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Original article

Superior vena cava syndrome in chronic intestinal failure patients: When the going gets tough

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SUMMARY

Background & aims: Catheter-related venous thrombosis is a severe complication of home parenteral nutrition (HPN) with potentially devastating consequences such as superior vena cava syndrome (SVCS). Early recognition and awareness of factors leading to its development are of paramount importance. However, studies are lacking in HPN patients focusing on this topic. In this study, we aimed to determine the incidence of SVCS in HPN patients and describe SVCS-related outcomes.

Methods: This retrospective cohort study comprised all adult HPN patients who developed SVCS between 2000 and 2022 at our national HPN referral center. Primary outcome was the incidence of SVCS. Secondary outcomes include SVCS-related symptoms, tip location of central venous access device (CVAD) post-insertion and at time of SVCS, diagnostics and treatment.

Results: SVCS was diagnosed in 38 of 616 patients (6%), with an annual cumulative incidence rate ranging between 0 and 4.2%. Most common presenting symptoms were facial edema (82%) and arm edema (50%). Post-insertion, 17% (6/36) of patients had a correct position of the CVAD tip and 11% (4/36) during SVCS diagnosis. Computed tomography was the most used diagnostic imaging technique (66%). Sixty-three percent of patients started, 11% switched, and 21% continued anticoagulant treatment.

Conclusions: The incidence of SVCS is relatively high in our vulnerable HPN population. It is key to recognize whenever such patients present with vascular obstruction-related symptoms and treat them in an early stage by a multidisciplinary team.

Key notes

- Comply to clinical guidelines regarding central venous access device's tip position (as close as possible to the caval atrial junction).
- Always consider superior vena cava syndrome when a patient with a central venous access device presents with vascular obstruction-related symptoms, such as facial or arm edema and/or distended chest or neck veins.
- A computed tomography scan provides the most optimal visualization of the superior vena cava.
- Central venous access device removal should only be considered in case of additional dysfunction of the device.

1. Introduction

Patients with chronic intestinal failure (CIF) lifelong depend on home parenteral nutrition (HPN), which requires the presence of a permanent central venous access device (CVAD) [1]. Current guidelines recommend the tip of such CVAD to be placed as close as possible to the junction of the superior vena cava (SVC) and the right atrium to prevent catheter-related venous thrombosis (CRVT) [2].

Obstruction at the level of the SVC may lead to superior vena cava syndrome (SVCS), which comprises a variety of symptoms, depending on the localization of the thrombus, severity, and speed of onset of obstruction [3,4]. Most common symptoms are facial and neck swelling and dilated neck and chest veins [4]. However, up to 10% of patients are asymptomatic [5]. A previous study showed SVCS prevalence of 5.1% in HPN patients [6]. Although malignancies account for 70% of SVCS, the overall incidence of device-related SVCS is around 30% and increasing, mainly because of the rising use of CVADs [4,7].

In general, the development of thrombosis is often related to Virchow's triad (hypercoagulability, stasis of blood flow, and

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endothelial injury) [8]. In the case of SVCS, this mostly concerns endothelial damage due to multiple catheter placement attempts, incorrect positioning, and multiple CVADs in the past [9,10].

Loss of access options to insert a CVAD, as is frequently seen with SVCS, poses a threat to both the patient and the continuation of HPN as a technique. Nonetheless, following SVCS, the remaining options for a CVAD are limited to less favorable sites such as the femoral vein, liver vein, or inferior vena cava. Construction of an arteriovenous fistula as a rescue to obtain venous access is often not an option because of the increased venous return in the acute situation of SVCS. In some cases, even direct placement into the right atrium through thoracotomy has to be considered [9,11]. Moreover, SVCS may have additional serious risks, for instance, a thrombotic infection or pulmonary embolism, the latter being a potentially life-threatening complication [7,12].

