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KILT Syndrome: A Systematic and Historical Review

Francisco S. Lozano-Sánchez[1,3], Paula Velasco-Hernández[1], Oliver Bonnelly[1], Julián D. Flórez-García[1], Lucía Sánchez-Molina[1], José A. Carnicero-Martínez[1,2,3], José A. Torres-Hernández[1,2,3] and María Begoña García-Cenador[1,3*]

[1]*Department of Surgery, University of Salamanca (USAL), Salamanca, Spain.*

[2]*Angiology and Vascular Surgery Service, Salamanca University Hospital, Salamanca, Spain.*

[3]*Biomedical Research Institute (IBSAL), Salamanca, Spain.*

***Corresponding authors**

María Begoña García-Cenador,
Department of Surgery,
University of Salamanca (USAL),
Salamanca, Spain.

Francisco S. Lozano-Sánchez,
Department of Surgery,
University of Salamanca (USAL),
Salamanca, Spain

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Abstract

Background: *Kidney and IVC Abnormalities with Leg Thrombosis (KILT) is a rare condition that affects young individuals. It involves a clinical triad that consists of deep vein thrombosis of the legs, usually caused by a congenital abnormality of the inferior vena cava (IVC) that, in turns, leads to venous stasis, with the third component, also incidental, being the presence of unilateral renal agenesis.*

Aims: *A systematic review is conducted of the literature to understand the syndrome's current state from the following perspectives: a) clinical (presentation, diagnosis, and treatment), b) historical (before-and-after of the KILT acronym), and c) critical (evaluation of the syndrome's three components).*

Methods: *A systematic review using PRISMA methodology to identify the observational studies published in PubMed/Medline and Wiley/Cochrane Library that describe cases of KILT syndrome. The search concluded on December 15, 2023.*

Results: *The search produced 620 potential publications. Following the removal of duplicates, non-relevant studies, and appropriate screening, the final sample consisted of 27 studies covering 29 cases of KILT (19 males, eight females, and four non-defined, aged 29.8 ± 2.7 years at the time of the diagnosis). A descriptive analysis of their characteristics is provided.*

Conclusions: *KILT syndrome is an uncommon disorder, and the conclusions are based on a limited literature sample. Most of the cases share the symptoms of painful edema on the legs, the iliac location of the thrombosis, and the incidental diagnosis of full or partial agenesis of the IVC (with the appearance of collateral venous pathways) and renal hypoplasia with hypertrophy of the contralateral kidney. The diagnosis is based on imaging scans, and the long-term use of anticoagulants is the main form of treatment. The dearth of case studies limits a more precise understanding of recurrent thrombotic episodes and the post-thrombotic syndrome.*

Keywords: KILT Syndrome, Deep Vein Thrombosis, Inferior Vena Cava, Kidney

Introduction

Kidney and IVC Abnormalities with Leg Thrombosis (KILT) is a rare complaint that affects young patients of both sexes. It involves a triad in which the main symptoms are the presence of deep vein thrombosis (DVT) on the lower extremities, most often caused by congenital anomalies of the inferior vena cava (IVC) that interrupt the blood flow (second component of the triad), with the syndrome's third component being the incidental presence of unilateral renal agenesis (URA) [1].

Van Veen et al. [1] coined the KILT acronym in 2002, but since then very few cases have been reported in the literature, which means our understanding of the syndrome is limited (i.e., genesis, epidemiology, and natural history), as are its diagnosis and therapeutic treatment.

The aim here is to conduct a systematic literature review on the syndrome to explore the state-of-the-art from the following

perspectives:

- clinical (presentation, diagnosis, and treatment),
- historical (before-and-after of the KILT acronym),
- critical (evaluation of its three components).

Material and Methods

A systematic review involving methodological aspects of the PRISMA statement has been conducted to identify the observational studies in print that describe cases of KILT syndrome or a series thereof [2].

Search Methods: two researchers (FSL and BGC) and a librarian (TZV) conducted a search in English in Medline (through PubMed) and the Cochrane Library (through Wiley) from their first records through to the end of the search (December 15, 2023). No restrictions have been applied regarding language, type of publication, or date.

Inclusion Criteria: studies reporting on a case or series of cases of patients of any age, diagnosed with DVT in one or both of their lower extremities related to IVC and kidney disorders, generally agenesis (full or segmental) and unilateral hypoplasia, respectively.

The following keywords (MeSH terms) were used: "KILT" or "KILT Syndrome" in isolation and "Lower Extremities Deep Venous Thrombosis" or "Idiopathic Deep Vein Thrombosis" with "Inferior Vein Cava Anomalies" or "Inferior Vena Cava Agenesis" or "Inferior Vena Cava Atresia" or "Inferior Vena Cava Aplasia" or "Inferior Vena Cava Hypoplasia" or "Kidney Agenesis" or "Kidney Atresia", or "Kidney Aplasia" or "Kidney Hypoplasia", or "Renal Agenesis", or "Renal Atresia" or "Renal Aplasia" or "Renal Hypoplasia".

Exclusion Criteria:

- Anomalies in the IVC with DVT (Salgado et al., 1998 [3]; Tsuji et al., 2001 [4]; Lambert et al., 2010 [5]; Mentesidou et al., 2023 [6]; Alexiou et al., 2022 [7]),
- Anomalies in the IVC with kidney disorders (Gayer et al., 2003) [8],
- Anomalies in the IVC in isolation (Shafi et al., 2020 [9]; Saab et al., 2023 [10]); and
- Congenital kidney anomalies (Westland et al., 2013 [11]; Hutchinson et al., 2021 [12]). These topics have already been studied accordingly, with the most recent reviews being systematic.

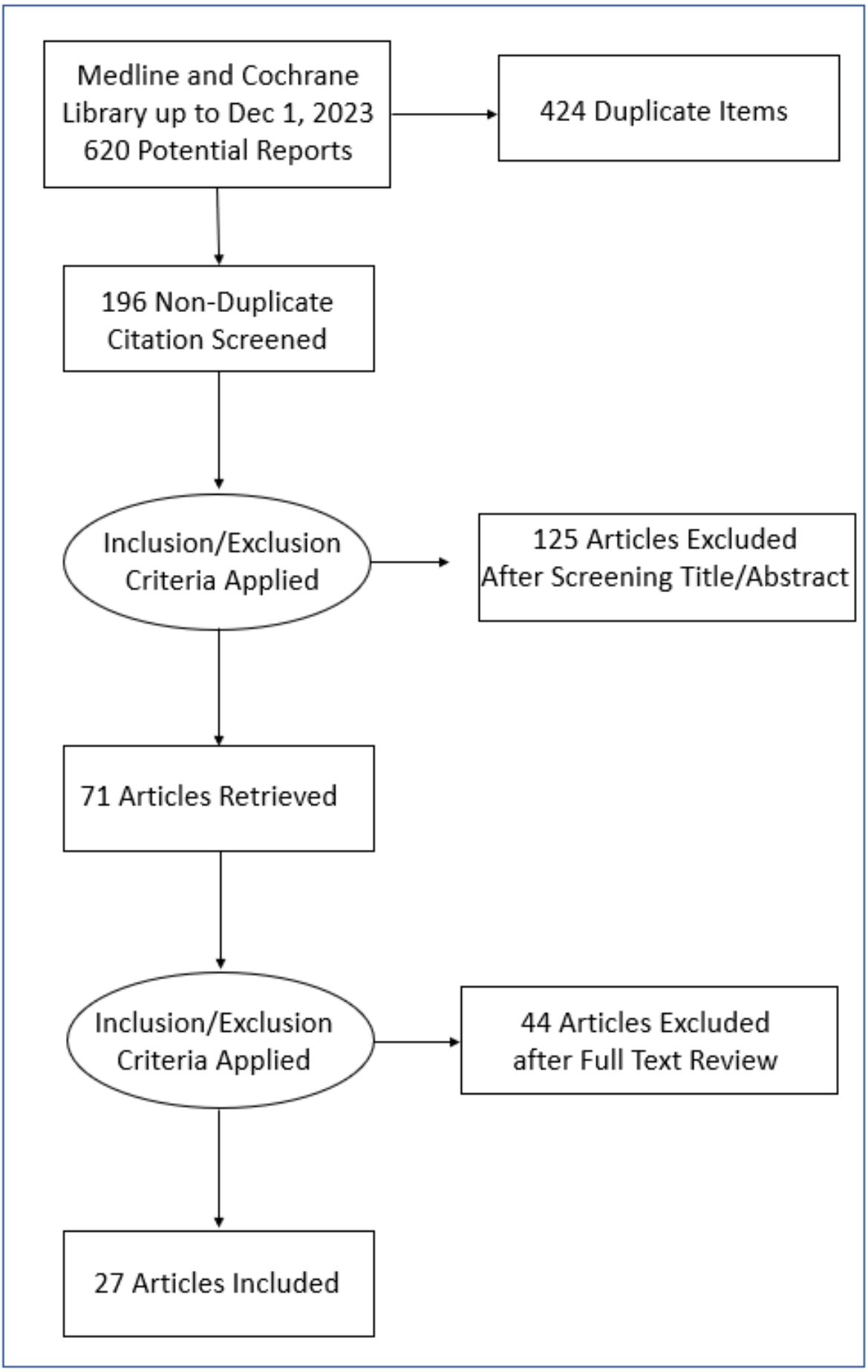
Data collection and analysis: a search has been made for KILT syndrome (*Kidney and IVC Anomalies with Lower Limb DVT*), with the aim being to highlight and understand their clinical, diagnostic, and therapeutic interest.

