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Patients with Lemierre syndrome have a high risk of new thromboembolic complications, clinical sequelae and death: an analysis of 712 cases

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Background. Lemierre syndrome is characterized by head/neck vein thrombosis and septic embolism usually complicating an acute oropharyngeal bacterial infection in adolescents and young adults. We described the course of Lemierre syndrome in the contemporary era.

Methods. In our individual-level analysis of 712 patients (2000–2017), we included cases described as Lemierre syndrome if these criteria were met: (i) primary site of bacterial infection in the head/-neck; (ii) objectively confirmed local thrombotic complications or septic embolism. The study outcomes were new or recurrent venous thromboembolism or peripheral septic lesions, major bleeding, all-cause death and clinical sequelae.

Results. The median age was 21 (Q1–Q3: 17–33) years, and 295 (41%) were female. At diagnosis, acute thrombosis of head/neck veins was detected in 597 (84%) patients, septic embolism in 582 (82%) and both in 468 (80%). After diagnosis and during in-hospital follow-up, new venous thromboembolism occurred in 34 (5.2%, 95% CI 3.8–7.2%) patients, new peripheral septic lesions became evident in 76 (11.7%; 9.4–14.3%). The rate of either was lower in patients who received anticoagulation (OR: 0.59; 0.36–0.94), higher in those with initial intracranial involvement (OR: 2.35; 1.45–3.80). Major bleeding occurred in 19 patients (2.9%; 1.9–4.5%), and 26

died (4.0%; 2.7–5.8%). Clinical sequelae were reported in 65 (10.4%, 8.2–13.0%) individuals, often consisting of cranial nerve palsy (n = 24) and orthopaedic limitations (n = 19).

Conclusions. Patients with Lemierre syndrome were characterized by a substantial risk of new thromboembolic complications and death. This risk was higher in the presence of initial intracranial involvement. One-tenth of survivors suffered major clinical sequelae.

Keywords: Lemierre syndrome, venous thromboembolism, pulmonary embolism, septic embolism, anticoagulation, *Fusobacterium necrophorum*.

Introduction

Lemierre syndrome is a life-threatening condition characterized by acute bacterial infection of the head or neck, such as exudative tonsillitis or peritonsillar abscess, local septic vein thrombosis and multiple septic emboli.[1] *Fusobacterium necrophorum*, a Gram-negative anaerobe highly prevalent in the oropharynx of healthy individuals[2,3] and amongst teenagers with tonsillitis or pharyngitis,[4,5] is frequently involved in the syndrome, which develops only in isolated cases due to the frequent susceptibility of this pathogen to commonly used antibiotics such as penicillin and other beta-lactams.[6] Bacterium-specific mechanisms suggested to be involved in the pathogenesis include tropism for vessels,[7] a tendency to cause bacteraemia and increase tissue permeability,[8,9] inhibition of the innate immune response[10,11] and direct activation of the coagulation cascade.[12,13] Other bacteria share with *Fusobacterium spp*. some of these pathogenic properties and have been detected in patients with a clinical syndrome indistinguishable from *Fusobacterium*-associated Lemierre syndrome.[14]

One hundred years after the first reports,[15,16] evidence remains poor on all aspects of the management of Lemierre syndrome and, in particular, on its potentially life-threatening thromboembolic complications. As a consequence, physicians facing uncommon thromboembolic conditions like Lemierre syndrome necessarily base their decisions on anecdotal cases or small case series, and borrow general principles of anticoagulation management from other similar diseases. Despite the non-negligible annual incidence rate of one per 100 000 population amongst children and young adults and more than 500 reports published in the literature over the past two decades, the clinical course and burden of Lemierre syndrome in the contemporary era remains to be studied.[1]

A systematic search and comprehensive analysis of the clinical presentation, treatment patterns, and early and long-term complications in Lemierre syndrome is needed to define its clinical features, identify basic determinants of prognosis, estimate its morbidity and fatality, and generate hypotheses concerning the role of anticoagulant therapy. We performed an individual patient level analysis of data collected in cooperation with the authors of studies published globally since the year 2000.

Patients and Methods

Data collection

The procedure of patient level data collection has been described in detail previously.[1] In brief, we searched all studies reporting cases of Lemierre syndrome published between January 2000 and August 2017. We searched the following sources without restriction of language or study design: MEDLINE (via PubMed), Embase (via Ovid), the Cochrane Library and the grey literature, which comprises all relevant research results not reported in the traditional academic publishing and distribution channels. In addition, we searched the references of retrieved articles. We identified data for extraction based on the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual patient data (PRISMA-IPD) statement, which was adapted to the current setting.[17] The study protocol is registered in the International Prospective Register of Systematic Reviews PROSPERO (CRD42016052572).

Cases were considered eligible if these criteria were met: (i) the primary site of bacterial infection was located in the head/neck area; (ii) local thrombotic complications or septic embolism were objectively confirmed by the use of imaging or by direct detection (e.g. thrombectomy or autopsy). These criteria correspond to the broadest definition of Lemierre syndrome. Amongst the cases selected, we further distinguished cases with typical Lemierre syndrome according to the most restrictive definition, which consists of oropharyngeal infection, isolation of *Fusobacterium spp.*, and

either head/neck vein thrombosis or septic embolism.[1,18]

For the present analysis, we considered the following variables: age, sex, year of publication, type of primary head or neck infection, isolation of *Fusobacterium spp.* or other pathogens, risk factors for bleeding, use of anticoagulation, early complications including thrombosis, suppuration, septic embolization, bleeding and death, as well as late complications.

We contacted the corresponding authors of the selected studies to integrate the original reports with additional patient level data and to assess potential publication bias.

Study outcomes

Early complications included (i) new or recurrent objectively diagnosed acute venous thromboembolism, (ii) new or worsening (peripheral) septic lesions, (iii) major bleeding and (iv) death from all causes occurring after the diagnosis of Lemierre syndrome either in-hospital or within 30 days of diagnosis.

Venous thromboembolism included lower- or upper-extremity deep venous thrombosis, cerebral vein thrombosis, pulmonary embolism, neck vein thrombosis and other major venous thrombosis (e.g. involving the splanchnic veins). New or worsening (peripheral) septic lesions were defined as not present at the time of diagnosis of Lemierre syndrome (e.g. new septic multiple subsegmental lung emboli, arterial ischaemia, septic arthritis) or objectively diagnosed worsening of initial embolic manifestations. Major bleeding was defined by the criteria of the International Society on Thrombosis and Haemostasis, which we applied retrospectively [19], and included fatal bleeding; symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; bleeding causing a fall in haemoglobin level of at least 20 g L^{-1}, or leading to transfusion of two or more units of whole blood or red cells. All other bleeding events were considered as nonmajor.

