increased with vitamin C administration, which can explain the dramatic and rapid effects on mPAP. In most cases there was a long progressive deterioration in the condition over weeks or months before the hospital assessment. In many cases the improvement in the condition was rapid after vitamin C was started. For example, "after 2 days, his symptoms improved and he was discharged home" [85], "[tricuspid regurgitation peak gradient] dramatically decreased [from 75 mmHg] to … 35 mmHg on day 3" [95], and after vitamin C "by 48 hours, her symptoms had resolved. Repeat right heart catheterization demonstrated … mPAP [from 41 to] 26 mm Hg" and PVR from 13 WU to 1.4 WU [96]. Given the long decline in health, such rapid improvements after starting vitamin C are consistent with the special role of the vitamin.

Discussion

Findings of the case reports

We identified 32 case reports that are informative about the effects of vitamin C on PH. One patient died before vitamin C was administered [78]. In the other 31 cases dramatic benefits from vitamin C were reported. In 18 cases with follow-up data, mPAP during scurvy was on average 2.4 times higher than during vitamin C administration (Fig. 1). In 8 cases which reported repeated mPAP measurements, vitamin C was shown to decrease the levels within days or weeks (Fig. 3). In 9 cases, the PVR was substantially elevated, and in 5 of those, vitamin C dramatically decreased the level (Fig. 2).

Low TAPSE (RV dysfunction) is an important predictor for decreased survival in PH [33, 108, 113–115]. Vitamin C rapidly improved TAPSE in 4 cases (Fig. 3).

Decreased survival in PH is associated with elevated LV eccentricity index (RV pressure overload), increased size of RA and RV, decreased RV fractional area change, increased RV systolic-to-diastolic duration ratio, and increased diameter of vena cava inferior [33, 113–120]. These endpoints were normalized rapidly by vitamin C in 4 cases (Fig. 4 and Figs. S3 and S4). Elevated BNP level is also associated with decreased survival [121]: 12 cases had elevated levels during scurvy, but only two reported follow-up levels which were normalized [82, 104].

Case reports such as those included in our analysis may be biased in the assessment of the treatment effects. The placebo effect and concurrent treatments might explain the observed benefits. However, the placebo effect is a concern for subjective outcomes, but less or not at all for objective outcomes [122, 123]. It does not seem plausible that the placebo effect of vitamin C could cause permanent declines in outcomes such as mPAP and PVR. Furthermore, in several RCTs, the mPAP level was not changed in the placebo groups of PH patients consistent with this argument [124–126]. Many of the included cases were administered drugs for treating PAH, and other vitamins and minerals, but it seems highly unlikely that the rapid and permanent benefits could be explained by factors other than vitamin C.

Intravenous vitamin C administration has often been proposed since it can lead to faster normalization and higher levels of plasma vitamin C [127]. In our set of cases, there was no indication of differences between intravenous and oral administration. Given the very low levels of vitamin C in plasma at the time of diagnosis, the route of administration may be a marginal issue. Furthermore, a meta-analysis comparing intravenous vs. oral vitamin C for the length of ICU stay found no difference [128]. Nevertheless, a meta-analysis on vitamin C and the incidence of atrial fibrillation (AF) found differences between oral and intravenous administration [129]. For very ill patients, who are also prone to gastroparesis, and have increased metabolic needs, intravenous vitamin C may be the only option, but oral vitamin C should not be generally underrated.

Classification of the included cases

PH is a heterogeneous condition, the end result of a variety of underlying disorders. It is currently categorized into 5 groups [33]. Group 1 encompasses patients with PAH, group 2 encompasses those who have PH due to left heart disease, group 3 PH is due to chronic lung diseases such as COPD and pulmonary fibrosis, and group 4 PH is due to chronic pulmonary thromboembolic disease. Group 5 encompasses etiologies outside the 4 other groups.

In 8 cases, there was evidence that the cases were PAH. The classification of the remaining 24 cases is not clear. In controlled trials, vitamin C has influenced left ventricular ejection fraction (LVEF) [130], which indicates that vitamin C can have effects on LV function. Controlled trials have also shown that vitamin C can influence pulmonary function tests [131, 132]. Therefore, it is conceivable that in some situations vitamin C may have an effect on PH groups 2 and 3. However, most of the unclassified PH cases are inconsistent with groups 2 to 5. The patient reported by Valencia et al. is the only one with data indicating a contribution to PH from the LV [105]. Therefore, our conclusion is that the majority of the unclassified cases probably fall into group 1 PAH.