The search found 620 potential publications, of which 424 were duplications. The titles and abstracts of the remaining 196 articles were examined separately by two researchers (FSL and BGC), following which 125 references were discarded. This meant that only 71 articles were considered for our review. A further 44 articles were dismissed after reading the full manuscripts because they dealt with aspects that were collateral to the search's core purpose. Finally, this review considered 27 publications (Figure 1), including cases with incomplete clinical information (e.g., those not reporting on follow-up care).

Statistical Study

A descriptive and analytical study was conducted. The quantitative results are stated as means ± standard deviation and the qualitative data as percentages. The "T-Student Test" has been used for the statistical analysis, with a threshold of $p < 0.05$ for statistical significance.

This small number of publications/cases rules out the application of criteria of meta-analysis.


Medline and Cochrane Library up to Dec 1, 2023 620 Potential Reports
424 Duplicate Items
196 Non-Duplicate Citation Screened
Inclusion/Exclusion Criteria Applied
125 Articles Excluded After Screening Title/Abstract
71 Articles Retrieved
Inclusion/Exclusion Criteria Applied
44 Articles Excluded after Full Text Review
27 Articles Included

Results

Historical Review

Van Veen et al. (2002) have been credited with the coining of the KILT acronym [1]. Nevertheless, studies had already been published on cases that were consistent with KILT [3-4, 13-15] (Table 1). There are five well-documented cases of patients with DVT in their legs, bilateral in three cases, confirmed by ultrasounds. They were subsequently diagnosed, on an incidental basis, by a computed tomography (CT) scan and/or magnetic resonance imaging (MRI), with detection of the renal and IVC malformations that characterize the syndrome; the search for congenital thrombosis was negative in all cases, and none of the patients showed signs of pulmonary embolism (PE). Finally, all the patients underwent long-term treatment with anticoagulants. Therefore, for the purposes of our review, the Danish scholars Glerup and Therkildsen [13] were the first, in 1994, to report on a case consistent with KILT syndrome.

Table 1: Cases reported in the literature compatible with KILT syndrome before Van Veen et al. (2002)

Author/s [Reference]	Country, year	Sex/Age	Kidney anomaly	IVC anomaly	DVT (presentation/limb)
Glerup and Therkilden [13]	Denmark, 1994	M/18	Hypoplasia right kidney	Absent segment (NR)	Initial/unilateral
Salgado Ordoñez et al. [3]	Spain, 1998	M/49	Hypoplasia right kidney	Absent IVC*	Recurrent/unilateral
Timmers et al. [14]	The Netherlands, 1999	M/37	Absent right kidney	Absent segment (IH)*	Initial/bilateral
Chee et al. [15]	UK, 2001	F/26	Hypoplasia left kidney	Absent (NR segment)	Initial/bilateral
Tsuji et al. [4]	Japan, 2001	M/21	Hypoplasia right kidney	Absent segment (IH)* Stenosed (H) segment	Initial/bilateral

IVC, inferior vena cava; DVT, deep vein thrombosis; NR, not reported.
IVC segment: IH, infrahepatic; H, hepatic.
*Hypertrophic collaterality for azygos and hemiazygos system.

Our systematic review has identified 23 new cases [8, 16-35] in the 20 years since Van Veen et al. [1]. Overall, the databases consulted have recorded a total of 29 cases of KILT over the period 1994-2024 (Table 2). The distribution by countries, years, and decades is shown in Table 3.

Table 2: KILT syndrome. Literature review (29 cases)

Author/s [Reference]	Country	Year	Sex/ Age	Kidney anomaly (Side affected)	IVC anomaly (Segment level)	Lower Limb DVT presentation (Presentation and localization)	PE
Glerup & Therkilden [13]	Denmark	1994	M/18	Hypoplasia (R)*	Absent segment (NR)**	Initial/Unilateral (L, F-P)	NR
Salgado Ordoñez et al. [3]	Spain	1998	M/49	Hypoplasia (R)*	Absent IVC**	Recurrent/Unilateral (R, I-F)	NR
Timmers et al. [14]	Netherlands	1999	M/37	Absent (R)	Absent segment (IH)**	Initial/Bilateral (I-F)	Not
Chee et al. [15]	UK	2001	F/26	Hypoplasia (L)	Absent (NR segment)	Initial/Bilateral (I-F)	Not
Tsuji et al. [4]	Japan	2001	M/21	Hypoplasia (R)	Absent segment (IH)**	Initial/Bilateral (I-F)	NR
Van Veen et al. [1]	UK	2002	F/16	Hypoplasia (L)*	Absent IVC	Initial/Bilateral (NR)	NR
Gayer et al. [8]	Israel	2003	M/46	Aplasia (R)	Hypoplasia IVC	Recurrent/Unilateral (NR, I-F)	NR
Iqbal & Nagaraju [16]	UK	2008	M/54	Agenesis (L)	Absent IVC**	Recurrent/Unilateral (R, I-F)	NR
Lawless & Dangleben [17]	USA	2012	M/50	Hypoplasia (L)	Agenesis IVC**	Recurrence/Unilateral (R, F)	NR