Long-term complications were classified as (i) clinical sequelae present at discharge from hospital or persisting during postdischarge follow-up, which included cranial nerve palsy or other neurologic complications, orthopaedic or other functional limitations; (ii) new septic thromboembolism or recurrent Lemierre syndrome after discharge; and (iii) need for admission to a rehabilitation institution.

We defined the time of observation during the hospital stay as the days between the day all diagnostic criteria for Lemierre syndrome were present and the day the complication was diagnosed or the patient discharged. For each patient, we noted the use of antibiotics, the use of anticoagulation and surgical procedures. We performed the analysis on study outcomes only in the cases which provided data on the clinical course beyond presentation.

Statistical analysis

We provided categorical variables as counts and percentages with corresponding 95% confidence intervals (CI) and continuous variables as median and interquartile range (Q1–Q3) or as mean and standard deviation, according to their distribution. We represented the distribution of age and initial head/neck infection with density plots. The clinical characteristics of patients with vs. without early complications were compared using the chi-square test for categorical variables, the Kruskal–Wallis rank sum test for continuous variables without a normal distribution and the t-test for normally distributed continuous variables. The odds ratios (ORs) with 95% CI estimated by simple and multivariable logistic regression were used to study the association between early complications and anticoagulation. Two models were tested: one adjusted for age, sex and anticoagulation status at the time of the complication, and one additionally adjusted for additional potential confounders. These variables were selected based on the following criteria: (1) clinical relevance, (2) absence of potential reverse (temporal and causal) association with the outcome and (3) number and distribution of the outcomes recorded. We conducted a sensitivity analysis by repeating the analysis of early complications only in the case series contributing at least five patients with complete in-hospital follow-up and an additional analysis focusing on typical Lemierre syndrome. Data management was done in SPSS, version 23.0 (SPSS Inc. Chicago, Illinois). Data analysis was conducted with R version 3.5.1 (The R Foundation for Statistical Computing, 2018).

Results

Study selection

Data were extracted or obtained by the authors of 540 studies identified in the literature based on our predefined criteria for Lemierre syndrome.[1] Of

Table 1. *Demographics and baseline characteristics of patients with Lemierre syndrome*

	Total (N = 712)	Typical Lemierre (N = 333)	Atypical Lemierre (N = 379)
Female sex, *n* (%)	295 (41.4)	129 (38.7)	166 (43.8)
Age (years), median (Q1–Q3)	21 (17–33)	21 (17–26)	23 (16–45)
Active cancer, *n* (%)	12 (1.7)	1 (0.3)	11 (3.0)
Head and neck infection			
Oropharyngeal, *n* (%)	520 (73.0)	333 (100)	187 (49.3)
Low respiratory tract, *n* (%)	330 (46.3)	189 (56.8)	141 (37.2)
Neck, *n* (%)	287 (40.3)	110 (33.0)	177 (46.7)
Other, *n* (%)	167 (23.5)	22 (6.6)	145 (38.3)
Bacteria isolated, *n* (%)	583 (81.9)	333 (100.0)	250 (66.0)
Gram-positive, *n* (%)	180 (25.3)	47 (14.1)	133 (35.1)
Gram-negative, *n* (%)	474 (66.6)	333 (100)	141 (37.2)
Fusobacterium spp., *n* (%)	415 (58.3)	333 (100)	82 (21.6)
Initial head/neck vein thrombosis, *n* (%)	597 (83.8)	248 (74.5)	349 (92.1)
Internal jugular vein thrombosis, *n* (%)	526 (73.9)	218 (65.5)	308 (81.3)
Cerebral vein thrombosis, *n* (%)	143 (20.1)	25 (7.5)	118 (31.1)
External jugular vein thrombosis, *n* (%)	43 (6.0)	20 (6.0)	23 (6.1)
Other, *n* (%)	116 (16.3)	46 (13.8)	70 (18.5)
Other venous thromboembolism, *n* (%)	15 (2.1)	5 (1.5)	10 (2.6)
Septic emboli at diagnosis, *n* (%)	582 (81.7)	310 (93.1)	272 (71.8)
Pulmonary, *n* (%)	506 (71.1)	286 (85.9)	220 (58.0)
Muscolo-skeletal, *n* (%)	108 (15.2)	48 (14.4)	60 (15.8)
Intracranial, *n* (%)	79 (11.1)	32 (9.6)	47 (12.4)
Liver, *n* (%)	14 (2.0)	5 (1.5)	9 (2.4)
Other, *n* (%)	50 (7.0)	21 (6.3)	29 (7.7)

Typical Lemierre syndrome consisted of acute oropharyngeal infection, isolation of *Fusobacterium spp.*, and either head/neck vein thrombosis or septic embolism.

these, 480 were single case reports, 48 series of up to 5 cases, 16 series of 6 to 20 cases and 2 series of more than 20 cases (N = 23 and N = 33).[20,21] Additional details are reported in the Supporting Information.

A total of 712 patients were included in the present study and used for analysis of baseline characteristics and initial clinical presentation. Of these patients, 60 were described in publications that did not provide follow-up information and only focused on the clinical picture before or at the time of diagnosis, such as educational cases in differential diagnosis or imaging. This left 652 patients with hospital follow-up data up to discharge or beyond; their data were used for analysis of treatment, in-hospital and early complications, and long-term complications.