The rationale behind the present study is that we were under the impression that SVCS occurred in increasing numbers during the COVID-19 pandemic, with its associated thrombotic risk [13]. Also, due to the subtle onset of symptoms, the diagnosis of SVCS, in hindsight, is often missed in its early stage, often with devastating consequences. In the present study, we therefore seek to address this apparent lack of awareness by reporting our experience, and we provide suggestions on how to deal with SVCS in these vulnerable patients.

2. Methods

2.1. Study design and patient selection

This retrospective cohort study was conducted at Radboud university medical center (Radboudumc), a tertiary referral center for CIF patients. Patients were selected from the Nijmegen intestinal failure (IF) Registry, a web-based Castor EDC database [14]. Patients aged ≥18 years were eligible for inclusion if they met the criteria for CIF [1].

2.2. Study outcomes, definitions, and data collection

Primary outcome was the incidence of SVCS. Secondary outcomes included SVCS-related symptoms, time to SVCS, tip location of CVAD post-insertion and at the time of SVCS, diagnostics, treatment, consequences and follow-up.

The following variables were collected from the Nijmegen IF registry: patient characteristics (sex, age, underlying disease, and co-morbidities), medication (anticoagulants and oral contraceptive pill), CVAD characteristics (type, number of lumen, site, and side of vein insertion, date of insertion, and removal), HPN characteristics (duration of HPN), small bowel transplantation (no transplantation, referral to a transplantation center, or small bowel transplantation) and follow-up at 1, 5, and more than 10 years after SVCS diagnosis (including imaging and symptoms related to SVCS). For this study, we assessed all patients' medical records, and all clinical data related to SVCS were collected. Two investigators (JK and VG) independently assessed SVCS cases and discussed with a third investigator (GW). The tip location at post-insertion radiography and during SVCS diagnosis, luminal occlusion and collateral formation were revised for every patient and discussed with an interventional radiologist (SJ).

SVCS was defined as a (partly) obstruction of the SVC on diagnostic imaging with or without associated symptoms. We included the percentage of luminal occlusion and collateral formation to establish the degree of SVC occlusion. The percentage of luminal occlusion was divided into categories: non-significant occlusion (<70%), significant occlusion (70–99%), and total occlusion (100%). For some patients, diagnostic imaging was not available for revision because imaging was dated, conducted in an external hospital, or insufficient to provide the needed variables. Incidence rates were calculated in two ways: first, by dividing the number of new SVCS cases by the number of CIF patients at risk, and second by the number of new SVCS cases per 1000 catheter days.

Persistent symptoms were defined as SVCS symptoms that were present continuously, intermittent or progressive after SVCS diagnosis and also included symptoms that were classified as volume load-related to the degree that TPN volume had to be decreased or infusion time extended. Decreased options for CVAD placement implied that a CVAD had to be inserted at a less favorable site (femoral vein, inferior vena cava or direct placement in the right atrium) after SVCS diagnosis.

A correct placement of the CVAD tip was considered at positions two, three, or four (Fig. 2) [2,15].

2.3. Statistical methods

Baseline characteristics were summarized using descriptive statistics. Continuous variables were presented as mean with standard deviation (SD) or median and interquartile range (IQR) if not normally distributed. Missing data were excluded from analyses. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp. Armonk, NY, USA).

2.4. Ethical approval

This study was approved by the research ethics committee of the Radboudumc in Nijmegen, the Netherlands (reference number 2020-6119) and was reported according to the STROBE guidelines [16].

3. Results

3.1. Demographics

Between 2000 and 2022, a total of 616 patients were under treatment for 1.16 million catheter days in the Radboudumc, of whom 38 (6%) individual patients were diagnosed with SVCS. Most patients were female (74%), and the mean age at diagnosis was 54 years. Baseline characteristics are presented in Table 1. In total, 25 patients had a history of venous thrombosis, of which 18 CRVTs, 4 pulmonary embolisms, 3 deep venous thromboses, and 10 other thromboses. Some patients had multiple thromboses.