Lavens et al. [18]	Belgium	2014	F/33	Aplasia (R)*	Hypoplasia IVC**	Recurrence/Unilateral (L, I-F)	Not
Bami et al. [19]	USA	2015	M/14	Hypoplasia (L)*	Agenesis segment (IR)**	Initial/Unilateral (L, I-F, F-P)	NR
Sagban et at [20]	Germany	2015	NR	Hypoplasia/ aplasia (L)	Agenesis (NR segment)	DVT confirmed (NR, I-F)	NR
			NR	Hypoplasia/ aplasia (R)	Agenesis (NR segment)	DVT confirmed (NR, I-F)	NR
			NR	Hypoplasia/ aplasia (R)	Agenesis (NR segment)	DVT confirmed (NR, I-F)	NR
Halpain et al. [21]	Australia	2015	M/14	Atrophic (L)*	Absent IVC	Initial/Unilateral (L, I-F)	NR
Duicu et al. [22]	Romania	2016	F/12	Hypoplasia (L)*	Absence complete**	Initial/Unilateral (R, I-F)	NR
Fung et al. [23]	China	2017	M/41	Hypoplasia (L)*	Atresia segment (IR)	Initial/Bilateral (I-F)	NR
Pomeranz et al. [24]	USA	2018	F/11	Atrophic (L)*	Absence complete**	Initial/Unilateral (L, F)	NR
Khalid et al. [25]	USA	2018	M/27	Hypoplasia (L)	Absence segment (H)**	Initial/Unilateral (R, I-F, F-P)	Not
Lauener et al. [26]	Switzerland	2019	M/40	Atrophic (R)	Atresia segment (H)**	Recurrent/Unilateral (R, NR)	Not
Rughani et al. [27]	Canada	2020	M/17	Atrophic (L)	Absence segment (S, R)	Initial/Bilateral (I)	Not
Moragón-Ledesma et al. [28]	Spain	2020	M/39	Atrophic (R)	Agenesis segment (H, S)**	Initial/Bilateral (I-F)	NR
Oblitas et al. [29]	Spain	2020	NR	Hypoplasia (NR)	Agenesis (NR)	Lower limb DVT confirmed (NR)	NR
Moshref et al. [30]	USA	2021	M/36	Atrophic (L)*	Agenesis IVC**	Initial/Unilateral (L, I-F, F-P)	NR
Kováčiková et al. [31]	Slovakia	2021	F/11	Hypoplasia (L)	Anomalies (NR)	Initial/Unilateral (NR)	NR
Klaib et al. [32]	Jordan	2021	M/24	Hypoplasia (R)*	Absence segment (H)**	Initial/Bilateral (I-F, F-P)	NR
Kannappan &Velavan [33]	USA	2023	M/35	Atrophic (L)*	Agenesis IVC**	Initial/Unilateral (L, I-F, F-P)	NR
Meyer & Hinestrosa [34]	Germany	2023	M/32	Hypoplasia (R)*	Agenesis IVC**	Initial/Unilateral (L, I-F)	NR
Lozano et al. [35]	Spain	2024	M/41	Agenesis (R)	Absence segment (H)**	Initial/Bilateral (I-F)	NR

M, male; F, female; IVC, inferior vein cava; DTV, deep vein thrombosis; PE, pulmonary embolism; R, right; L, left; NR, not reported.

*Associated with compensatory hypertrophy contralateral kidney; **Hypertrophic collaterality for azygos and hemiazygos system.

The four IVC segments: hepatic (H) (intrahepatic or retrohepatic), and infrahepatic (IH): suprarenal (S), renal (R) and infrarenal (IR).

Limb (R or L) and veins (I-F, iliac-femoral; F-P, femoro-popliteal; F, femoral).

Note: the terminology used in the table is that used by the authors in their respective articles.

Table 2: KILT syndrome. Literature review (cont.)

Author/s [Reference]	Diagnostic (Methods)	Thrombophilia	Treatment (Methods)	Follow up (Months)	PTS
Glerup & Therkilden [13]	US, V, CT	Negative	AC, VKA	NR	NR
Salgado Ordoñez et al. [3]	US, V, MRI, CT	Negative	AC	NR	NR
Timmers et al. [14]	US, CT, MRI	Negative	UFH, VKA, ES	NR	NR
Chee et al. [15]	US, CT	Negative	UFH, VKA	22 (no recurrence DVT)	NR
Tsuji et al. [4]	US, CT, MRI, V	Negative	UFH, UK, VKA, A, ES	NR	NR
Van Veen et al. [1]	CT	NR	NR	NR	NR
Gayer et al. [8]	CT	NR	NR	NR	NR
Iqbal & Nagaraju [16]	US, CT	NR	LMWH, VKA	NR	NR
Lawless & Dangleben [17]	US, V, MRI	NR	ICV filter	NR	NR
Lavens et al. [18]	US, CT	Negative	LMWH, VKA, ES	3	NR
Bami et al. [19]	US, CT, MRI	Negative	LMWH, VKA	NR	NR
Sagban et at [20]	US, CT, MRI	NR	AC	NR	NR
	US, CT, MRI	NR	AC	NR	NR
	US, CT, MRI	NR	AC	NR	NR
Halpain et al. [21]	US, CT, MRI	Negative	AC, VKA	12 (no recurrence DVT)	Yes
Duicu et al. [22]	US, CT	Negative	LMWH, VKA, A, ES	3 (no recurrence DVT)	Not
Fung et al. [23]	US, CT	NR	LMWH, VKA	NR	NR
Pomeranz et al. [24]	US, MRI	Negative	LMWH, VKA	3	NR
Khalid et al. [25]	US, CT	Negative	LMWH, DOA, ES, ET (1)	NR	NR
Lauener et al. [26]	US, CT	Negative	LMWH, VKA, DOA, ES, ET (2)	36	Yes
Rughani et al. [27]	US, CT	Factor VIII elevated	LMWH	6	Yes
Moragón-Ledesma et al. [28]	CT	Negative	LMWH, VKA	36	Not
Oblitas et al. [29]	US, CT, MRI	NR	LMWH	NR	NR
Moshref et al. [30]	US, CT, V	Factor V Leiden heterozygous	VKA, ET (3)	2	Yes
Kováčiková et al. [31]	US, CT, MRI	MTHFR mutation heterozygous	AC	NR	NR
Klaib et al. [32]	US, CT	F V Leiden/MTHFR heterozygous	LMWH, VKA	16 (no recurrence DVT)	NR
Kannappan &Velavan [33]	US, CT, V	Negative	UFH, A, ET (1)	NR	NR
Meyer & Hinestrosa [34]	US, MRI	Negative	UFH, VKA	NR	NR
Lozano et al. [35]	US, CT, MRI	Negative	LMWH, VKA, ES	60 (no recurrence DVT)	Yes

PTS, post-thrombotic syndrome; NR, not reported; MTHFR, methylenetetrahydrofolate reductase; ES, elastic stockings.
-Diagnostic methods: US, ultrasound; V, venography; CT, computed tomography; MRI, magnetic resonance imaging.
-Pharmacological treatment: AC, anticoagulation; UFH, unfractioned heparin; VKA, vitamin K antagonist (dicumarol or warfarin); LMWH, low molecular weight heparin; DOA, direct oral anticoagulant (rivaroxaban or apixaban); UK, urokinase; A, antiplatelet.
-Endovascular treatment (ET): (1) Direct thrombolysis, mechanical thrombectomy and balloon angioplasty; (2) Two endovascular treatments (venous stents) for PTS; (3) mechanical thrombectomy with catheter-directed thrombolysis.

Table 3. Summary (29 cases of KILT syndrome)