Baseline characteristics

Table 1 shows the characteristics of the study population. The median age was 21 (Q1–Q3: 17–33) years, and 295 (41%) were female. The age distribution of cases with typical (n = 333, 47%) and atypical (n = 379, 53%) Lemierre syndrome is depicted in Fig. 1. At the time of presentation, a total of 520 (73%) patients had signs or reported a recent episode of acute oropharyngeal infection. Oropharyngeal infections, along with low respiratory tract infections (n = 330, 46%) and neck infections (n = 287, 40%), were more prevalent in patients aged 10–40, whereas otomastoiditis (n = 85, 12%) characterized the neonatal and childhood period (Fig. 2). Eleven (1.5%) patients had a history of intravenous drug abuse. Thrombosis of a head or neck vein was detected in 84%

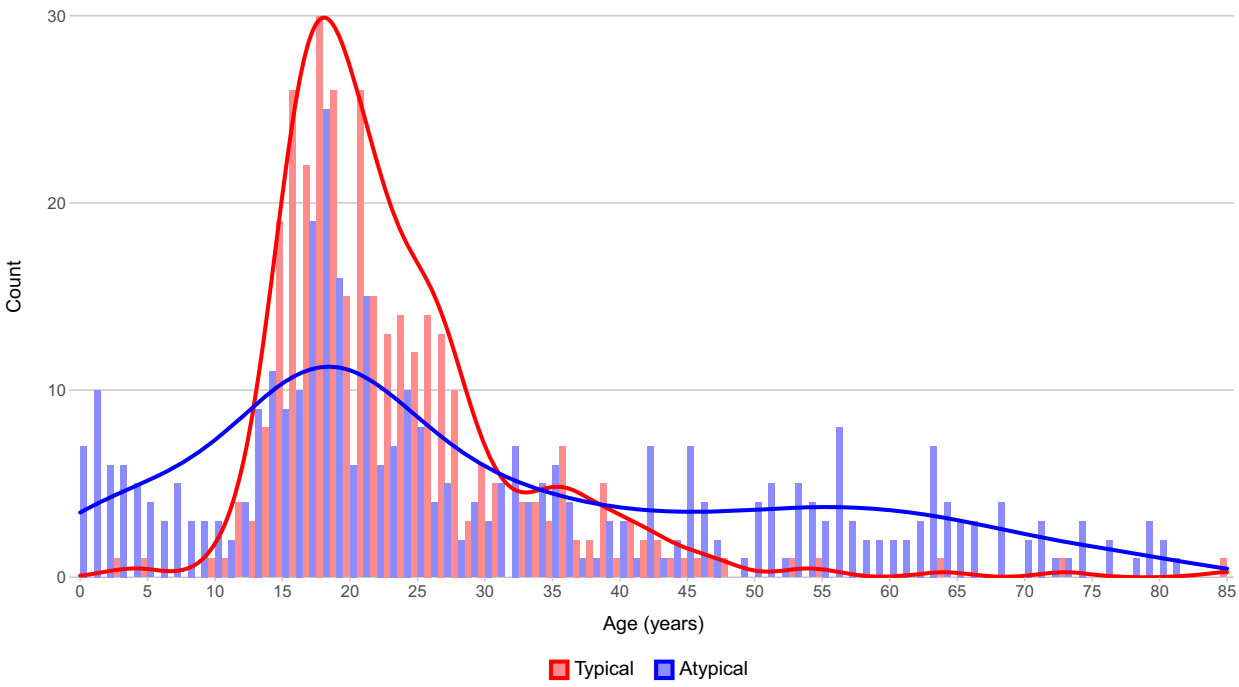

Fig. 1 *Age distribution of patients diagnosed with Lemierre syndrome. Density plot illustrating the age distribution of patients with typical or atypical Lemierre syndrome. Typical Lemierre syndrome consists of acute oropharyngeal infection, isolation of* Fusobacterium spp.*, and either head/neck vein thrombosis or septic embolism*

(n = 597) of patients at diagnosis, involving the internal jugular veins in 74% (n = 526) and the cerebral veins in 20% (n = 143) of patients. The internal or external jugular vein thrombosis was bilateral in 30 patients (4%). A total of 583 (82%) patients had concomitant septic embolism, most often located in the lungs (71%, n = 506).

Fusobacterium spp. was isolated in 415 (58%) patients, corresponding to 56% of females and 60% of males. The most frequently isolated *Fusobacterium* species was *necrophorum* (n = 360), followed by *nucleatum* (n = 30) and other or unspecified species (n = 25). *Streptococcus spp.* and *Staphylococcus spp.* were the most frequent bacteria isolated in patients with no detection of *Fusobacterium spp.* The bacterial genus was not specified (or bacteria could be characterized only as anaerobes or by Gram strain) in 139 (18%) patients (Table 1).

Medical and surgical treatment

In the 652 patients with in-hospital follow-up data, use of antibiotic therapy before or during hospitalization was reported in 646 (99.7%). Penicillins were the most used agents (n = 357, 61%), followed by metronidazole (n = 311, 53%), cephalosporins (n = 275, 47%) and clindamycin (n = 223, 34%). More than half of the patients received three or more different antibiotics (Table 2).

A total of 362 (56%) patients received anticoagulation during or after hospitalization (Table 2). Parenteral anticoagulation was used in 295 patients and included low-molecular-weight heparins (n = 229), unfractionated heparin (n = 76) and fondaparinux (n = 6), most frequently at therapeutic doses (58%). Oral anticoagulation consisted of vitamin K antagonists in 131 (30%) patients; the use of initial parenteral anticoagulation was explicitly reported in 118 of them. Direct oral anticoagulants were used in three patients.

Surgical procedures were performed in 337 (53%) patients. The most common were abscess drainage (n = 245), mastoidectomy (n = 40), jugular vein ligation or embolectomy (n = 31), pleural decortication (n = 14) and invasive cranial surgery (n = 16).