3.2. Superior vena cava syndrome incidence

Figure 1 shows the SVCS cumulative annual incidence rate ranging between 0 and 4.2 % over the years 2000–2022, with an outlier of eight cases in 2021. Since 2020, three of eleven (27%) patients were diagnosed with COVID-19 within three months prior to SVCS diagnosis. The incidence of SVCS was 0.03 per 1000 catheter days. Patients had a mean of four HPN catheters before SVCS was diagnosed. The median time between CVAD placement and diagnosis was five months (IQR 2–17) (Table 2).

3.3. Superior vena cava syndrome symptoms

Thirty-seven out of 38 (97%) patients presented with symptoms at the time of their SVCS diagnosis. Patients presented with: 31 facial edema (82%), 19 arm edema (50%), 10 headache (26%), 8 dyspnea (21%), 8 distended chest veins (21%), 5 facial plethora (13%), 5 increased central venous pressure (13%), 4 distended neck

Table 1
Characteristics of patients with superior vena cava syndrome.

Patient characteristics	n = 38
Female – no. (%)	28 (74)
Age at start HPN – mean (±SD)	49 (±17)
Age at SVCS diagnosis – years mean (±SD)	54 (±16)
Cause of intestinal failure – no. (%)	
Short bowel syndrome	17 (45)
Gastrointestinal motility disorder	14 (37)
Extensive small bowel mucosal disease	2 (5)
Intestinal fistula	1 (3)
Mechanical obstruction	1 (3)
Other	3 (8)
Number of previous CVADs – mean (±SD)	4 (±4)
Medical history – no. (%)	
Inflammatory bowel disease	11 (29)
Active malignancy	2 (5)
History of venous thrombosis	25 (66)
Inherited hypercoagulable state	3 (8)
Medication use prior to SVCS – no. (%)	
Oral contraceptive pill	4 (11)
Anticoagulant use	14 (37)
CVAD characteristics	
Type of CVAD – no. (%)	
Tunneled catheter	29 (76)
Subcutaneous port system	6 (16)
Non-tunneled	1 (3)
Arteriovenous fistula	1 (3)
Unknown	1 (3)
CVAD lumen – no. (%)	
Single lumen	21 (55)
Multi lumen	3 (8)
Unknown	7 (18)
Not applicable	7 (21)
Side of vein insertion – no. (%)	
Left	21 (55)
Right	17 (45)
Vein used for insertion – no. (%)	
Jugular	14 (37)
Subclavian	20 (53)
Femoral	1 (3)
Arteriovenous fistula	1 (3)
Basilica	1 (3)
Unknown	1 (3)

Abbreviations: CVAD, central venous access device; no, number; SD, standard deviation; SVCS, superior vena cava syndrome.

veins (11%), 3 occlusion alarm of feeding pump (8%), 3 visual symptoms (8%), 3 facial/neck pain (8%), 2 dizziness (5%), and 5 other symptoms (13%). Other symptoms included 1 snoring, 1 stridor, 1 syncope, 1 hoarseness, and 1 central cyanosis.

The median symptomatic period until diagnosis was 14 days (IQR 3–28), with five outliers of 49, 106, 122, 130, and 137 days.

Table 2
Outcomes of patients with superior vena cava syndrome.

Superior vena cava-related outcomes	n = 38
Time between CVAD placement and diagnosis (months) – median (IQR)	5 (2–17)
Time between start HPN and diagnosis (months) – median (IQR)	39 (13–80)
Difficult CVAD placement – no. (%)	5 (13)
Imaging technique used for diagnosis – no. (%)	
Computed tomography scan	25 (66)
Fluoroscopy	6 (16)
Phlebography	5 (13)
Ultrasound	1 (3)
Unknown	1 (3)
Treatment with anticoagulants – no. (%)	
New	24 (63)
Switch	4 (11)
Continue	8 (21)
None	1 (3)
Unknown	1 (3)
Endovascular therapy – no.	
PTA	16 in 8 patients
Stent	11 in 9 patients
Recanalization	5 in 4 patients
Snare	1 in 1 patient
Thrombolysis	1 in 1 patient
Thrombectomy	1 in 1 patient
Consequences/complications of SVCS – no. (%)	
CVAD removal	24 (63)
Decreased options for CVAD placement	25 (66)
Persisting symptoms	23 (61)
Stent thrombosis	5 (13)
Bleeding while on anticoagulant use	4 (11)
Vena cava inferior syndrome	4 (11)
Septic lung embolism	1 (3)
Infected thrombosis	9 (24)