Publications		
By country Japan	16 countries (6 USA, 4 Germany, 4 Spain, 3 UK, and one Denmark, the Netherlands, Israel, Belgium, Australia, Romania, China, Switzerland, Canada, Slovakia, and Jordan)	
By year	29 cases between 1994 and 2024 (30 years; < 1/year) 24 cases post-definition KILT (Van Veen et al., 2002)	
By decade	1994-2000: 3 (Denmark, Spain, and the Netherlands) 2001-2010: 5 (3 UK, Japan, and Israel) 2011-2020: 15 (4 USA, 3 Germany, 2 Spain, Belgium, Australia, Romania, China, Switzerland, and Canada) 2021-2024: 6 (2 USA, Slovakia, Jordan, Germany, and Spain)	
Cases		
Sex (n, %)	19 males (76%) / 6 females (24%)4 NR	
Age in years (mean ± SD, interval)	Overall: 29.8 ± 2.7 (11-54) Male: 33.4 ± 2.9 (14-54) Female: 18.2 ± 3.8 (11-33	19/25 cases (76%) in 2nd - 4th decade 13/19 cases (68%) in 2nd - 4th decade 4/6 cases (67%) in 2nd decade
DVT (n, %)		
Presentation	Recurrent	6 (20.7%)
	Initial (not recurrent)	19 (65.5%)
	NR	4 (13.8%)
	Bilateral	9 (30.0%)
	Unilateral (6 Right, 8 Left, 2 NR)	16 (55.2%)
	NR	4 (13.8%)
Localization	Iliac-femoral veins	14 (48.3%)
	Iliac-femoral-popliteal veins	5 (17.2%)
	Femoral-popliteal veins	3 (10.3%)
	NR	7 (24.1%)
Pulmonary embolism	Reported	7 (24.1%)
	No PE	6 (85.7%)
	PE	1 (14.3%)*
	NR	22 (75.9%)
IVC (n, %)		
Anomaly	Full agenesis (absent)	10 (34.5%)
	Segmental agenesis	9 (31.0%)
	Full/segmental agenesis (NR)	6 (20.7%)
	Full hypoplasia	2 (6.9%)
	Segmental atresia	2 (6.9%)
Compensation	Azygos/hemiazygos system	18 (62.1%)
	NR	11 (37.9%)
Kidney (n, %)		
Anomaly	Agenesis (absent)	3 (10.3%)
	Aplasia	2 (6.9%)
	Hypoplasia/atrophy	21 (72.4%)
	Hypoplasia/aplasia	3 (10.3%)
Side affected	Right	13 (44.8%)
	Left	15 (51.7%)
	NR	1 (3.4%)
Compensation	Contralateral hypertrophy	13 (44.8%)
	NR	16 (55.2%)

*Not fatal; DVT, deep vein thrombosis; IVC, inferior vena cava; NR, not reported.

Table 3: Summary (cont.)

Diagnosis		
Clinical limb presentation (n, %)	Reported	16 (55.2%)
	Pain and swelling	9 (56.2%)
	Swelling	3 (18.7%)
	Pain	2 (12.5%)
	Swelling and cyanosis	1 (6.2%)
	Pain and cyanosis	1 (6.2)
	NR	13 (44.8%)
Methods (n, %)	Reported	29 (100%)
	Ultrasound	26 (89.7%)
	Venography/Cavography	5 (17.2%)
	Magnetic Resonance Imaging	14 (48.3%)
	Computed Tomography	26 (89.7%)
Thrombophilia	Reported	20 (69.0%)
	Test positive	4 (20.0%)
	Test negative	16 (80.0%)
	NR	9 (31.0%)
Alteration (n)	Factor V Leiden mutation heterozygous	1
	MTHFR mutation heterozygous	1
	F V Leiden and MTHFR heterozygous	1
	Factor VIII elevated	1
Treatment		
Pharmacological (n, %)	Reported	27 (93.1%)
	Anticoagulation (NR type)	7 (25.9%)
	Unfractionated heparin	4 (14.8%)
	Low molecular weight heparin	13 (48.1%)
	Antivitamin K	17 (63.0%)
	Direct oral anticoagulant	2 (7.4%)
	Urokinase	1 (3.7%)
	Antiplatelet	3 (11.1%)
	NR	2 (6.9%)
Endovascular techniques (n, %)	Number of cases	4 (13.8%)
	- Catheter/directed thrombolysis	2
	Mechanical thrombectomy	2
	Balloon angioplasty	1
	Venous stents	1
	Filter IVC	1
Association of methods (n, %)		19 (65.5%)
Reported elastic stockings (n, %)		7 (24.1%)
Follow/up		
Cases reported (n, %)	Reported	11 (37.9%)
	NR	18 (62.1%)
Months (mean ± SD, interval)	18.1 ± 5.7 (2-60)	

DVT recurrence (n, %)	Reported	5 (17.2%)
	Recurrence	0 (0)
	No recurrence	5 (100%)
	NR	24 (62.8%)
Post-thrombotic syndrome (n, %)	Reported	7 (24.1%)
	Positives	5 (71.4%)
	Negatives	2 (28.6%)
	NR	22 (75.9%)

NR, not reported; IVC, inferior vena cava.

The most extensive literature review (non-systematic) thus far is the one by the Swiss team of Lauener et al. [26]. They compiled 18 cases up to 2019, although these should be cut to 16 cases, as we understand that one of the cases reported by Duicu et al. [22] and the one described by Sing and Bhatt [36] do not involve the IVC of the lower extremities.

Systematic Review

It initially needs to be stressed that the term "KILT syndrome" applies solely to eleven references in PubMed/Medline [1, 19, 23-24, 26-28, 30-32, 34]. Nevertheless, there were expected to be many more cases (Table 2). Our review almost triples that figure by finding 29 cases, whose epidemiological and clinical aspects are grouped in Table 3.

KILT syndrome is more prevalent among males (by a ratio of 8:2) and LCV is diagnosed at an early age (mean of 29.8 within the range of 11-54 years), especially among females (18.2 ± 3.8 vs 33.4 ± 2.9; T = - 3.2098; p = 0.004).

It is important to note that DVT records high percentages of recurrent cases (20.7%) and bilateral ones (30.0%), and mostly affects the iliac sector (65.5%). Its most common clinical manifestation involves the spontaneous appearance of pain, edema, or both, in the leg(s). PE is rare (only in one reported case).

Its most common associated anomalies involve full or segmental agenesis of the IVC (86.2%) and renal hypoplasia/atrophy (72.4%). The azygos/hemiazygos system is often highly developed in these situations (62.1%), with hypertrophy of the contralateral kidney (44.8%). The renal lesion does not preferentially affect either kidney (51.7% of cases involve the left kidney).

DVT is usually confirmed by ultrasounds (89.7%). Subsequently, and incidentally, CT (89.7%) and/or MRI (48.3%) scans are used to detect IVC agenesis. The search for congenital thrombophilia tends to be negative (80% of the reported cases).

The treatment in all cases involved the long-term use of anticoagulants, with the most common medication being low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKAs). Direct oral anticoagulants (DOACs) were used solely in two cases. None of the patients with KILT underwent open surgery, although four underwent some form of endovascular procedure.

Follow-up care is reported in a third of the cases, with the duration varying (18.1 ± 5.7 months), reflecting the absence of thrombotic recurrences and five post-thrombotic syndromes - PTSs (with 71.4% of the cases evaluating this aspect).

Discussion

A critical reading of the literature sheds light on several matters that need to be discussed:

1. Are we dealing with an actual syndrome or simply with an acronym;
2. What is the exact definition of the syndrome?
3. Does the terminology (and synonyms) that define the syndrome's triad need to be clarified?
4. The syndrome's frequency;
5. Analysis of the triad's components, and finally,
6. Singling out the main aspects of clinical interest (diagnosis, treatment, follow-up, and prognosis).

Syndrome or Acronym?

KILT syndrome? Was the title of the first study on the subject; the question mark in the title already revealed the authors' doubts over whether they were dealing with a syndrome or simply coining a new acronym in English that would serve as a mnemonic aid [1]. The Oxford English Dictionary (OED) indicates that the word "syndrome" comes from Greek and means "a concurrence of several symptoms in a disease; a set of such concurrent symptoms", indicating a specific disorder or condition [37]. We may therefore affirm that we are dealing with a syndrome.

Definition of the Syndrome

This rare pathological association is encapsulated in the acronym KILT, proposed in 2002 by Van Veen et al. (Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Sheffield, UK). In the authors' own words: *"In view of the kidney and IVC abnormalities with leg thromboses, an appropriate name for this condition could be KILT syndrome"*; in other words, they defined it as a syndrome consisting of a triad involving kidney anomalies, IVC anomalies, and thrombosis in the leg [1].

All the scholars that cite the acronym KILT in their studies [16, 18-19, 22-23, 25-28, 30-32, 34-35] accept the above

definition. Nevertheless, considering that "*anomalies*" and "*leg thrombosis*" are somewhat vague terms, we concur with the definition provided by Moshref et al. [30]: "*Disorder consisting of renal and IVC maldevelopment, and Deep Vein Thrombosis*". This definition describes the complaints that affect the IVC and kidney as abnormal developments and affirms that the thrombosis should affect the deep venous system in the lower extremities.