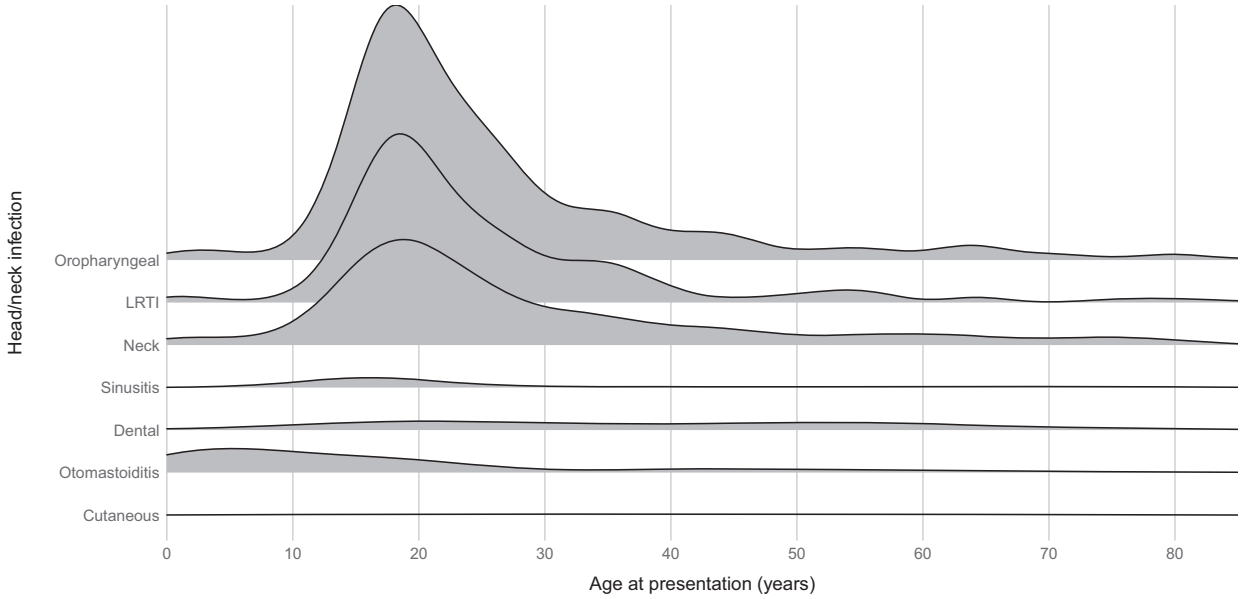

Fig. 2 *Age distribution of the initial infections at presentation. Density plots scaled to the count of each initial head/neck infection. LRTI = lower respiratory tract infection.*

In-hospital and early complications

A total of 112 (17.2%; 95% CI 14.5–20.5%) of 652 patients suffered from at least one early complication detected after the diagnosis of Lemierre syndrome in-hospital or within 30 days, including new or recurrent venous thromboembolism, new or worsening (peripheral) septic lesions, major bleeding or death.

A total of 93 (14.3%; 95% CI 11.8–17.2%) patients were diagnosed with new venous thromboembolism or peripheral septic lesions during hospitalization (Table 3), after a median of 4 (Q1–Q3 2–9) days from the diagnosis of Lemierre syndrome (Fig. 3).

New or recurrent venous thromboembolism occurred in 34 (5.2%; 95% CI 3.8–7.2%) patients after a median of 4 days from diagnosis. The most common manifestations were deep vein thrombosis (n = 17) and cerebral vein thrombosis (n = 15) (Table S1).

New or worsening (peripheral) septic lesions occurred in 76 (11.7%; 95% CI 9.4–14.3%) patients. Most peripheral septic lesions were pulmonary (n = 51) or intracranial (n = 25); Table S2. Concomitant infective endocarditis was diagnosed in 5 (0.7%) patients during hospitalization. Of the 93 patients developing new venous thromboembolism or septic lesions, 40 (43%) required at least one additional surgical procedure as a direct consequence of the complication itself, often including abscess drainage (n = 29) of pleural empyema (n = 14) or intracranial abscesses (n = 5). Other procedures prompted by a complication included jugular vein ligation (n = 8), soft tissue debridement (n = 5) and pleural decortication (n = 5).

Patients who developed early thromboembolic complications received less often anticoagulant therapy (42%; vs 54%), were more likely to have intracranial involvement at diagnosis (39% vs. 24%), underwent more surgical procedures (78% vs. 49%) and were administered more frequently four or more antibiotics (43% vs. 26%) than those without early thromboembolic complications (Table 3). The results of our multivariable logistic regression models, as shown in Table 4, confirmed that the use of anticoagulant before the complication and the absence of central nervous system involvement at presentation may represent favourable prognostic factors, independently from key clinical variables (sex, age, presence of septic embolism at diagnosis, isolation of *Fusobacterium spp.*, and the use of a combination of clindamycin or metronidazole with a beta-lactam antibiotic or carbapenem).

Table 2. *Medical therapy and invasive procedures*

	Total (N = 652)	Typical Lemierre (N = 311)	Atypical Lemierre (N = 341)
Antibiotic therapy, *n* (%)	646 (99.7)	310 (99.7)	336 (99.7)
Penicillins	357 (54.8)	184 (59.2)	173 (50.7)
Metronidazole	311 (47.7)	188 (60.5)	123 (36.1)
Cephalosporins	275 (42.2)	122 (39.2)	153 (44.9)
Clindamycin	223 (34.2)	119 (38.3)	104 (30.5)
Carbapenems	131 (20.1)	63 (20.3)	68 (19.9)
Vancomycin	109 (16.7)	39 (12.5)	70 (20.5)
Quinolones	87 (13.3)	52 (16.7)	35 (10.3)
Macrolides	76 (11.7)	48 (15.4)	28 (8.2)
Aminoglycosides	72 (11.0)	39 (12.5)	33 (9.7)
Other	80 (12.3)	31 (9.9)	49 (14.4)
Not reported	63 (9.7)	19 (6.1)	44 (12.9)
Number of antibiotic agents used (any time), *n* (%)			
0	2 (0.3)	1 (0.3)	1 (0.3)
1	56 (8.6)	22 (7.1)	34 (10.0)
2	194 (29.8)	92 (29.6)	102 (29.9)
3	170 (26.1)	85 (27.3)	85 (24.9)
4 or more	167 (25.6)	92 (29.6)	75 (22.0)
Unknown	59 (9.0)	19 (6.1)	40 (11.7)
Use of anticoagulation, *n* (%)	362 (55.5)	148 (47.6)	214 (62.8)
Low-molecular-weight heparin	229 (35.1)	81 (26.0)	148 (43.4)
Fondaparinux	6 (0.9)	1 (0.3)	5 (1.5)
Unfractionated heparin	76 (11.7)	35 (11.3)	41 (12.0)
Direct oral anticoagulants	3 (0.5)	0	3 (0.9)
Switch to vitamin K antagonists after the acute phase, *n* (%)	131 (20.1)	44 (14.1)	87 (25.5)
Length of anticoagulation (days), median (Q1–Q3)	84 (21–120)	45 (15–90)	90 (28–180)
Surgical procedures, *n* (%)	337 (51.7)	164 (52.7)	173 (50.7)
Abscess drainage	245 (37.6)	132 (42.4)	113 (33.1)
Mastoidectomy	40 (6.1)	4 (1.3)	36 (10.6)
Jugular vein ligation or embolectomy	31 (4.8)	18 (5.8)	13 (3.8)
Debridement	25 (3.8)	9 (2.9)	16 (4.7)
Tonsillectomy	19 (2.9)	14 (4.5)	5 (1.5)
Invasive cranial surgery	16 (2.5)	5 (1.6)	11 (3.2)
Pleural decortication	14 (2.1)	10 (3.2)	4 (1.2)
Myringotomy	11 (1.7)	3 (1.0)	8 (2.3)
Tooth extraction	9 (1.4)	0	9 (2.6)
Other	2 (0.3)	0	2 (0.6)

Invasive cranial surgery includes craniectomy, craniotomy, sinusotomy and sinuplasty. Typical Lemierre syndrome consists of acute oropharyngeal infection, isolation of *Fusobacterium spp.*, and either head/neck vein thrombosis or septic embolism. Information is reported for the 652 patients with in-hospital follow-up data.

