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Contributi scientifici su volume e libro di testo 2015-2025 Dr. Antonio Bozzani.

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Autologous immuno magnetically selected CD133+ stem cells in the treatment of no-option critical limb ischemia: clinical and contrast enhanced ultrasound assessed results in eight patients

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Abstract

Objectives: Demonstrate the safety and effectiveness of highly purified CD133+ autologous stem cells in critical limb ischemia (CLI).

Design: Prospective single-center not randomized. Clinicaltrials.gov identifier: NCT01595776

Methods: Eight patients with a history of stable CLI were enrolled in a period of 2 years. After bone marrow stimulation and single leukapheresis collection, CD133+ immunomagnetic cell selection was performed. CD133+ cells in buffer phosphate suspension was administered intramuscularly. Muscular and arterial contrast enhanced ultra sound (CEUS), lesion evolution and pain management were assessed preoperatively and 3, 6 and 12 months after the implant.

Results: No patient had early or late complications related to the procedure. Two patients (25 %) didn't get any relief from the treatment and underwent major amputation. Six patients (75 %) had a complete healing of the wounds, rest pain cessation and walking recovery. An increase in CEUS values was shown in all eight patients at 6 months and in the six clinical healed patients at 12 months and had statistical relevance.

Conclusions: Highly purified autologous CD133+ cells can stimulate neo-angiogenesis, as based on clinical and CEUS data.

Keywords: Peripheral arterial disease, Critical limb ischemia, Stem cell therapy, Contrast enhanced ultrasound

Background

Symptomatic peripheral arterial disease (PAD) has a prevalence of 3 % in a population aged 40 years and above and of 6 % in patients over 60. Critical Limb Ischemia (CLI) is the worst and terminal clinical picture of PAD often preceding gangrene and amputation: typical symptoms are rest pain refractory to analgesics lasting more than 2 weeks and ischemic lesions (Fontaine classification stage 3–4 and Rutherford classification stage 4–6). CLI diagnosis is confirmed instrumentally by calf arterial pressure <50 mmHg, Ankle/Brachial Index (ABI) <0.5 and Transcutaneous PO_2 ($TcPO_2$) <30 mmHg. The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) [1] stresses the absolute indication to revascularization for these patients either by surgical or endovascular treatment. Nevertheless in some cases, mostly due to lack of distal run off, revascularization is not feasible or shows very low success rates. For

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the above mentioned reasons, the prognosis of these CLI patients is poor, with a major amputation rate of about 50 % at 1 year.

Many non-interventional treatments have been proposed for these "no-options" patients: spinal cord stimulation, prostanoids and prostaglandins administration, hyperbaric oxygen therapy and so on. More recently some authors have focused the attention on the local administration of stem cells, and particularly Endothelial Progenitor Cells (EPCs). EPCs local administration effectiveness in post-ischemic myocardial damage has been demonstrated in animal models and in humans [2–5]. Many observations lead to argue that the EPCs play a basic role in re-endothelization and neo-vascularization processes: actually the EPCs number may be reduced in peripheral blood in cardiovascular diseases, diabetes and rheumatoid arthritis and under the action of exogenous (as smoke habit) or endogenous (as high C-reactive protein levels) factors. Otherwise EPCs number may be increased by factors as physical exercise, estrogens, erythropoietin, statins and several cytokines or secreting proangiogenic factors like hepatic growth factor (HGF), insulin like growth factor (IGF-1) and the vascular endothelial growth factor (VEGF). These observations persuaded some authors to apply this cell therapy approach to CLI [6].

Our starting experience in the treatment of no options CLI with EPCs in three patients has been previously reported [7]. The bench marks of our study are the use of a selected EPCs population to investigate more precisely the cellular mechanisms, and to assess whether patients with PAD treated with EPCs show variation in muscle perfusion as displayed by contrast enhanced ultrasound (CEUS).