Without rejecting the original definition mentioned, other scholars include renal and IVC agenesis in the triad, which Lauener et al. [26] describe as follows: "*The association of kidney atrophy, IVC atresia and thrombosis in the legs*", while Meyer et al. [34] define it as "*Dysplasia renal and vena cava inferior agenesia with thrombosis*". Nevertheless, these attributions are not wholly accurate, as these definitions exclude other anomalies that may also correspond to congenital renal and IVC anomalies caused by maldevelopment (abnormal development before birth), and which may also be part of the triad.

The question therefore is what anomalies of the kidneys and/or the IVC should be included in the definition? All congenital anomalies or only some of them? The original definition provided by Van Veen et al. therefore remains valid until there is greater consensus for its clarification.

Terminology and synonyms for the triad

The terminology used in the literature is clearly very varied and may sometimes lead to confusion (e.g., renal absent or absence, renal atresia, renal dysgenesis, IVC absent or absence, IVC interruption, and thrombophlebitis). We therefore propose the following [37]:

Regarding the renal component: include the congenital renal anomalies or agenesis that affect the number, shape, and/or macroscopic size of the kidney

- Renal agenesis: total absence of the kidney and its embryonic trace. Bilateral cases are not compatible with life.
- Renal aplasia: absence of a kidney due the failed development of its embryonic trace. The kidney may appear as a small, non-differentiated and non-functional lump of fibrous tissue. Some scholars use it as a synonym for agenesis.
- Renal hypoplasia: this describes a small kidney due to its partial development caused by pathological events in fetal stages. The kidney is congenitally reduced in volume, weight, and size. The term renal atrophy (used in as many as eight studies on KILT) may function as a synonym for hypoplasia, provided that the atrophy is congenital and not acquired. Atrophy involves the reduction in an organ's size through the loss of protoplasmic mass. They are regressive changes accompanied by a reduction in the size of an organ or tissue once it has reached its full size or development; in other words, a normal organ begins to shrink. The difference with hypoplasia is that this reduction in size takes place after an organ's normal development.
- Renal atresia: the term "atresia" is better employed for tubular structures and not for solid organs (see IVC atresia below).
- Renal dysgenesis: partial or full maldevelopment of the organ, especially during the embryonic stage. It is a very general and ambiguous term.
- Renal dysplasia: this refers to qualitative anomalies that affect tissue quality, as do metaplasia and anaplasia. Its diagnosis is histological.

Renal aplasia and hypoplasia may also be included under the broader term of renal dysplasia, whereby these malformations fully constitute renal digenesis.

In sum, we recommend using the terms "agenesis", "aplasia", and "hypoplasia" (the last of these is preferable to "kidney atrophy"), and discard "kidney atresia", "kidney dysgenesis", and "kidney dysplasia".

Concerning the IVC component: this should include the congenital malformations or anomalies of the IVC that lead to narrowing (stenosis) or interruption (complete blockage)

- Full agenesis of the IVC: complete absence of the vein and its embryonic trace.
- Segmental agenesis of the IVC: partial break in the vein's pathway due to the absence of one or more of its four segments during its development. It also interrupts the normal flow of blood.
- IVC atresia: narrowing, reduction, or full blockage of the vein lumen. It is partly synonymous with full or segmental agenesis. It diminishes blood flow.
- Aplasia and hypoplasia of the IVC. Some scholars use other terms, which are akin to full or partial agenesis.

We recommend discarding the following: IVC absent or absence and IVC interruption, which do not accurately define the pathological state that affects the IVC.

As regards the thrombosis component: venous thrombosis should affect the following: a) the lower extremities, and b) the deep vein system, excluding the superficial venous thrombosis that affects the saphenous systems. This means that the use of the term "thrombophlebitis" is inappropriate.

Following these minor recommendations, future studies on KILT syndrome might be rendered more uniform and, together with other matters that will be discussed here in due course, lead to its better understanding and analysis. This will facilitate the syndrome's identification and avoid confusions or pseudo-KILT [6, 22, 36, 38-43] (Table 4).

Table 4: Eleven cases reported in the literature "compatible" with KILT syndrome (pseudo-KILT)

Author/s [Reference]	Country, year	Sex/ Age	Kidney anomaly	IVC anomaly	DVT localization (limb)
Provost et al. [38]	USA, 1971	M/20	Aplasia (R)	Hypoplasia IVC	Dilated veins in abdominal wall
Obernosterer et al. [39]	Austria, 2002	M/24	Triplicate renal artery (R) and duplicate renal artery (L)	Hypoplasia hepatic segment Absent renal segment	Ilio-femoral veins (bilateral)
		M/35	Duplicate renal artery (R)	Hypoplasia hepatic segment	Previous iliac vein (R) Ilio-femoral veins (L)
Lau et al. [40]	China, 2003	M/7	Bilateral partial rotation*	Absent renal segment	External iliac vein (R)
Garcia-Fuster et al. [41]	Spain, 2006	F/27	Hypoplasia renal vein (L)	Duplicate IVC	Common iliac vein (L)
		F/30	Agenesis (R)	Duplicate IVC	Common iliac vein (L)
La Spada et al. [42]	Italy, 2011	M/35	Atresia renal vein (L) Non-functional kidney (L)	Absent hepatic segment	Ilio-femoral veins (bilateral)
Duico et al. [22]	Romania, 2016	M/12	Hypoplasia (L)	Absent infra-hepatic segments	No DVT in limbs Renal thrombosis (R) and azygos veins
Singh & Bhatt [36]	India, 2017	F/28	Hypoplasia (L)	Agenesis IVC	No DVT in limbs Pelvic Congestion Syndrome
Gantes et al. [43]	Portugal, 2020	F/28	Absent (R)**	Absent IVC	Ilio-femoral veins (bilateral)
Mentesidou et al. [6]	Greece, 2023	F/8	High echogenicity***	Agenesis IVC	Ilio-femoral veins (bilateral)

IVC, inferior vena cava; DVT, deep vein thrombosis; M, male; F, female; R, right; L, left.
*With anomalous venous drainage (both kidneys); ** Nephrectomy for nephroblastoma ***Kidneys of normal shape and side.

NOTES

1. In a normal kidney ultrasound, the renal parenchyma should be hypoechogenic. In renal malformations, this hypoechogenicity is a sign of renal dysplasia, often with microscopic cysts. The loss of the difference in echogenicity between the renal medulla and cortex is likewise a sign of the lack of tissular differentiation or renal dysplasia.
2. The four IVC segments: hepatic (intrahepatic or retrohepatic), and infrahepatic: suprarenal, renal, and infrarenal.
3. Cursive lettering is used to indicate the failed component in the KILT triad.

Prevalence of the Syndrome

KILT syndrome is rare and little known, with its diagnosis usually being incidental in the imaging scans required for a better understanding of DVT in young patients. Although there are likely to be many more cases that have not been reported, we have managed to identify 29 (1/year).

Components of the syndrome's triad

DVT in the legs in young patients

Since Rudolf Ludwing Karl Virchow described the triad that bears his name (1856), the incidence of venous thrombosis has been reported to increase with age among both males and females, largely as of the age of 40-60. According to the 2004 LITE study, the race- and sex-adjusted incidence of venous thromboembolism (VTE) per 1,000 person-years was 0.72 in those aged 40 to < 55, 1.58 in those aged 55 to < 65, 2.47 in those aged 65 to < 75, 3.12 in those aged 75 to < 85, and 6.96 in those aged ≥ 85 [44]. The incidence increases twofold per ten-year tranches, and 60% of all VTE events occur in patients aged > 65 [45].