Table 3. *Early complications and case fatality rates after the diagnosis of Lemierre syndrome*

	No VTE or PSL	New VTE or PSL	*P* value	No new VTE	New VTE	*P* value	No new PSL	New PSL	*P* value	No death	Death	
N	559	93		616	34		576	76		626	26	
Anticoagulant, *n* (%)	304 (54.4)	39 (41.9)	0.035	331 (53.7)	12 (35.3)	0.055	313 (54.3)	30 (39.5)	0.020	331 (52.9)	12 (46.2)	0.64
Female sex, *n* (%)	232 (41.5)	40 (43.0)	0.87	259 (42.0)	13 (38.2)	0.80	237 (41.1)	35 (46.1)	0.49	260 (41.5)	12 (46.2)	0.79
Age (years), median (Q1–Q3)	21 (17–33)	21 (16–31)	0.64	21 (17–33)	20 (16–26)	0.23	21 (17–33)	20 (16–30)	0.37	21 (17–32)	23 (15–38)	0.71
Fusobacterium spp, *n* (%)	328 (58.7)	63 (67.7)	0.12	366 (59.4)	23 (67.6)	0.44	337 (58.5)	54 (71.1)	0.048	376 (60.1)	15 (57.7)	0.97
Oropharyngeal infection, *n* (%)	403 (72.1)	69 (74.2)	0.77	444 (72.1)	26 (76.5)	0.72	415 (72.0)	57 (75.0)	0.69	453 (72.4)	19 (73.1)	1.0
Head/neck thrombosis at diagnosis, *n* (%)	466 (83.4)	81 (87.1)	0.45	515 (83.6)	32 (94.1)	0.16	483 (83.9)	64 (84.2)	1.0	529 (84.5)	18 (69.2)	0.071
Septic emboli at diagnosis, *n* (%)	460 (82.3)	79 (84.9)	0.63	507 (82.3)	31 (91.2)	0.26	474 (82.3)	65 (85.5)	0.59	518 (82.7)	21 (80.8)	1.0
Intracranial involvement at diagnosis, *n* (%)	132 (23.9)	36 (38.7)	0.0040	151 (24.8)	16 (47.1)	0.0074	139 (24.4)	29 (38.2)	0.015	153 (24.7)	15 (57.7)	0.00042
Surgical procedures, *n* (%)	265 (48.7)	72 (78.3)	<0.0001	311 (51.7)	25 (75.8)	0.012	276 (49.3)	61 (80.3)	<0.0001	325 (53.2)	12 (48.0)	0.76
Four or more antibiotics used, *n* (%)	129 (25.8)	38 (42.7)	0.0017	148 (26.7)	18 (54.5)	0.0012	136 (26.3)	31 (43.1)	0.0049	162 (28.5)	5 (23.8)	0.82
Typical Lemierre syndrome, *n* (%)	299 (53.5)	42 (45.2)	0.17	326 (52.9)	15 (44.1)	0.41	308 (53.5)	33 (43.4)	0.13	326 (52.1)	15 (57.7)	0.72

P values were calculated from the chi-square test for categorical variables, the Kruskal–Wallis rank sum test for continuous variables. Information is reported for the 652 patients with in-hospital follow-up data. VTE = venous thromboembolism. PSL = peripheral septic lesion.

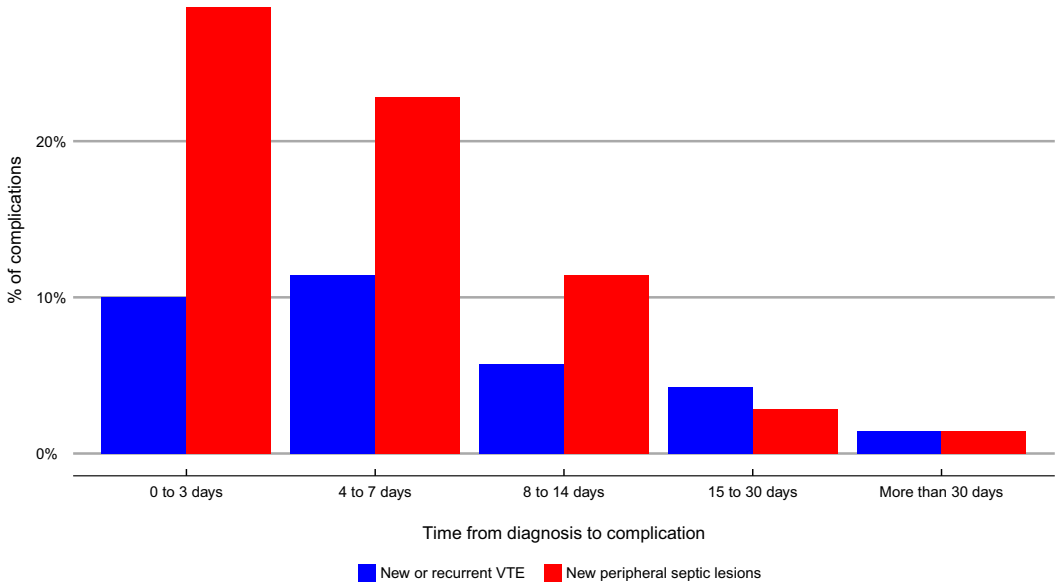

Fig. 3 *Time from Lemierre diagnosis to new/recurrent venous thromboembolism or peripheral septic lesion. Data from 64/93 (68.8%) patients for whom the time of complication was known. VTE = venous thromboembolism*

An overview of all bleeding events is provided in Table S3. In-hospital major bleeding occurred in 19 (2.9%, 95% CI 1.9–4.5%) patients after a median of 9 (Q1–Q3: 5–15) days from diagnosis. The most prevalent risk factors amongst bleeders were thrombocytopenia (42%), use of antiplatelet agents (21%) and pathological lesions or recent invasive procedures at the bleeding site (16%). Eight (42%) of the 19 patients were receiving anticoagulation at therapeutic dose (unfractionated heparin, $n = 7$; enoxaparin, $n = 1$) at the time of bleeding, whilst anticoagulation was used in 349 (55%) of the 633 patients who did not experience bleeding.