According to the current guidelines, reliable diagnostic tools for the management of patients with PAD, are ankle-brachial index (ABI), duplex ultrasound, transcutaneous oxygen pressure ($TcPO_2$), magnetic resonance (MR), contrast computer tomography (CT scan) and conventional angiography (CA). Among imaging modalities under development, micro bubble—based CEUS is a real-time, high spatial-resolution imaging technique that can easily be applied. Its high sensitivity, which provides detection of extremely low concentrations of micro bubbles, combined with the true blood pool distribution of contrast agent, gives CEUS the potential to help visualize and quantify the vasculature in vivo. CEUS was recently proposed as a valuable method to detect perfusion deficit and collateralization in patients with PAD [8, 9]. This method has been also validated for the detection of impaired microcirculation in patients with diabetes mellitus [10].

We present our experience in eight no-options CLI patients transplanted with peripheral immune-selected apheresis-derived autologous CD133+ cells and followed up with CEUS for 12 months.

Patients and methods

Type of the study

Prospective single centre not randomized.

Clinicaltrials.gov identifier: NCT01595776

Aim of the study

To assess the safety, feasibility and efficacy of local intramuscular administration of autologous immuno-selected CD133+ cells in patients suffering from CLI. The protocol started at our institution in July 2011 with the local Ethical Committee (EC) approval (number CHVAS-01-08-10/03/08). The investigation conforms with the principles outlined in the Declaration of Helsinki.

Enrolment criteria

All the patients enrolled were suffering from clinical stable CLI according to the TASC 2 definitions [1] and had no revascularization option, on the basis of contrast CT scan, RM or angiography imaging and the evaluation of our vascular and endovascular team. A detailed informed consent, approved by our EC, had been required.

Exclusion criteria

Patients under 18 and over 70 years of age. Elderly patients have been excluded because of expected bone marrow low responsiveness. Clinical unsteadiness of CLI (such as gangrene requiring major amputation) and poor life expectancy are exclusion criteria for supposed latency of the EPCs action. Severe systemic illness was judged to increase the risk of bone marrow stimulation. Complete inclusion and exclusion criteria are depicted in Table 1.

Patients

Between September 2011 and September 2013 we enrolled eight patients with a history of Rutherford stage 4 (rest pain) or 5 (small ischemic lesions) PAD. All patients had previous vascular imaging (contrast CT or MR or angiography) excluding revascularization options, either endovascular and surgical and encountered inclusion criteria. Every patient underwent routine physical and instrumental examination including electrocardiogram, chest X-ray and blood sample analysis. The patients' features are summarized in Table 2. The median age was 46.8 (SD 11.8, range 37–69 years), with a M:F ratio of 3:1. Younger patients met Buerger disease criteria (n = 4, 50 %), whereas others had pure atherosclerotic lesions. Only one patient (ID 7, female) had diabetes mellitus. Six patients out of eight had ischemic lesions on

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Age between 18 and 70 years
CLI (TASC 2)
None surgical nor endovascular option
Written informed consent
Exclusion criteria
Clinical instability
Extensive gangrene (proximal to forefoot)
All serious systemic disease
Life expectancy <24 months
Child bearing age
Allergy
Previous similar studies
Previous experimental drug studies within 3 months
Conflict of interest with the study

the forefoot (Rutherford stage 5) with poor healing and a long history of wound treatment. All patients complained moderate/severe pain and took high doses of analgesics (slow release opiates in two cases).

CEUS imaging protocol

Two operators who were blinded to treatment performed CEUS for all patients. The imaging criteria were: (1) reduced transmit power, at approximately 7–10 frames per second and one focus well below the level of the target to ensure a more uniform pressure field. (2) dual-mode presentation of a grayscale image side-by-side with the contrast image facilitating real-time identification of anatomic structures and region of interest (ROI) selection. (3) Image loops of approximately 60 s. (4) Uniform gain across the image and avoid gain saturation. (5) The time gain compensation (TGC) set such that before contrast arrival a uniform black image was shown.

A vial of contrast agent (SonoVue BR1; Bracco, Milan, Italy) was prepared at a concentration of about 2×10^8 sulfur hexafluoride—filled micro bubbles per milliliter, according to the manufacturer's recommendations. The position of the probe was recorded for each patient in order to maintain the same position during follow up. The injection was made with the patient supine and after 10 min of rest to avoid exercise related micro-vascular dilatation. The radiologist maintained a constant image plane with the aid of the tissue (fundamental image) of the "Contrast Side/Side" imaging mode.