PAH is a severe disease with a 3-year survival rate of about 50% [133], but PAH is rare [33]. On the other hand, a population-based study in the Netherlands found that 8% of people older than 85 years had echocardiographic signs of PH [134]. Even mild PH increases mortality [38]. The potential role of vitamin C on group 2 and 3 PH should be investigated.

Low vitamin C levels are not rare

Although the evidence from the included case reports indicates strongly that low vitamin C levels can lead to PH, it is important to emphasize that the plasma vitamin C levels were particularly low. Therefore, caution is needed when extrapolating these findings to less extreme vitamin C deficiency.

While the majority of the cases reported unmeasurable plasma vitamin C levels, 2 cases reported plasma vitamin C levels in the range 6–11 μmol/L [76, 92]. Thus, 11 μmol/L might be considered a potential upper limit for the range with an increased risk of PH due to vitamin C deficiency. This level needs to be compared with levels reported in various population groups.

In the NHANES 2003–2004 survey in the USA, median plasma vitamin C level was 54 μmol/L among the population aged over 20 [135]. However, 5% of those examined had vitamin C levels below 8 μmol/L. Furthermore, in some populations plasma vitamin C level is much lower than in the USA. For example, vitamin C plasma level < 11 μmol/L was reported in 25% of low-income males in the UK [136], in 39% of females in Mexico [137], and in 59% of subjects of a survey in India [138]. Finally, in Northern Russia mean vitamin C plasma level was 2.5 μmol/L in 1992 and 5 μmol/L in 2002 [139]. Therefore, if vitamin C level < 11 μmol/L increases the risk of PH, the issue is of concern in many population groups globally. Furthermore, one survey intentionally searched for scurvy symptoms and signs in geriatric patients and concluded that 12% had scurvy [140].

Finally, plasma vitamin C is a poor measure of vitamin C status in the body. Scurvy is usually associated with vitamin C plasma levels below 0.2 mg/dl (11 μmol/L), but 11 μmol/L should not be interpreted as a definitive level below which scurvy symptoms start to appear. For example, Hodges commented in their empirical vitamin C deficiency trial that "a distressing feature is the lack of precision of serum ascorbic acid levels. According to most authorities, deficiency appears after the serum level has fallen below 0.2 mg/100 ml, yet several men in these studies had obvious scurvy at a time when their serum levels were above this value" [141]. Emergence of scurvy symptoms had a much closer correlation with the total body pool of vitamin C than with plasma vitamin C level. Hodges further stated that "… a comparison between plasma levels of ascorbate and pool sizes showed a very poor correlation… it is fair to say that scurvy appeared when the [vitamin C] body pool size fell below 300 mg" [142]. However, it is not feasible to measure total body pool of vitamin C in hospitalized patients.

When the deficiency of vitamin C is considered, often the main focus is on the gums. However, only half of the included cases reported pathological changes in gums. Of the remaining cases, seven were thorough reports such that we would expect mentioning gum pathology if such existed. Accordingly, too much weight should not be put on the presence of gum pathology when considering the possibility of vitamin C deficiency.

Ethical issues around not giving vitamin C to patients with severe vitamin C deficiency

RCTs are strongly encouraged to validly test whether a treatment is effective or not. However, there are ethical concerns regarding withholding vitamin C from patients who suffer from vitamin C deficiency. In old times, vitamin C deficiency led to the end of many lives [1–3, 143, 144]. The harms of vitamin C deprivation have not vanished. One of the cases included in our analysis died of scurvy, with the pathophysiological explanation being cardiogenic shock [78]. Four other modern case reports of vitamin C deficiency described patients who died [145–148]. Vitamin C deficiency has caused ECG changes, which also discourages randomizing half of deficient patients to a placebo group [149–153]. The Helsinki declaration states that "while the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects" [154]. It does not seem ethically acceptable to randomize any patients with vitamin C deficiency to a group that is not given the vitamin.

The LOVIT trial examined the effect of 4-day intravenous vitamin C administration on sepsis patients, and unexpectedly mortality was found to be elevated in the vitamin C group [155]. However, a secondary analysis showed that the increased mortality did not occur during vitamin C administration, but immediately after the abrupt termination of the vitamin [156]. A recent vitamin C for critically-ill COVID-19 patients trial observed similar harm from the abrupt termination of the 4-day vitamin C administration [157, 158]. Rapid termination of vitamin C can lead to very low plasma levels through the rebound effect [156]. It even seems possible that the extra deaths after the sudden termination of vitamin C in the LOVIT trial might have been due to RHF since vitamin C deficiency increases the risk of RHF [1–11], and RHF is common in sepsis patients [159, 160].