A total of 26 (4.0%; 95% CI 2.7–5.8%) patients died during hospitalization. The most common cause of death was septic shock ($n = 11$, 42% of all deaths). Eight patients (31%) died for central nervous system involvement by cerebral infarction and/or intracranial septic embolization. Two (8%) deaths were reported as due to fatal pulmonary embolism. One (4%) death was due to a bleeding complication (haemoptysis in a patient with severe thrombocytopenia). Table S4 reports in detail the causes of death.

Long-term complications

A total of 76 (12.1%; 95% CI 9.8–14.9%) of 626 patients who survived the acute phase of Lemierre syndrome had sequelae, postdischarge recurrence and/or required the admission to another institution for rehabilitation.

Clinical sequelae were described in 65 (10.4%; 95% CI 8.2–13.0%) survivors (Table 5 and Table S5) and included neurologic impairment such as cranial nerve palsy ($n = 22$), blindness or reduced visual acuity ($n = 7$), paralysis or paresis ($n = 6$), or orthopaedic and functional limitation ($n = 19$). Of the survivors with no clinical sequelae reported, 290 were healthy at discharge and followed thereafter; 224 were healthy at discharge with no further follow-up; and 47 had no description of the discharge status, but a favourable clinical course or good response to therapy were mentioned (Fig. 4).

Three patients had postdischarge recurrence: they developed internal jugular vein thrombosis within one month of discharge, recurrent purulent osteomyelitis 2.5 months after discharge and recurrent Lemierre syndrome 14 months after discharge, respectively.

Sensitivity analysis

The eight large case series included in the sensitivity analysis contributed a total of 102

Table 4. *Multivariable logistic regression for the association between clinical characteristics and in-hospital venous thromboembolism or peripheral septic lesion*

	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Age (per year increase)	1.00 (0.98, 1.01)	1.00 (0.99, 1.02)
Males (vs. females)	0.95 (0.61, 1.49)	0.98 (0.62, 1.55)
Use of anticoagulant (vs. no anticoagulant)	0.61 (0.39, 0.95)	0.60 (0.37, 0.96)
Intracranial involvement at diagnosis (vs. no intracranial involvement)	-	2.38 (1.46, 3.84)
Septic embolism at diagnosis (vs. no septic embolism)	-	1.11 (0.60, 2.20)
Fusobacterium spp. (vs. other bacteria)	-	1.57 (0.93, 2.72)
Combination of clindamycin or metronidazole + beta-lactams or carbapenems not used (vs. used)	-	1.32 (0.82, 2.10)

Intracranial involvement at diagnosis was defined as cerebral venous thrombosis or intracranial suppuration at diagnosis. Septic embolism at diagnosis was defined as any distance embolism at diagnosis. The use of anticoagulants and of a combination of antibiotic therapy specific for *Fusobacterium spp.* was defined at the time of complication (cases) vs. during hospitalization (controls). OR = odds ratio. CI = confidence interval.

patients.[20–27] The proportion of patients experiencing early complications was as follows: 2.9% for new or recurrent venous thromboembolism ($n = 3$, 95% CI 1.0–8.3%), 8.8% for new or worsening peripheral septic lesions ($n = 9$, 95% CI 4.7–15.9%), 2% for major bleeding ($n = 2$, 95% CI 0.5–6.9%) and 4.9% for death ($n = 5$, 95% CI 2.1–11.0%), with confidence intervals similar to those of the main analysis. The majority of these studies did not report on long-term complications.

The results of the analysis restricted to patients with typical Lemierre syndrome were similar to those of the main analysis (Table S6).

Time trends

Both the absolute number of studies and that of reported patients with Lemierre syndrome increased between 2000 and 2016. This increasing trend was less evident if one calculated the ratio to the total number of articles published in PubMed, accounting for the increasing number of articles published in the overall biomedical literature (Table S7).

The proportion of patients with initial oropharyngeal infection decreased from 139/174 (79.9%) in 2000–2005 to 156/202 (77.2%) in 2006–2011 and 225/336 (67.0%) in 2012–2016. The isolation of *Fusobacterium spp.* was reported in 134/174 (77.0%) patients in 2000–2005, in 113/202 (55.9%) in 2006–2011 and in 168/336 (50.0%) in 2012–2016. Medical therapy was marked by a decreasing use of macrolides (20.4% to 6.8%) and a higher prevalence of anticoagulation therapy (from 42.1% to 62.5%), particularly low-molecular-weight heparin.

The case fatality rate was 5.9% in 2000–2005, 5.2% in 2006–2011 and 2.3% in 2012–2016 (Table S7). The rate of early complications was 15.8%, 14.1% and 13.6%, respectively.

Discussion

Comprehensive analyses of the clinical presentation, patterns of treatment, early course and long-term complications of Lemierre syndrome are not available to this date. Our individual patient level analysis of more than 700 patients diagnosed with Lemierre syndrome during the past two decades represents the largest study ever performed on this condition. We found that, beyond the serious initial thromboembolic manifestations of the disorder, the rates of new or recurrent thromboembolic complications and septic lesions remain high despite hospitalization. Although the case fatality has clearly decreased compared with the pre-antibiotic era, it is still substantial in a patient population of otherwise healthy children and young adults. Moreover, we described the rate of long-term complications in these patients, showing that about one out of ten survivors

Table 5. *Clinical sequelae, postdischarge recurrence, and need of rehabilitation in Lemierre syndrome survivors*

Long-term complications	*n* (%, 95% CI)
Clinical sequelae	65 (10.0%, 7.8–12.6%)
Cranial nerve palsy	24 (3.8)
Orthopaedic or functional limitations	19 (3.0)
Blindness or reduced visual acuity	7 (1.1)
Tetraparesis, tetraplegia, hemiparesis, hemiplegia	6 (1.0)
New surgery or invasive procedure required	5 (0.8)
Hearing loss	4 (0.6)
Radiculopathy	3 (0.5)
Ataxia or generic gait problems	3 (0.5)
Seizures reported after discharge	3 (0.5)
Postdischarge recurrence	3 (0.5%, 0.2–1.4%)
New venous thromboembolism	1 (0.2)
New peripheral septic lesion	1 (0.2)
Recurrent Lemierre syndrome	1 (0.2)
Discharge to rehabilitation institution	14 (2.2%, 1.3–3.7%)

suffers debilitating sequelae or requires additional care after discharge.