Image analysis

The main image analysis tasks were: (1) identification of anterior tibialis artery (ATA) area, (2) selection of a representative region of normal anterior tibialis muscle (ATM) and (3) formulation of time-intensity curves (TIC). Two manually defined ROI, 2 and 4 cm sided-squares, were placed, respectively, over the ATM with no evidence of arterial branches, over ATA and over a small tibialis arterial branch. The ROIs were placed in the same anatomical position for each patient to avoid unwanted differences during follow up examinations. One TIC was obtained for each ROI. The image loops were transferred to a personal computer for further analysis. From the analysis of TIC, we computed regional blood flow (RBF) and regional blood volume (RBV). TIC were extracted using commercial quantification software (QontraXt v.3.60, AMID, Rome, Italy). This software allows manual ROI selection, measurement of the selected ROI area and provides linear data for the TIC. For the ROI in the normal ATM, effort was made to place the region in an area without large vessels. The ATA ROI was a 2 cm square area and the ATM ROI was a 4 cm square area. TICs were obtained by computing the mean intensity of pixels comprised within the ROI at each time point. For each image loop were calculated:

Table 2 Patients baseline

ID	Sex	Age	Risk factors	Diagnosis	Lesion' site and extension	Rest pain
1	m	57	AH, hyperuricemia, HC, ESH	PAD	Left leg ulcer, 16 cm	+++
2	m	39	ESH	BD	Left foot ulcer, 2 cm	++
3	m	37	Hyperhomocysteinemia, ESH	BD	Left forefoot amputation dehiscence, 15 cm	+++
4	m	69	AH, ESH, HC	PAD	Right foot ulcer, 5 cm	++
5	f	41	ESH	BD	Right foot ulcer, 1 cm	++
6	m	34	ESH	BD	Left finger amputation dehiscence, 10 cm	+++
7	f	52	AS, AH, DM	PAD	None	+++
8	m	49	ESH	PAD	None	++

AH arterial hypertension, *HC* hypercholesterolemia, *ESH* ex smoke habit, *PAD* peripheral arterial disease, *BD* buerger disease, *AS* active smoker, *DM* diabetes mellitus

Pain scale: + mild, ++ moderate, +++ severe

- RBV which consists in the total amount of contrast media within the selected ROI, in a period of time. Due to the characteristics of US contrast media, it reflects the quantity of blood in a defined region. It is directly related to the area under the curve (AUC).
- RBF consists in the contrast media flow (related to the blood flow) in a selected ROI. It is related to the mean transit time.

Bone marrow stimulation
Human recombinant granulocyte colony-stimulating factor (rhGCSF) was administered subcutaneously for 4–5 consecutive days at a dosage of 10 μg/kg daily, split in two doses. Starting from the third day of stem cells mobilization, the CD34+/133+ cells count was monitored daily by cytofluorimetric analysis. The minimum CD34+/133+ cells count acceptable for leukapheresis collection was 20 and 10/μl, respectively. Patients were monitored for any G-CSF related side effects.

Leukapheresis (LKF) collection
A single LKF collection was planned for each patient using a third generation cell separator device (Spectra Cobe, Lakewood, CO, USA), processing at least 2.5 blood volumes according to our internal protocol for stem cell collection. Immediately after the LKF collection, a sample from patient's peripheral blood was taken for haemocytometric analysis to evaluate platelet count and haemoglobin levels. Each LKF collection was diluted with 10 % acid citrate dextrose (ACD-A) and maintained overnight at 4 °C degrees before immuno-magnetic cell selection.

Immunomagnetic cell selection
CD133+ immunomagnetic cell selection (ICS) was performed the day after LKF collection using the CliniMACS (Miltenyi Biotec) device according to the manufacturer's standard protocol.

Quality controls
A sample taken from the CD133 cell positive fraction was seeded for short term (14 days) clonogenic assays to evaluate the quality of immunoselected stem cells in terms of proliferative capacity. A standard mixture of methylcellulose plus recombinant human growth factors was employed (Stem Cell Technologies, Vancouver, BC, Canada; MACS Media, Miltenyi Biotec GmbH, Bergisch Gladbach,Germany). Microbial cultures on the waste bag containing the negative fraction were carried out to detect aerobic-anaerobic bacteria and fungal contamination. A sample of 10 ml was inoculated in the culture medium (Bact/Alert FA and BacT/Alert FN, Organon Teknika Corp., Durham, NC) and incubated for 10 days at 37 °C.