Abbreviations: CVAD, central venous access device; IQR, interquartile range; no, number; PTA, percutaneous transluminal angioplasty; SD, standard deviation; SVCS, superior vena cava syndrome.

3.4. CVAD tip during insertion and diagnosis

Seventeen percent (6/36) of patients who presented with SVCS had a correct position of the CVAD's tip on the post-insertion radiograph, and 11% (4/36) of patients had a correct position of the CVAD's tip on SVCS diagnosis imaging (Fig. 2).

3.5. Superior vena cava syndrome diagnosis and treatment

Table 2 presents all SVCS-related outcomes. A diagnosis was made in 66% using a computed tomography (CT) scan. At diagnosis, 30 patients had a significant occlusion, of which six had a total occlusion, and one had a non-significant occlusion. Diagnostic

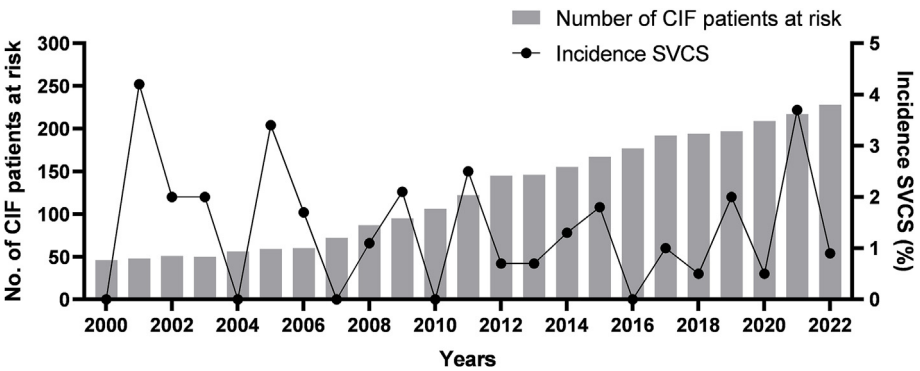

Fig. 1. Cumulative annual incidence rate of superior vena cava syndrome over the years 2000–2022. Abbreviations: CIF, chronic intestinal failure; No, number; SVCS, superior vena cava syndrome.