So, there are serious ethical issues if vitamin C is not administered to patients with vitamin C deficiency. Furthermore, when the size of the effect is large relative to the expected prognosis, RCTs are not necessary for drawing definite conclusions [161]. Thus, the findings described in our study should not be dismissed with a requirement that an RCT should be carried out to test whether maintaining scurvy maintains elevated mPAP levels.

Other cardiac effects of vitamin C

Our study focuses on PH, but vitamin C appears to have other cardiac effects. Meta-analyses indicate that vitamin C can lower systemic blood pressure [162], increase low levels of LVEF [130], decrease the risk of AF in high-risk populations [129], decrease troponin levels in cardiac stress [163], and improve endothelial function [164]. One RCT found that vitamin C prevented postangioplasty restenosis [165], and another that vitamin C prevented myocardial injury after elective PCI [166]. An RCT on patients with HF found that a 4-week vitamin C administration increased the distance covered in a 6-min walk test by 49 m (26%) [167].

As to the possible effects of low vitamin C levels on HF, certain cohort studies are interesting. Among males of the EPIC study, a vitamin C plasma level of 23 μmol/L was associated with a 40% higher risk of HF compared with 70 μmol/L [168]. Another study with males found that a vitamin C plasma level of < 14 μmol/L was associated with twice the risk of HF compared with > 40 μmol/L [169]. Two further studies found that low vitamin C intake in patients with HF was associated with higher rates of cardiac events [170, 171].

Two Mendelian randomization studies on vitamin C and cardiac outcomes did not find association [172, 173]. However, the comparisons in these two studies corresponded to vitamin C groups with mean plasma levels of 47.3 and 52.7 μmol/L [174, 175]. Comparison of two groups with such high and closely similar vitamin C levels is uninformative about the effects of low plasma levels for cardiac health; compare with the plasma levels in the above mentioned cohort studies.

Case reports indicate that vitamin C deficiency can lead to cardiomegaly [176, 177], hypertension [178], hypotension [179–183], lower limb pitting edema [184–189], and vasoplegia [190]. Other case reports described exertional dyspnea together with cardiac tamponade [191], lightheadedness [192], or lightheadedness and abnormalities of LV wall motion [193].

In the Sheffield study on experimental vitamin C deficiency, 2 participants had chest pain and ECG changes [149–151]. The 2 participants showed striking improvement within a few days after vitamin C administration. In the Iowa City study on experimental vitamin C deficiency, 2 participants had exertional dyspnea during deprivation [142]. In addition, 4 participants had reduced responsiveness of resistance vessels of the forearm to lower body negative pressure as compared to the state after vitamin C repletion [194]. In these two studies, there were 4 participants with chest pain or dyspnea due to vitamin C deprivation, which is 27% of all vitamin C deficient participants in the two studies (4/15).

Finally, in physiological laboratories vitamin C administration has shown a wide range of effects that are relevant to the cardiac system, such as increasing coronary artery diameter [45–49], coronary flow [195–201], improving effects of inotropic agents [202–206], increasing baroreflex sensitivity [207–210], alleviating postural tachycardia [211], increasing left ventricular diastolic function [212] and preventing nitrate tolerance [213–215]. Most of these physiological studies were short. However, our current analysis indicates that some of the reported mechanisms may have long term relevance.

After we received the reviewer reports, we noted a report on two cases of PH induced by scurvy [216]. The two cases are consistent with the set we analyzed, see a brief summary in our Supplement 1. We did not append them to our analysis.

Conclusions

We identified 32 case reports that are informative about the effects of vitamin C deficiency on PH. The majority of the included cases seem to fall into the PAH group. Thus, PH should be included in the list of conditions associated with scurvy.

Neuropsychiatric symptoms such as ASD were common in the reported cases and vitamin C intake should be considered in such patients. It would seem appropriate to measure plasma vitamin C levels of patients with all forms of PH and examine the possible effects of vitamin C administration on all PH groups. The potential role of vitamin C for preventing and treating HF should be investigated in populations that have particularly low vitamin C intakes.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

H.H.: conceptualisation, search for case reports, extraction of data, statistical analysis, writing (original draft and review/editing). A.M.: search for case reports, extraction of data, writing (review/editing).

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Availability of data and materials

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This is a secondary analysis, not applicable.

Consent for publication
Not applicable.

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