Cytofluorimetric analysis
Samples obtained from peripheral blood before mobilization with G-CSF, at time of LKF and after immunomagnetic cell selection were analyzed by flow cytometry to evaluate the expression of specific stem cell and endothelial antigens. Becton–Dickinson FACSCanto was employed for all flow cytometric analysis with a lyse no-wash technique, using the following monoclonal antibodies: anti-CD45 fluorescein isothiocyanate (FITC) (Becton–Dickinson, San Jose, CA, USA), anti-CD34 Peridinin-chlorophyll-protein complex (PerCP) (8G12 clone, Becton–Dickinson), anti-CD133 phycoerythrin (PE) (AC133 clone, Miltenyi Biotec) and anti-VEGF-R2 allophycocyanin (APC) (R&D systems), following the manufacturer instructions.

Each sample was acquired with BD FACSCanto recording 100.000 events inside the lymphocyte plus monocyte gate. Data files were analyzed with FACS Diva 6.1 software. Viability was assessed using 7-amino-actinomycin D (7-AAD) (Molecular Probes, Eugene, OR, USA).

Implant procedure
After loco-regional anesthesia and below the knee cutaneous disinfection, 45–48 ml of autologous CD133+ cell in buffer phosphate (Miltenyi Biotec) suspension was administered intramuscularly with 1 ml deep injections through a 18G needle. The injections were so allocated: 10 ml in the anterior compartment of leg, 10 ml in the superficial posterior compartment, 10 ml in the deep posterior compartment, 10 ml in the lateral compartment and the remaining part in the foot (Additional file 1: Figure S1).

Baseline assessment and follow up
Pain assessment was carried out with a personal scale of 3 degrees (mild, moderate and severe) and the pain killing drugs use monitored. Ischemic lesions were treated weekly by a wound management skilled nurse. CEUS, lesion evolution and pain management were assessed at baseline and 3, 6 and 12 months after the implant.

Statistical analysis
All quantitative variables were normally distributed (Shapiro–Wilk test) and so the results were expressed as mean values and standard deviation (SD); qualitative variables were summarized as counts and percentages. Pearson's r coefficient was used to test correlation between two study variables. Linear regression models for repeated measure were used to assess the increase over time of the CEUS parameters. Data analysis was performed with STATA

statistical package (release 11.1, 2010, Stata Corporation, College Station, TX, USA).

Results

Patient's mobilization and LKF

No relevant side effects related to G-CSF administration were registered. A single LKF collection per patient was performed. No side effects were registered. Patients did not require any red blood cells or platelet transfusion after LKF procedures. Total nucleated cells (TNC) content and viability in peripheral blood of the eight patients enrolled are depicted in Table 3.

Immunomagnetic cell selection

The immunomagnetic cell selection was carried out the day after LKF collection. Almost all cells expressing CD133 antigen also expressed CD34 antigen. The mean CD133+ cell recovery was 46.1 % (SD 21.5, range 9.9–81.7). The mean purity was 85.4 % (SD 19.6, range, 37.2–96.5). TNC viability was always >90 %. Results of cytofluorimetric analysis performed on samples obtained from the positive fraction are detailed in Table 3. The mean number of CD133+ infused cell per limb kilogram was 25.2 × 10^6 (SD 13.8; range 2.6–42.2). Clonogenic assays demonstrated the maintained proliferative capacity of immunoselected stem cells. The result of microbial cultures was always negative.

Clinical results

No patient had early or late complications related to the procedure. Two patients (number 3 and 7, 25 %) didn't get any relief from the treatment and underwent major amputation. Patient number 3 had lesion and pain worsening and was amputated below the knee after 5 months. Patient number 7 had pain worsening and final gangrene of the foot and underwent above the knee amputation after 7 months; this patient had diabetes and a heavy smoking habit (40 cigarettes/day) persisting in spite of physician's indication. Five patients (number 1, 2, 4, 5 and 6, 62.5 %) had a complete healing of the wounds, complete rest pain cessation and walking recovery or increased pain free walking distance. One patient (number 8, 12.5 %) had rest pain cessation, and a mild improvement in pain free walking distance. None statistical correlation has been found between the number of infused CD133+ cells and the clinical results:

CEUS

An increase in RBF and RBV was shown in all eight patients at 3 and 6 months and in the six clinical healed patients at 12 months and has statistical relevance: at 12 months mean increasing for TAM-RBV was 48.8 % ($p = 0.018$), for TAM-RBF 59.4 % ($p = 0.0016$), for ATA-RBV 52.8 % ($p = 0.017$) and for ATA-RBF 48.6 ($p = 0.007$). The trends in increasing values at 3, 6 and 12 months for RBV and RBF, both in artery and in muscle, are depicted in Fig. 1. No statistical correlation between RBF and RBV value, and CD133+/CD34+ infused cells was found at 6 and at 12 months. Additional file 2: Figure S2 shows the correlation between clinical healing and CEUS values improvement in patient 1. Table 4 shows a synopsis of the results.

Discussion

CLI is a manifestation of PAD that includes patients with typical chronic ischemic pain at rest or patients with ischemic skin lesions, either ulcers or gangrene. The term CLI should only be used in relation to patients with chronic ischemic disease, defined as symptoms lasting more than 2 weeks. The diagnosis of CLI should be confirmed by ABI, toe systolic pressure or transcutaneous oxygen tension. Ischemic rest pain most commonly occurs below an ankle pressure of 50 mmHg or a toe pressure less than 30 mmHg [1].

Table 3 Cytofluorimetric analysis

ID	PB at collection			LKF		IS	Recovery (%)	Purity (%)	CD133+ infused (10^6/limb kg)
	WBC (10^3/uL)	CD34+ (n/uL)	CD133+/CD34+ (n/uL)	CD34+ (10^6)	CD133+/CD34+ (10^6)	CD133+ (10^6)			
1	48.6	51.0	34.5	311.4	232.3	140.6	60.5	92.5	30.0
2	47.2	95.9	56.6	486.0	484.7	233.1	48.1	89.2	41.1
3	52.9	105.7	105.5	737.9	706.3	361.1	51.1	93.9	42.2
4	39.1	35.2	25.1	401.0	282.6	100.3	35.5	92.9	16.4
5	51.6	63.1	50.7	333.0	205.4	20.4	9.9	37.2	2.6
6	77.0	55.4	42.2	369.2	317.6	94.0	29.6	90.0	16.1
7	41.7	47.7	7.0	223.0	154.9	126.5	81.7	96.5	20.1
8	26.6	58.5	44.1	603.5	455.2	238.9	52.5	91.1	33.2
MV	48.1	54.7	45.7	433.1	354.9	164.4	46.1	85.4	25.2

PB peripheral blood, *LKF* leukapheresis, *IS* immunoselection, *WBC* white blood cells, *MV* mean values