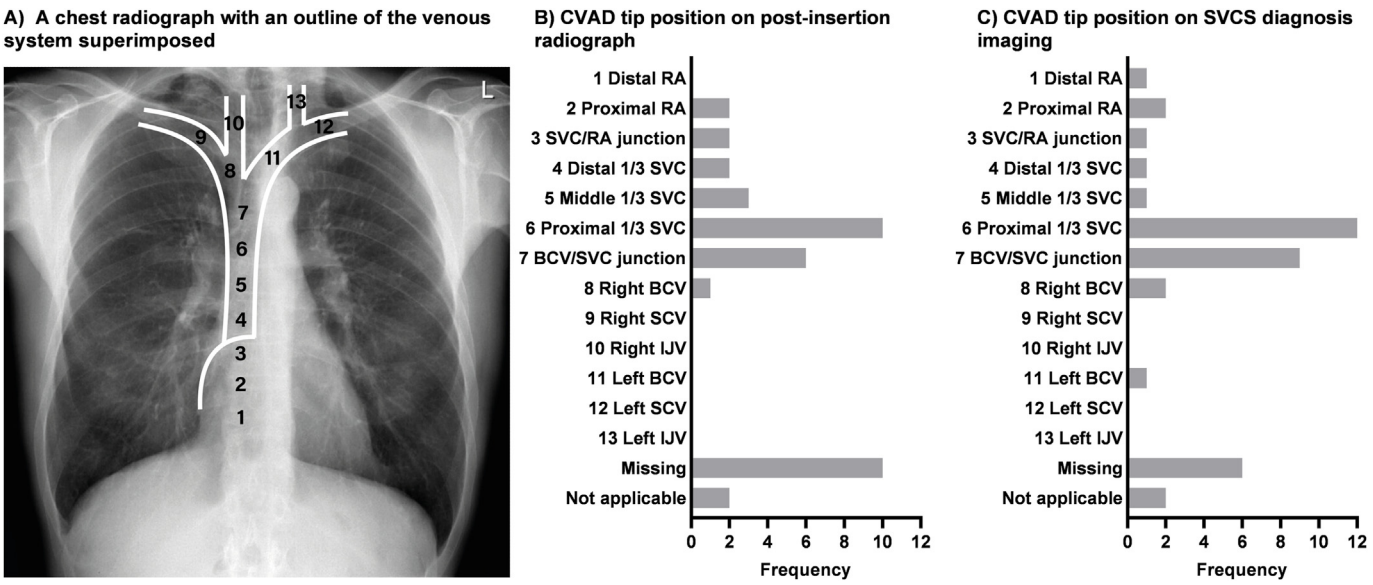

Fig. 2. A chest radiograph with an outline of the venous system superimposed (A) and CVAD tip position on post-insertion radiograph (B) and on SVCS diagnosis imaging (C). Line tip position given as: 1 distal RA, 2 proximal RA, 3 SVC/RA junction, 4 distal 1/3 SVC, 5 middle 1/3 SVC, 6 proximal 1/3 SVC, 7 brachiocephalic vein (BCV)/SVC junction, 8 right BCV, 9 right subclavian vein (SCV), 10 right internal jugular vein (IJV), 11 left BCV, 12 left SCV, 13 left IJV [17]. Not applicable: patients with arteriovenous fistula or CVAD located in femoral vein. Missing: no diagnostic imaging available. Abbreviations: BCV, brachiocephalic vein; CVAD, central venous access device; IJV, right internal jugular vein; RA, right atrium; SCV, subclavian vein; SVC, superior vena cava.

imaging was missing in seven patients. In addition, collateral vein formation was identified in 29 patients, while one did not have signs of collateral vein formation. In eight patients, diagnostic imaging was not available.

Subsequently, 63% of the patients started with anticoagulants; coumarin derivatives in 19 patients (83%), and four patients with low molecular weight heparin (LMWH, 17%). Four patients switched anticoagulant therapy, all from coumarin derivatives to LMWH. Eight patients continued their current anticoagulant (four patients (50%) coumarin derivatives and four patients their LMWH (50%)).

In total, 13 patients (34%) needed endovascular therapy after diagnosis. The most frequently used procedures were percutaneous transluminal angioplasty (PTA, 16 times) and stenting (11 times). The median time till endovascular therapy was 15 weeks (range 0–58 weeks). Endovascular treatment was performed repeatedly in six patients due to recurrent or persistent symptoms.

3.6. Superior vena cava syndrome consequences and follow-up

In total, 24 (63%) CVADs were removed, 19 (79%) due to SVCS-related symptoms or consequences, and 5 (21%) because of another reason (3 infections, 1 mechanical damage, and 1 stop HPN). Most CVADs were removed within 30 days after diagnosis, but two CVADs after a longer period (115 and 189 days) due to persisting symptoms.

Appendix Table 1 shows the long-term follow-up and illustrates patients reporting symptoms and/or whether imaging was available during follow-up. At 1 year of follow-up, 11 patients had a significant occlusion on imaging, of whom four had a completely occluded SVC, and two had a non-significant occlusion. Subsequently, at 5 years of follow-up, three patients had a significant occlusion, of whom two had a completely occluded SVC, and two had a non-significant occlusion. At 10 years of follow-up, all five patients had a significant occlusion, of whom four had a completely occluded SVC.