The estimated average annual rate of overall VTE among persons of European ancestry ranges from 104 to 183 per 100,000 person-years. VTE predominantly affects older people and is rare prior to late adolescence [46-47]. The incidence of DVT is estimated to be 1 per 1,000 person/year, being tenfold less in adults aged 20-40 [48]. DVT in minors (aged < 18) is much lower (< 1 per 10,000 per annum) than in adults (0.5-1 per 1,000 per annum) [49].

Within this context, different registers record a peak in DVT during childhood and adolescence [27]. These peaks are related largely to the presence of diverse congenital thrombophilia and congenital malformations of the IVC. It is estimated that young patients with DVT record higher rates of IVC anomalies than the general population (5% vs 0.5%) [15, 19, 50].

It should be noted that PE as a complication of DVT associated with IVC agenesis is rare, probably due to an anatomical anomaly of the IVC [5, 51], although there are exceptions [52-55], as also occurred in our case [35].

Anomalies of the IVC

The most frequent anomalies of the IVC are agenesis, duplication, and the presence of a retro-aortic left renal vein (RLRV). In 1920, Huntington and McClure proposed a classification of IVC anomalies consisting of as many as 11 theoretical variations of the IVC [56].

Malformations of the IVC as a whole are rare and appear in 0.3-0.5% of the general population and in 0.6-2% of patients with cardiovascular conditions [26]. In an extensive study conducted recently, the prevalence of IVC malformations was 1.8% (normal cohort), rising to 6.3% in the group with DVT, while the most common malformation in the normal group involved duplication (1.0%), with the group with DVT manifesting agenesis (hypoplasia (4.0%) and aplasia (0.9%)) [57].

The first recorded case of agenesis of the IVC (defined as atresia) was reported in a ten-month old child in 1793 by a British surgeon called John Abernethy [10]. In 1891, Wardrop Griffith reported an adult case. Finally, in 1900, Dwight compiled 20 cases, one of which was found during the autopsy on a 91-year-old man [58]. The rate of agenesis of the IVC in the general population ranges between 0.0005% and 1% [59].

The embryogenesis of the IVC is somewhat complex, as during the sixth and eighth weeks of gestation, the IVC undergoes a process of fusion and regression that involves three pairs of primitive veins (postcardinal, subcardinal, and supracardinal), which form the four segments of the adult IVC (hepatic, suprarenal, renal, and infrarenal) [56]. The absence of the IVC can therefore be explained by the complete or partial failure of the cardinal veins to develop accordingly. Agenesis of the suprarenal segment is the most common variant, while agenesis of the renal and infrarenal segments is rarer [61]. Although the reason for such failure is not known, there are two mechanisms that are considered responsible for this malformation: 1) embryonic dysontogenesis between the sixth and eighth weeks of gestation [5, 8, 39], and 2) an intrauterine or perinatal thrombosis that obstructs and subsequently inhibits the development of the IVC [26, 60].

The literature abounds in cases of full or segmental agenesis of the IVC reported by pediatricians, radiologists, and surgeons [38]. Nevertheless, even the complete interruption of the IVC is usually asymptomatic and normally detected incidentally. Indeed, agenesis of the IVC remains asymptomatic in most cases until the appearance of DVT, and only rarely does it cause non-specific symptoms such as lower back or abdominal pain, mainly after intense physical exercise, or bilateral varicose veins or edema in the legs [4-5]. These IVC anomalies are therefore considered an independent risk factor of DVT in the legs [9, 15, 19, 50, 55, 57]. Fortunately, PE is not common in these situations [51-53].

A systematic review conducted in 2020 on congenital anomalies of the cava vena in adults and their clinical implications [9] identified 16 relevant articles whose analysis revealed two significant clinical findings: 1) congenital IVC anomalies are associated with a 50–100-fold higher risk of DVT, particularly among younger patients, and 2) persistent left superior vena cava (PLSVC) is associated with a 2–3-fold higher risk of supraventricular arrhythmias.

A second systematic review conducted more recently in 2023 involved 376 patients with atresia of the IVC. It reported how 64.3% of the cases had DVT, with 65.7% affecting the iliac veins [10].

In IVC agenesis, the body compensates for its absence through extensive collateral circulation; nonetheless, the blood flow in the legs is slower, increasing the pressure in the veins, venous stasis, and occasionally DVT [39]. In the specific case of an abnormal development of the infrarenal IVC, blood from the iliofemoral veins is diverted via paravertebral anastomosis and then by the system of azygos and hemiazygos veins. Inadequate venous drainage is not fully compensated for and may lead to chronic venous stasis and DVT in the legs, as is commonly observed in those patients affected [24, 56].

In 1998, Salgado et al. [3] compiled six cases of IVC malformations associated with DVT. Three years later, Tsuji et al. [4] gathered a further ten cases (four of which involved KILT syndrome; that is, with additional renal hypoplasia/aplasia). Both reviews cite Halbmayer et al., 1993 [62] as the authors of the first study on the matter. Our own group's cases should be added to these earlier ones [63].

In 2010, Lambert et al. [5] reported ten individual cases of IVC agenesis associated with DVT and included a review of the literature on 62 more cases (including six KILT). The DVT in this review was bilateral in 35.4% of the cases, with PE in 9.7%. Thrombophilia studies were requested in 18.6% of the cases involved.

Finally, it should be noted that an increase in inherited coagulation anomalies in patients with IVC agenesis has been suggested [20]. A previous systematic review involving 376 patients with IVC atresia describes changes in coagulation in 85 patients (22.6%). The subgroup of 242 cases with atresia and DVT recorded coagulation anomalies in 82 patients (33.8%), with only three recording IVC atresia without DVT [10]. Certain hypercoagulable conditions such as factor V Leiden, methylenetetrahydrofolate reductase (MTHFR) gene mutation, and homocysteinemia were reported to be more prevalent in the IVC atresia group [10, 20].

Kidney Abnormalities

"CAKUT" is an acronym in urology that stands for Congenital anomalies of the kidney and urinary tract. It encompasses a broad spectrum of congenital conditions, including renal anomalies such as aplasia, hypoplasia, multicystic dysplasia, renal dysplasia, ureter anomalies such as megaureter,

ureteropelvic junction obstruction, ureterovesical junction obstruction and incompetence, duplex kidneys/ureters, and bladder and ureter anomalies.

Congenital renal anomalies are polymorphous, given that they are interrelated with each other and with other kinds of malformations. They may be classified according to their number, position, shape, and size.

- Anomalies in number: a) bilateral renal agenesis: the absence of both kidneys is incompatible with life; b) unilateral renal agenesis: more frequent, compatible with life and asymptomatic; and c) supernumerary kidneys: rare, deformed, ectopic, and sometimes fused.
- Anomalies in position: a) malrotation: generally around the kidney's vertical axis, unilateral or bilateral; b) ectopia: the abnormal location of the kidney. More prevalent among males, on the left-hand side and in the pelvic cavity.
- Anomalies in shape: a) horseshoe kidney; b) renal fusion: it generally involves a crossed renal ectopia, with both kidneys being fused.
- Anomalies in size: a) renal aplasia: this involves a small lump of fibrous tissue that is non-differentiated and non-functional; b) renal hypoplasia: the kidney is congenitally reduced in volume, weight, and size. It may affect one or both kidneys in a complete or partial manner.

Kidney development involves the following three phases: pronephros, mesonephros, and metanephros, which proceed sequentially in a craniocaudal direction, slightly overlapping in time. The development of the metanephros or definitive kidney has two parts: the metanephric mesoderm, which forms the nephrons, and the ureteral bud formed by the evagination of the mesonephric or Wolffian duct, giving rise to the ureters, renal pelvis, calyces, and collecting tubules. The kidneys are formed around the fifth week of the embryo's development, with generation of the metanephric mesoderm, and they move toward the lateral section of the embryo body. The maldevelopment of the distal mesonephric duct leads to the absence of the ureteral bud, and consequently renal agenesia or dysplasia. The kidneys are initially located in the pelvis, but they ascend at the end of the embryonic stage, during the eighth week of embryonic development (tenth week of gestation), due to the major development of the lumbar region and sacrum [64].