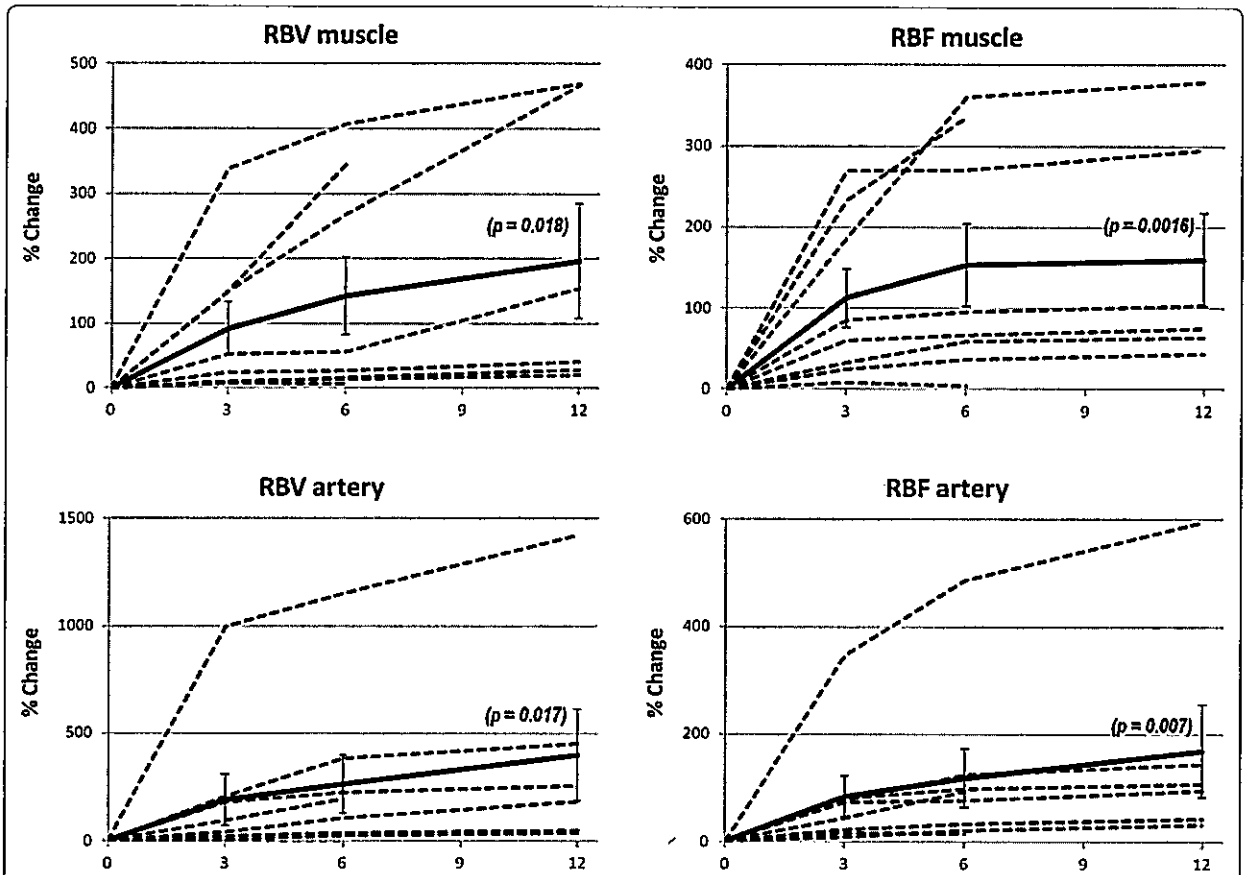

Fig. 1 The diagrams show the percentage increase of both RBV and RBF both in muscle and in anterior tibial artery. *RBF* regional blood flow, *RBV* regional blood volume. In the *x axis* are months of follow-up. In the *y-axis* is the percentage of increase of the values of RBV and RBF compared to the baseline. *Dotted lines* represent single patient values. *Continue line* represents the mean percentage increase with the statistical significance. P values compare the value of mean increase to the baseline

The first large report on the use of bone marrow-derived mononuclear cells (BM-MNC) in limb ischemia was the therapeutic angiogenesis by cell transplantation (TACT) study by Tateishi-Yuyama et al. At 4 weeks, ankle-brachial index (ABI) was significantly improved in legs injected with BM-MNC and similar improvements were seen for transcutaneous oxygen pressure. They concluded that autologous implantation of BM-MNC could be safe and effective for achievement of therapeutic angiogenesis, because of the natural ability of marrow cells to supply endothelial progenitor cells and to secrete various angiogenic factors or cytokines [11]. Since then, several trials were published, both using BM-MNC, and mobilized peripheral blood mononuclear cells (PBMNC) with intra-arterial or intra muscular administration, well reviewed by Lawall et al. [12].

In their review, Lawall et al. sustain that the role of "EPCs" in human angiogenesis in the setting of peripheral vascular obstruction remains doubtful, and the translation of a truly "EPC" based endothelial repair into clinic practice has not been achieved so far. The well substantiated concept of arteriogenesis strengthens the importance of several different bone marrow cell types, however all sharing a monocytic phenotype. They migrate to the perivascular space of sprouting collaterals and induce collateral artery growth by the release of angiogenic growth factors. A growing body of evidence strongly suggests that these secreted molecules mediate a number of protective mechanisms including cell survival, neo-vascularization, remodeling, and proliferation. The regulatory system governing paracrine factor release appears to be complex and dependent on spatiotemporal parameters. [13].