Despite treatment, one in seven patients developed severe early complications including new or recurrent venous thromboembolism (5.2%) and/or new (peripheral) septic lesions (11.7%). The rate of new peripheral septic lesions we observed might be even higher than the rate of septic embolism after the initiation of antibiotic therapy in patients with infective endocarditis, estimated at 7.3% in a 2005 study[28] and 8.5% in a 2013 study.[29] New or worsening (peripheral) septic lesions were more frequent than new venous thromboembolism, and their time distribution indicated that they were usually detected in the first days after diagnosis. This may be explained by a higher embolization rate during the acute stage of the disease, when the bacterial load is high, and lower probability of septic emboli after antibiotic treatment is started. In contrast, bacteria in the initial thrombus may be protected from antibiotics and remain able to cause thrombophlebitis for a longer time.

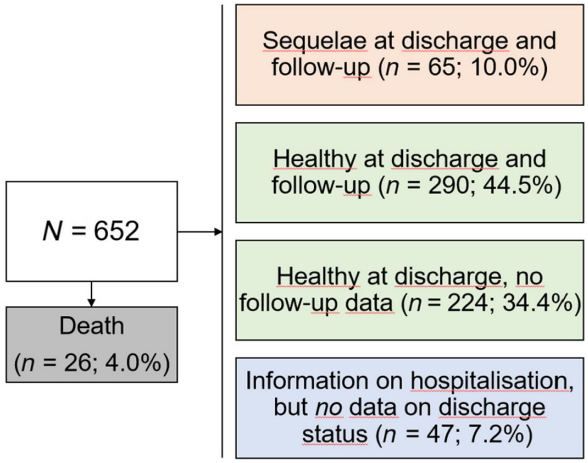

Fig. 4 *Postdischarge follow-up according to the health status at discharge*

The role of anticoagulant treatment for Lemierre syndrome has long been debated.[30] We showed not only that initial thromboembolic manifestations involve multiple sites and often extend to the cerebral veins, but also that the risk of new complications persists throughout hospitalization. Despite this, use of any-dosage anticoagulation was reported in only 56% of patients. This may have been due to a (perceived) unacceptably high risk of major bleeding, but also to the fear that anticoagulants may fragment the fresh septic thrombus and cause new septic lesions. Our data show that anticoagulants were not used more frequently amongst patients with major bleeding or new septic complications compared with those who had an uncomplicated course. Whilst unfractionated heparin was used considerably more often than other anticoagulant agents at the time of bleeding, this may reflect its use in patients with worse clinical conditions or more severe infections. The number of bleeding events is too low to perform subgroup analyses stratified by the type of anticoagulant agent. In addition, the proportion of anticoagulant use was lower amongst patients who had new or recurrent thromboembolic events. The interpretation of these results must be very cautious and primarily oriented to generate hypotheses. International guidelines on venous thromboembolism prevention and treatment unanimously recommend that all hospitalized patients with an acute medical illness undergo routine risk assessment to decide on thromboprophylaxis and stipulate that therapeutic-dose anticoagulation is indicated in the

presence of an objectively diagnosed acute venous thromboembolic event, provided that no major bleeding risk factors exist. It is our opinion that the latter would also apply to Lemierre syndrome and that routine anticoagulant treatment should be considered in patients without contraindications. In this perspective, Lemierre syndrome shares many similarities with infective endocarditis, for which the continuation of anticoagulant treatment is deemed safe in the absence of major bleeding.[31] The controversies on optimal anticoagulation in children and teenagers with venous thromboembolism fall beyond the purposes of the present study.[32,33]

Of the 20 patients first described by André Lemierre in 1936, 18 died.[15] Subsequent case series reported fatality rates ranging from 5 to 20%.[34] In the largest survey (n = 58 cases) on sepsis due to *Fusobacterium necrophorum* reported in Denmark between 1998 and 2001, the authors described an overall fatality of 9%.[35] In our analysis, we estimated a fatality of 4%: the majority of deaths were due to septic shock, followed by cerebral infarction or intracranial septic embolization, pulmonary embolism and bleeding. These figures may reflect the improved management in the modern antibiotic and anticoagulant era [36] but, at the same time, point to a risk of in-hospital death still substantial for a young population of otherwise healthy individuals. In a larger perspective, the question remains unanswered whether these deaths could be prevented by reducing the incidence of Lemierre syndrome amongst teenagers and young adults with acute oropharyngeal infection. Our results suggest that patients in whom *Fusobacterium spp.* was isolated and those who did not receive antibiotic therapy active against anaerobes might have been characterized by a higher rate of in-hospital complications, reinforcing the concept that a timely diagnosis and appropriate therapy are crucial in the management of Lemierre syndrome.

More than 10% of the survivors experienced serious long-term complications, including neurologic deficits and debilitating conditions potentially requiring long and resource-intensive additional care. This figure is similar to the 9% of permanent cerebral or pulmonary sequelae described in patients with sepsis due to *Fusobacterium necrophorum*.[35] As most patients with Lemierre syndrome are young and otherwise healthy, these sequelae may severely affect the patients' quality of life, self-sufficiency and work ability. Over the past few years, chronic functional limitations emerged as relevant complications in patients with venous thromboembolism, including but not limited to suboptimal cardiopulmonary function in combination with exercise intolerance and persisting symptoms.[37] Post-traumatic stress disorder is frequent in survivors after sepsis or hospitalization in a critical care unit.[38,39] These aspects remain to be systematically investigated in relation to Lemierre syndrome. All findings held when we repeated our analyses in both the cases corresponding to the most restrictive definition (typical Lemierre syndrome) and those satisfying a wider definition (atypical Lemierre syndrome), with no substantial differences in either early or long-term complications.

Although publication trends cannot be used to make inferences on incidence, and the publication date of a report may not reflect the year of diagnosis in the patients that it describes, we observed a slight increase in the number of published reports on Lemierre syndrome. This was true both for absolute numbers and for the ratio of Lemierre-related papers to the total number of articles on the PubMed repository in the same period. Several factors may have contributed to this increase, including the publication of epidemiological studies [3], narrative reviews and case reports in major journals [40,41]; an increasing interest for the concept of 'inflammatory thrombosis'; and publication bias, leading to more 'unusual' cases of Lemierre syndrome (not due to oropharyngeal infection by *Fusobacterium necrophorum*, or less often associated with septic embolism) being reported in recent years [42–44]. As indirect as this evidence can be, the apparent increase in the number of reports and patients is consistent with a recently published retrospective multicentric population-based study reporting that invasive infections caused by *Fusobacterium necrophorum* increased in Sweden from 2010 to 2017 [45]. Population-based data from other countries should confirm this finding. Over the course of the period considered, the fatality rate appeared to decrease from 5.9% in 2000–05 to 2.3% in 2012–16. Whether this represents an actual improvement or only reflects differences in patient characteristics over time cannot be extrapolated from our data.