Although rare, renal agenesis, aplasia, and hypoplasia are the most common kidney malformation described in patients with no IVC [8, 19, 31]. The three are due to a deficient renal development [64]. Agenesis is the total absence of a kidney due to its complete failure to develop, with no traces of nephrogenic issue where the kidney is normally located. Aplasia means there is only a small indistinguishable or barely differentiated mass of tissue where the kidney should normally be; the ureter, if indeed present, does not reach the organ and there is no evidence that the affected kidney is functioning. In hypoplasia, the organ is present and identifiable, but it is very small; it performs its excretory function, although generally well below normal [8].

Unilateral renal agenesis is often asymptomatic and may go undiagnosed until later in life, when incidental findings during medical explorations reveal the condition [65]. The healthy kidney often plays a compensatory role (hypertrophy). An estimate of the incidence of bilateral agenesis is 0.1/1,000 births [66]. Unilateral renal agenesis is more common, although the frequency is difficult to estimate, as it is usually clinically silent. A systematic review of unilateral renal agenesis (which covers over 2,000 cases, out of more than 4,250,000 individuals surveyed) reveals an incidence of 0.5/1,000; there is also a slightly higher frequency of unilateral agenesis in the left kidney and a significantly higher rate among males [11].

It is difficult to differentiate between a diagnosis of renal agenesis and renal aplasia; indeed, many researchers conclude that most of the cases of renal agenesis that are clinically diagnosed could be more accurately referred to as renal aplasia [67]. At the same time, from a functional perspective, an aplastic kidney should in practice be considered on a par with agenesis, which is why numerous scholars affirm that aplasia means the total absence of the kidney. In short, they are different conditions, although similar in practice.

Beumer, in 1878, and Ballowitzer, in 1895, were the first to report hypoplasia or congenital atrophy. Congenital renal hypoplasia is a rare cause of a small unilateral kidney, with a higher rate of those pathological situations that lead to acquired renal atrophy. The incidence of small kidneys was reported to be as high as 2/1,000. Nevertheless, congenital renal hypoplasia occurs in 0.27/1,000 pregnancies (bilateral cases are sevenfold less frequent) [68-69].

Hypoplasia/atrophy involves fewer calices and nephrons, albeit without dysplastic or embryonic components; in other words, the kidney is structurally sound, as opposed to renal dysplasia. This means that at least in certain places in hypoplasia, the parenchyma is normal, and the kidney can function. Hypoplasia is diagnosed when the following criteria coincide [66]: 1) Reduction by two standard deviations in the mean of the true size according to age; 2) Exclusion of renal damage with 99m technetium dimercapto-succinic acid (99mTc-DMSA), and 3) in cases of unilateral renal hypoplasia, compensating hypertrophy of the contralateral kidney. The clear distinction between these two conditions therefore depends on a histological examination of the kidney tissue obtained by a biopsy or surgical nephrectomy, which are rarely performed.

The etiology of congenital hypoplastic kidney is attributed mainly to a halt in development due to ischemia during embryogenesis. The absence of IVC at this stage, as referred to previously, may compromise the venous drainage of the right-hand metanephros, leading to the abnormal growth of the right kidney. The left kidney is not affected because of the alternative drainage pathway; the left metanephros drains via the gonadal vein and the lumbar perforators [70]. Nevertheless, the literature describes patients with IVC malformation coexisting with agenesis or atrophy (aplasia and/or hypoplasia)

of the left kidney [8, 19, 24]. In 1914, Papin, reported that the condition was more common on the right-hand side, whereas in 1954 Bell stated that it was the left-hand side. Our review of KILT cases also reveals a preference for the left (51.7%, which increases to 65.0% in cases of hypoplasia/atrophy; 13 out of 20).

These circumstances lead to hypertrophy (not hyperplasia) of the kidney contralateral to the atrophied one [24]. Our review describes contralateral hypertrophy in more than half of the cases of renal hypoplasia/atrophy (12/21; 57.1%).

In 2003, Gayer et al. [8] recorded 11 past cases of IVC malformation associated with aplasia of the right kidney (five of which were KILT syndrome; that is, also with DVP in the legs). Their study cites Provost et al., 1971 [38], as the authors of the first publication on the topic.

Finally, some publications cite the exceptional case of the sole incidence involving two young siblings (male and female) with malformation of the IVC and renal aplasia reported by Duicu et al. [22]; it should be noted, however, that the brother never recorded a DVP in his legs, and does not therefore complete the triad of the KILT syndrome.

Despite the above, the renal part of KILT syndrome is a priori the one with the least clinical impact from both a symptomatic and prognostic perspective (see prognosis at the end of the article).

Diagnostic aspects of the Syndrome

The diagnosis of KILT syndrome is generally incidental. It is usually detected when patients seek medical help because of edema and/or spontaneous pain in one or both legs, with no other condition of interest. The performance of an ultrasound scan or Doppler echocardiography test confirms/dismisses the existence of DVT, as their high sensitivity and accuracy have been well established for locating venous thrombosis.

Considering that DVT in the legs is diagnosed mainly in young adults, the information in the literature on pediatric cases is very scarce or non-existent [39].

The clinical profile that may point to KILT syndrome involves a young patient (aged 20-40) with an unprovoked iliofemoral DVT, presenting a medical history without any apparent factors of risk of thrombosis [8]. The bilaterality and recurrence of thrombosis are other "telltale" signs to be considered.

The percentage of IVC anomalies in patients with DVT has probably been underestimated because, in most cases, a standard ultrasound scan does not provide a suitable examination of the abdominal veins [50]. This means that DVT in children, adolescents, and young adults with no other risk factors should be thoroughly examined using a multimodal imaging approach [5, 51, 71].

Computed tomography (CT) scans with contrast and/or magnetic resonance imaging (MRI) of the thorax, abdomen, and pelvis are the techniques of choice when searching for anomalies of the IVC and kidney [5, 51, 71-72]. The venography/cavography some recommend may be performed in certain cases [73].

If, therefore, an ultrasound is insufficient because of the scanner or patient factors, MRI is sensitive enough to detect IVC anomalies without the need to use ionizing radiation. Anesthesia may be required in children. CT angiography (CTA) tends to be the most common imaging technique for the initial detection of IVC conditions and corresponding pathological findings [72].

Some scholars have conjectured an increase in inherited anomalies in coagulation among patients with IVC agenesis and DVT, which therefore calls for a detailed study of thrombophilia [20]. Regardless of whether this is true or not, it remains to be confirmed among young people with DVT. The diagnostic procedure should include laboratory tests to exclude the possibility of autoimmune processes, as well as studies on inherited thrombophilia (e.g., Factor V Leiden) [24].

In sum, damage to the IVC should be considered in young patients with DVT, especially when it is proximal and there are no apparent risk factors (i.e., immobility, contraceptives, and traumatism) [5, 73]. Inherited anomalies in coagulation often appear to be a factor that contributes to DVT as regards damage to the IVC [20].

Our review of the literature that involves the acronym KILT (Tables 2 and 3) confirms the youthfulness of patients when they are diagnosed with DVT, together with its possible bilaterality and recurrence. Full or partial agenesis of the IVC is by far its main alteration. The left kidney was the one affected in 15 cases, mainly by renal hypoplasia/atrophy. This finding contrasts with a review (IVC agenesis and DVT) in which the right kidney was affected slightly more often (4.9% and 2.4% for right and left, respectively) [20]. These percentages also coincide with those stated in the sections on embryology, but not with the data presented in this systematic review.