Based on available data, cell therapies in PAD based on the application of whole BM-MNC or on whole stimulated PBMNCs are more successful than methods which use subfractionated cell preparations [12], e.g. CD 133+ [14] or highly purified CD 34+ cells from peripheral blood after granulocyte- colony stimulating factor (G-CSF) mobilisation only [15]. Nevertheless available data are very scarce about efficacy of a specific subset cells population versus the entire pool of mononuclear cells, because great majority of the previous and ongoing studies employ BM-MNC or PBMNCs, due to both lower costs and relative simplicity of the method. Except the case report of Canizo et al., the only previous study employing autologous selected CD 133+ cells is by Burt et al.: they treated nine patients with positive results in 7 [16].

Previous EPCs in CLI studies considered only data measured with ABI and $TcPO_2$. As a matter of fact both ABI and TCpO2 have an intra and inter patient variability due to detection method, operator experience, vasodilatation state and emotional stress, that make standardization difficult. Moreover, in case of very low velocity flow, as in peripheral blood circulation in CLI, ABI detection variability increases [17]. CEUS offers a reliable method to measure peripheral blood flow, and is a valid alternative: it's equally a non-invasive method, because the medium contrast hasn't got any contraindication, except hypersensitivity, and the assessment method is not operator, but dedicated software related. It has only a minimal intra patient variability, when the detection method is accurate.

The aims of our study are (1) to demonstrate that a highly purified autologous stem cells population can induce neo-angiogenesis in a safe, feasible and effective way and (2) to assess neo-angiogenesis with a non-invasive method as most objective and reproducible as possible. In consideration of the end stage disease character of CLI, we didn't considered ethical randomizing eligible patients. The possible advantages in studying a specific cells population in order to understand the mechanisms of neo-angiogenesis are to avoid the overlapping effects of entire MNC populations infused and as second step to better identify the cytokines pattern, derived from a single cell type, given the hypothesis of a paracrine mechanism.

Stem cells mobilization with G-CSF administration induce a high white blood cells count (WBCc) and a subsequent theoretical blood hyper viscosity. In patients with CLI blood hyper viscosity can be an issue. In our series the mean WBC count at the 4th day after mobilization was 48.1×10^6/ml (range 26.6–77). These values are similar to these observed in healthy donors mobilized for allogeneic hematopoietic stem cell transplant. Even in the patient (ID = 7) with the highest WBCc (77.0×10^6/ml) we didn't observe any significant side effect related to blood hyper viscosity. However, we administered a prophylactic dose of low molecular weight heparin (3800/4000 UI/daily) considering the pro thrombotic risk related to G-CSF administration and patient immobilization. Remarkably also the CD34+ and CD133+ mobilization in these patients is comparable to healthy donors showing that their stem cell reservoir is not depleted. Stem cell collection was performed following our internal protocol, processing 2.5 blood volumes without any relevant side effects. On the whole we can argue that patients with compromised peripheral circulation can tolerate very well both mobilization and LKF. The wide range of CD133+ cell recovery after the ICS may be related to the different antigen expression on the stem cell surface. All the immunoselected CD133+ cell samples showed an high in vitro clonogenic potential (similarly to hematologic field) demonstrating the good quality of the product infused. Nevertheless the purity was always very high (≥90 %), except in one case (ID = 5), showing that every patient, but one, was treated with a single cell population. From this point of view, we obtained results comparable with the study of Burt et al. [16].

Altogether, 6 out of 8 patients (75 %) had clinical improvement, with ulcer healing, cessation of rest pain, increased walk pain free distance and above all, avoided amputation and maintained their improvement for a long period of time. Indeed they had the longest follow up so far in literature, 12 months with CEUS and at least 18 months from a clinical point of view. The graphics in Fig. 1 show the increase (in percentage) from baseline of RBV and RBF, both for ATM and ATA: mean percentage increase (continuous line) is always positive and statistically significant (see also Table 4 for p values). Clinical improvement is consistent with instrumental data showing an increased blood flow in the limb, reasonably related to an induced neo-angiogenesis. Nevertheless other important local factors may be involved both in initiating and maintaining angiogenesis, like resident cells and chemokines and cytokines environment. Data demonstrate that the resident progenitor cells could differentiate into a variety of cell types in response to different culture conditions. However, collective data were obtained mostly from in vitro culture assays and phenotypic marker studies. There are many unanswered questions concerning the mechanism of cell differentiation and the functional role of these cells in vascular repair and the pathogenesis of vascular disease [18].