We acknowledge limitations of our study. First, because our data were collected through a systematic review of the published and grey literature and

are based on small cases series or case reports, they are subject to selection and publication bias. As a consequence, our analysis represents an accurate snapshot of current global observations and practice, but cannot serve to draw firm conclusions on the optimal diagnostic and therapeutic measures in the management of Lemierre syndrome. However, we made the best efforts to measure and limit the potential impact of some biases, especially publication bias, in the data collection procedure and the selection of the in-hospital follow-up cohort, and we conducted a sensitivity analysis in the largest cases series that showed rates of early complications, including death, similar to those found in the primary analysis. Second, the retrospective nature of our data does not allow us to establish causal associations or evaluate the merits of alternative management strategies. However, our study may provide hypotheses helpful for planning future prospective registries and clinical trials that may achieve these goals.

In conclusion, Lemierre syndrome occurs in young otherwise healthy individuals and is characterized by a substantial risk of new thromboembolic complications during hospitalization, death and major clinical sequelae. Therefore, a timely diagnosis, close clinical/imaging monitoring and a multidisciplinary management appear necessary. Whilst the characteristics of our study cannot provide evidence of the utility of anticoagulation, we could not find disease-specific elements of concern regarding its safety.

Individual contributions

Luca Valerio involved in design of the study, statistical analysis, interpretation of the results, critical revision of the manuscript, writing of the manuscript and final approval. Federica Zane, Clara Sacco and Alessandro Pecci involved in study design, collection of data, interpretation of the results, critical revision of the manuscript, and final approval. Serena Granziera, Tommaso Nicoletti, Mariaconcetta Russo, Gabriele Corsi, Karin Holm, Michel-André Hotz and Christian Righini involved in collection of data, interpretation of the results, critical revision of the manuscript and final approval. Petros D. Karkos, Seyed Hamidreza Mahmoudpour, Nils Kucher, Peter Verhamme, Marcello Di Nisio, Robert M. Centor and Stavros V. Konstantinides involved in interpretation of the results, critical revision of the manuscript and final approval. S. Barco involved in concept and design of the study, collection of data, interpretation of the results, writing of the manuscript and final approval.

Declaration of interests

P. Verhamme received support from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb and Daiichi Sankyo outside the submitted work. M. Di Nisio received consulting fees from Aspen, Bayer, BMS-Pfizer, Daiichi Sankyo and Leo Pharma outside the submitted work. S.V. Konstantinides reports grants and nonfinancial support from Bayer AG; grants and personal fees from Boehringer Ingelheim, personal fees from Bayer AG, grants and personal fees from Actelion, grants and personal fees from Daiichi Sankyo, grants and personal fees from Biocompatibles Group UK, personal fees from Pfizer-Bristol-Myers Squibb, grants and personal fees from MSD, outside the submitted work. S. Barco received lecture/consultant fees from Bayer HealthCare, BTG Pharmaceuticals, and Leo-Pharma; and economical support for travel/congress costs from Daiichi Sankyo and Bayer HealthCare, outside the submitted work. The remaining authors declare no competing financial interests.

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Author contribution

Luca Valerio: Data curation (lead); Formal analysis (lead); Investigation (equal); Methodology (equal); Project administration (equal); Software (lead); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Federica Zane:** Conceptualization (supporting); Data curation (equal); Investigation (equal); Methodology (supporting); Validation (equal); Visualization

(supporting). **Clara Sacco:** Conceptualization (supporting); Funding acquisition (equal); Investigation (supporting); Methodology (equal); Resources (supporting); Validation (equal). **Serena Granziera:** Data curation (equal); Methodology (supporting); Project administration (supporting); Resources (supporting); Validation (supporting); Writing-original draft (supporting). **Tommaso Nicoletti:** Data curation (supporting); Formal analysis (supporting); Investigation (supporting); Validation (supporting); Visualization (supporting). **Mariaconcetta Russo:** Data curation (supporting); Investigation (supporting); Methodology (supporting); Validation (supporting). **Gabriele Corsi:** Data curation (supporting); Investigation (supporting); Methodology (supporting); Project administration (supporting); Software (supporting); Validation (supporting); Visualization (supporting). **Karin Holm:** Investigation (supporting); Methodology (supporting); Supervision (supporting); Visualization (supporting); Writing-original draft (supporting). **Michel Hotz:** Conceptualization (supporting); Data curation (supporting); Investigation (supporting); Supervision (supporting). **Christian Righini:** Data curation (supporting); Funding acquisition (supporting); Supervision (supporting); Visualization (supporting). **Petros Karkos:** Data curation (supporting); Formal analysis (supporting); Investigation (supporting); Resources (supporting); Supervision (supporting); Visualization (supporting). **Seyed Hamidreza Mahmoudpour:** Formal analysis (supporting); Methodology (supporting); Validation (supporting). **Nils Kucher:** Funding acquisition (equal); Methodology (supporting); Resources (equal); Validation (supporting). **Peter Verhamme:** Conceptualization (supporting); Investigation (supporting); Validation (supporting); Visualization (supporting). **Marcello Di Nisio:** Data curation (supporting); Methodology (supporting); Supervision (supporting); Visualization (supporting); Writing-original draft (supporting). **Robert Centor:** Investigation (equal); Supervision (equal); Visualization (equal); Writing-original draft (supporting). **Stavros Konstantinides:** Funding acquisition (equal); Methodology (equal); Supervision (equal); Visualization (equal); Writing-original draft (supporting); Writing-review & editing (supporting). **Alessandro Pecci:** Data curation (supporting); Formal analysis (supporting); Methodology (supporting); Supervision (supporting); Validation (supporting); Visualization (supporting); Writing-original draft (supporting). **Stefano Barco:** Conceptualization (lead); Data curation (supporting); Formal analysis (supporting); Funding acquisition (equal); Investigation (lead); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (lead); Validation (lead); Visualization (equal); Writing-original draft (equal); Writing-review & editing (supporting).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Cases of new or recurrent venous thromboembolism.

Table S2. Cases of new or worsening septic lesions.

Table S3. Bleeding events.

Table S4. Deaths.

Table S5. Long-term complications.

Table S6. In-hospital complications and overall fatality rates for patients with typical Lemierre syndrome.

Table S7. Reports of Lemierre syndrome patients in the published literature, baseline characteristics, and follow-up: trend 2000–2016.