Treatment, follow-up, and prognosis of the syndrome (and its components)

There is no known algorithm for treating KILT syndrome, among other reasons because of the rarity of the complaint and the lack of studies accordingly. The most suitable treatment for most patients with acute DVT clearly requires administering anticoagulants. Nevertheless, there is no agreement on the treatment itself (e.g., medication and duration). The unfractionated heparin (UHF) used in the first cases was superseded by low molecular weight heparin (LMWH), followed by vitamin K antagonists (VKAs) (dicoumarol-derived anticoagulants or warfarin) and more recently direct oral anticoagulants (DOAs) (rivaroxaban or apixaban) [25-26]. A few cases include a platelet agglutination inhibitor (aspirin or clopidogrel) in the treatment, always accompanied by anticoagulants [4, 22, 33].

There are no data on the appropriate duration for the treatment with anticoagulants. As the absence of the IVC is a permanent risk factor in DVT, a very long-term approach [13, 26] or even an indefinite one [19, 22, 24] appears to be the logical anticoagulant treatment. Furthermore, there is little information on the benefits of DOAs in long-term treatment.

With a view to providing information on DOAs, we have referred to a recent retrospective study that reports on a cohort of 11 patients diagnosed with IVC agenesis following a DVT (not KILT), who subsequently received extended treatment (4.5-year follow-up) with a DOA (nine with rivaroxaban and two with apixaban). These findings offer reassuring insights into the extended utilization of DOA, demonstrating both antithrombotic efficacy (no relapse) and a favorable safety profile (no bleeding) [74].

Besides indefinite treatment with anticoagulants, the use of elastic stoking (ES) is recommended as a gold standard in this treatment [5, 19, 55, 75]. Nevertheless, the use of ES, which should be mandatory (as its theoretical benefits outweigh the risks involved), is mentioned in only 24.1% of the articles on KILT [4, 14, 18, 22, 25-26, 35].

The gradual incorporation of endovascular techniques (mechanical and pharmacological thrombolysis) are recent options that further complicate the search for the most appropriate treatment. In selected cases of acute DVT involving alterations of the IVC, catheter-directed thrombolysis (CDT) and/or the insertion of a stent have been successfully applied [5, 55, 71, 76-77]. Mechanical thrombectomy (by suction) has been successfully used to treat DVT in a patient with IVC hypoplasia [78]. The next step involves anticoagulants and ES. These options have been used in four cases of KILT [25-26, 30, 33].

An interesting systematic review has been conducted of patients with congenital IVC anomalies, comparing the conservative treatment of DVT with catheter-directed thrombolysis-CDT [7]. The review involves 56 patients (68% with anticoagulants and 32% with thrombolysis). Residual chronic symptoms are more frequent in the anticoagulant group (42.3% vs 11.5%, respectively), as is the recurrence of DVT (13% vs 7%, respectively) and PTS (11.5% vs 0%, respectively).

Open surgery (different bypass configurations were used, with a number of patients undergoing concomitant arteriovenous fistula or temporary IVC filter placement), is reserved for cases with serious symptoms. In the case of PTS, consideration should be given to the possible benefits of surgery for correcting the venous defect, as proposed by Dougherty et al. in 1996 [79], and which has subsequently been selectively applied by others [20, 42, 77, 80-81].

As in other parts of this discussion addressing the topic of surgical treatment, we have referred to the findings of a systematic review of IVC agenesis. Out of 376 cases, 89 (23.6%) were treated with endovascular or open surgery. The IVC was repaired in 41 patients (18.3%), with 22 involving endovascular rechanneling and 19 open reconstruction. Open and endovascular surgical interventions to treat IVC atresia have been reported in 18.3% of patients reviewed, with acceptable medium-term results in terms of patency and symptomatic relief [10].

Follow-up and Prognosis

It is rare to encounter any follow-up to the cases analyzed, and in those cases that do so (37.9%) it is only for a limited period (18.1 months on average). This does not provide for an accurate percentage of thrombotic relapses or the appearance of PTS over 3-5 years.

Although it does not involve KILT patients, a retrospective study on 18 patients (aged 13-18) with IVC atresia and DVT from two different locations identified three cases of PE (17%), five of recurrent DVT (28%), and ten of PTS (56%). They are mostly moderate (according to the Villalta scale), with an average follow-up of 21 months [55].

With the appropriate and uninterrupted use of coagulants, the prognosis for the life expectancy of these patients is good [5]. Nevertheless, the data are too limited to provide a benign prognosis, as the risk of morbidity is high largely because the patients diagnosed are young and morbidity is expected to increase with age; this means it is essential to apply a thorough vascular and nephrological control throughout their lifetime. This allows for the early detection of possible complications.

The congenital anomalies that affect one of the kidneys do not usually have a serious impact on the overall renal function. A systematic review [12] of 885 patients diagnosed with unilateral renal agenesis has found that the risk of developing proteinuria, hypertension, and/or impaired renal function among children is low (< 10%). However, the evidence available in the literature is weak, so monitoring for signs of kidney damage is therefore recommended throughout life [82]. Control of the renal function and regular follow-up examinations facilitate the early detection of any potential complications or changes in kidney health [65]. Hypoplastic kidneys secrete small amounts of urine and may lead to infections of the urinary tract and urolithiasis [83].

Finally, we agree with Lauener et al. [26] about the importance of providing the patient and their parents with extensive information at the time of the diagnosis to ensure the syndrome is properly treated throughout their lifetime and avoid possible complications. Nevertheless, the current data on KILT are limited, whereby there is a need for studies that address its early diagnosis, with the aim being to prevent complications and decide upon the expediency of lifelong treatment with anticoagulants.

Clinical Relevance

1. KILT syndrome involves the concurrence of three anomalies: agenesis (full or partial) of the IVC, agenesis/aplasia/renal hypoplasia, and DVT in the legs.

2. In young patients (aged < 30) with idiopathic thrombosis (without any apparent risk factors, such as immobility, contraceptives, and traumatism), this may indicate a vascular malformation of the abdominal/pelvic area.
3. The appearance of bilateral DVP and any relapse thereof in young patients constitutes a warning sign.

Conclusions

KILT syndrome is a rare phenomenon, and the conclusions are based on only a limited amount of literature. The common points in most cases are the symptoms of DVT as a form of manifestation, the iliac location of the thrombosis and the incidental diagnosis of full or segmental agenesis of the IVC (with collateral supplementary circulation), and renal hypoplasia with hypertrophy of the contralateral kidney. The diagnosis is incidental involving imaging scans, and the treatment requires the very long-term use of anti-coagulants. The short follow-up period for these cases restricts our more precise understanding of thrombotic recurrences and PTS.

1. A rare condition. There are no data on its incidence or prevalence.
2. The complaint's genesis, epidemiology, and natural history and not known.
3. The diagnosis is usually incidental. Eco-Doppler for confirming DVT and CT and/or MRI for completing the syndrome's triad. Importance of the study of thrombophilia.
4. There is no consensus on the guidelines for treating this syndrome. The treatment is based mainly on the long-term or indefinite use of anticoagulants for preventing complications and thrombotic relapses.

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Ethics Declarations

Ethics Approval and Consent to Participate

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Consent for Publication

Not applicable.

Competing Interests

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Availability of Data and Materials

The datasets supporting the conclusions of this article are included within the article.

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Authors' Contribution

Research Design: Francisco S. Lozano-Sánchez, Paula Velasco-Hernández

Research: Francisco S. Lozano-Sánchez, Paula Velasco-Hernández, Oliver Bonnelly, María Begoña García-Cenador.

Results Analysis: Francisco S. Lozano-Sánchez, María Begoña García-Cenador, Paula Velasco-Hernández, José A. Carnicero-Martíne, José A. Torres-Hernández

Results Discussion: All authors

Manuscript Draft: Francisco S. Lozano-Sánchez, Paula Velasco-Hernández.

All authors participated actively in the writing of the manuscript. They also reviewed and approved the final version of the article before submission for publication.

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