Of all patients, seven were referred to a transplantation center, of which only one eventually underwent a small bowel transplantation. The other six patients are still on the transplantation list, did not want a transplantation, or were deceased.

4. Discussion

Since HPN patients lifelong depend on their vascular access, which they often see as their lifeline, SVCS is a major threat in this regard. Because data on catheter-related SVCS are mostly anecdotal, we aimed to provide more robust data on the incidence and management of catheter-related SVCS in our large HPN referral center cohort. As shown in Fig. 1, we identified a cumulative annual SVCS incidence ranging from 0 to 4.2% per year. Although it has been suggested that the overall SVCS incidence seems to increase in this population in recent years, this was not corroborated by our findings [7].

Overall, our data support previous findings in HPN settings. Buchman et al. diagnosed 22 patients who developed either inferior vena cava syndrome or SVCS (4.2% of 527 HPN patients) with an incidence of 0.02 per catheter year [18]. Barco et al. reported SVCS in 12 patients out of 236 receiving HPN (5.1%), while Beers et al. diagnosed 15 cases in 107 HPN patients (14%; incidence 0.04 per patient-year) [6,9]. Interestingly, in 2021 we observed an outlier of eight SVCS cases (Fig. 1), of whom three were diagnosed with COVID-19 within three months prior to SVCS diagnosis. Obviously, the global pandemic may play a role here, given the known increased thrombosis risk of this infection as well as the associated immobility [19,20].

Most SVCS patients were symptomatic (97%), in contrast to the findings of Beers et al., who reported that 40% of patients were asymptomatic [9]. Most reported symptoms in our patients, in line with the literature, were facial (82%) and arm edema (50%) [4,21,22]. The median symptomatic period until diagnosis was quite substantial at 14 days (3–28), with five outliers, reasons for which were: other possible mimicking diagnoses considered (e.g. allergies, peripheral thrombosis, frontal sinusitis, and Cushing's syndrome), nontypical presentation, or lacking signs of (peripheral) thrombosis on ultrasound imaging. In the latter group, no other diagnostic modality, such as computed tomography (CT), had been

used. In addition, it is important to mention that one patient had a non-significant occlusion at imaging because all vessels draining the SVC were occluded, causing SVCS. The above findings emphasize that whenever a patient with a CVAD presents with possibly vascular obstruction-related symptoms, SVCS should always be ruled out using accurate radiological techniques, such as a CT scan.

In general, to decrease the CRVT risk, vessel wall damage should be minimized by using ultrasound-guided catheter insertion, with the tip of the CVAD placed at the atrio-caval junction [2]. The latter should be verified with diagnostic imaging (e.g., X-rays) during placement of the CVAD. We previously found that a right-sided approach is preferable over a left-sided placement to reduce the risk for CRVT [23,24]. SVCS in HPN patients is considered to be triggered by vascular damage and/or luminal obstruction with diminished blood flow due to the presence of a CVAD. An incorrect position with the tip too far away from the atrio-caval junction may increase the CRVT risk because the suboptimal alignment of the CVAD in the vessel causes the tip to damage the vessel wall and alter blood flow in the SVC [9,25]. In our cohort, in hindsight, only 17% of CVAD tips met the criteria for optimal placement, and even fewer patients at the time of SVCS diagnosis (11%, Fig. 2). This contrasts with findings by Beers et al., who reported only 13% atypical CVAD placements, but most likely relates to accepting a higher tip position (mid to distal SVC) by these authors and because insertion was only verified intra-operatively [9]. All CVAD tip positions in our study were revised by post-insertion radiography because the catheter position may alter upon changing to an upright position [25]. The origin of thrombosis may also originate from vascular damage following previous CVAD placement. This was suggested during revision by signs of pre-existing thrombosis, mainly septation and venous collaterals. These findings emphasize the urge for correct tip placement and (when feasible) considering an arteriovenous fistula as access mode rather than a new catheter in case of thrombotic central vessel damage.

In our cohort, in two-thirds of cases, a CT scan was used to diagnose SVCS; other options included fluoroscopy, phlebography, or ultrasound (Table 2). CT scan provides the most optimal visualization of the SVC and is, therefore, preferable for diagnosing SVCS [4,26]. Other imaging modalities may be sufficient in some cases, but these may lead to missed diagnoses. In our study, there was a diagnostic delay in three patients. One had SVCS clinical symptoms without such evidence on ultrasound. Four months later, a CT scan was performed due to persisting symptoms, and SVCS was diagnosed. This case exemplifies the importance of adequate imaging to avoid any delay in diagnosis and the start of appropriate treatment.

The treatment approach in HPN patients with SVCS is multidisciplinary and includes the treating HPN physician, (interventional) radiologist, vascular surgeon, and vascular specialist [4]. Initial management for HPN patients with SVCS includes tilting the head-side of the bed to decrease hydrostatic pressure in the superior body, lowering TPN volume, and/or extending infusion time. Next, anticoagulation is the mainstay of treatment [27]. Almost every patient in our cohort started or continued anticoagulant treatment. In one patient, CVAD removal proved sufficient for symptom control, although we usually do not remove CVADs upon SVCS development unless there is catheter dysfunction. Persistent symptoms can be managed using PTA, stenting, and recanalization, the most frequently used endovascular therapies in our cohort (Table 2).

The development of SVCS frequently has major consequences. We found that 95% of patients had remaining issues, the most prevalent being reduced options for CVAD placement (66%) and persistent symptoms (61%). Since the SVC is the final common pathway for all venous return to the heart, a problem at this level usually leads to serious problems for any new CVAD insertion. Although the femoral vein is often used as an alternate approach, this is less ideal due to the risk of infections and its location, especially in patients with an ostomy [24]. Moreover, these patients face the risk of developing inferior vena cava syndrome, which occurred in 4 (11%) of our patients. In case of reduced vascular access options, there are other exotic options like the placement of a CVAD through the thrombus or insertion of a CVAD through the hepatic veins into the caval vein or directly into the right atrium. In case of total loss of options for vascular access, intestinal transplantation is the last resort and in line with concurrent guidelines of IF and HPN care, timely referral to such a specialized unit should be urgently considered once SVCS develops.

This study comes with strengths and limitations. SVCS remains an underexposed topic in HPN care, and this is the first study that completely focuses on this topic. In addition, this is the first study that thoroughly revised all catheter tip positions with an expert interventional radiologist, and we provide guidance for such evaluation and further research. Our retrospective approach precludes statements on causality and carries a risk of underreporting information on SVCS, although we rigorously analyzed all patient data from our comprehensive HPN patient population. The available literature is seriously hampered by the absence of a uniform definition of SVCS. Future research would benefit from a uniform definition of new or recurrent SVCS.

In conclusion, in our CIF population, in contrast with our initial impression, we found no evidence of an increase in SVCS incidence in recent years, including the period that covers the COVID-19 pandemic. We describe the devastating consequences of SVCS, which should – whenever suspected – be recognized and treated as early as possible in HPN patients by a multidisciplinary expert approach. In addition, it is crucial to check for adequate placement of the CVAD tip to prevent or limit the development of this adversity.

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Author contributions

JK: Methodology, Formal analysis, Investigation, Visualization, Writing – original draft. VG: Methodology, Formal analysis, Investigation, Visualization, Writing – original draft. YW: Writing – review & editing. SJ: Investigation, Writing – review & editing. GW: Conceptualization, Methodology, Writing – review & editing.

Data share

Data described in the manuscript will be made available upon request pending application and approval by the corresponding author.

Conflict of interest

GW reports grants from Geistlich Pharma, and consulting fees from Geistlich Pharma and Zealand Pharma outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.11.027.

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