Patient 3, despite the maximum values of cell dose infused (42.2×10^6/limb kg) showed a complete lack of responsiveness both clinical, and instrumental (Table 4). Conversely, Patient 5 received the lowest dose of CD133+ cells with the lowest purity (Table 3): however she showed a satisfactory clinical response (ulcer healing, rest pain relief and increased pain free walk distance) and TAM-RBV/RBF increasing (+28.6 and +42.9, respectively). We can speculate that these opposite results are

Table 4 Results

ID	Follow-up (months)	Early and late procedure related complications	Lesions healing	Limb salvage	Pain control[a]	CEUS assessment											
						TAM-RBV			TAM-RBF			ATA-RBV			ATA-RBF		
						Baseline	12 months	Δ %	Baseline	12 months	Δ %	Baseline	12 months	Δ %	Baseline	12 months	Δ %
1	12	None	Complete	Yes	+++	547.17	1391.05	+60.7	21.3	43.35	+50.8	661.37	3645.24	+81.8	29.61	72.08	+58.9
2	12	None	Complete	Yes	+++	40.89	231.72	+82.4	3.15	12.43	+74.6	620.4	2199.88	+71.8	45.89	89.03	+48.4
3[b]	5	None	None	No	+	358.13	(382.13)	(+6.2)	(15.03)	(15.6)	(+3.6)	1111.76	983.62	−13.0	41.73	47.86	+12.8
4	12	None	Complete	Yes	+++	1486.92	1789.42	+16.9	42.42	69.48	+38.9	1391.05	3899.2	+64.3	43.35	89.89	+51.8
5	12	None	Complete	Yes	+++	629.66	881.69	+28.6	21.68	38.00	+42.9	1468.95	1978.16	+25.7	50.87	66.58	+23.6
6	12	None	Complete	Yes	+++	1172.09	1499.72	+21.8	37.67	53.83	+69.9	2153.68	3192.85	+32.5	72.51	102.73	+29.4
7[c]	7	None	–	No	+	183.88	819.66	(+77.6)	7.68	33.49	(+77.0)	269.96	790.27	+65.8	17.8	34.41	+48.3
8	12	None	–	Yes	++	134.49	765.48	+82.4	6.06	29.01	+79.1	361.46	5501.74	+93.4	14.39	99.97	+85.6
Mean values						631.24	999.34	+48.8 (p = 0.018)	21.27	38.02	+59.4 (p = 0.0016)	1004.8	2773.9	+52.8 (p = 0.017)	39.5	75.3	+48.6 (p = 0.007)

TAM tibial anterior muscle, *ATA* anterior tibial artery, *RBV* regional blood volume, *RBF* regional blood flow

[a] +: satisfactory; ++: good; +++: very good

[b] Amputation at 5 month

[c] Amputation at 7 month

related not exclusively to the cell dose infused, but also to responsiveness of the resident stem cells. Indeed we didn't find any statistical correlation between the number of infused CD133+ cells (10^6 per limb kg) and the clinical and CEUS results.

Patient 7 showed apparently conflicting results: at 6 months TAM-RBV/RBF were increased around 77 % with a slightly improvement of clinical condition. Unfortunately the following month she developed a sudden worsening in the limb ischemia, with subsequent above the knee amputation. It's crucial to emphasize that the patient had insulin dependent diabetes mellitus (IDDM) and a heavy smoking habit (around 40 cigarettes daily). We can suppose a negative role of IDDM and a precipitating role of the smoke habit during the transient neo-angiogenesis process, as assessed by CEUS values increasing. However impaired angiogenesis in diabetes has been already demonstrated both in animal models and in humans [19, 20].

In conclusion, our study shows interesting perspective and issues. Highly purified autologous CD133+ cells, routinely employed in transplant for oncohematologic diseases, can stimulate neo-angiogenesis, either directly or through a paracrine effect, as based on clinical (ulcer healing, rest pain cessation, increasing pain free walk distance and limb salvage) and CEUS data. Our study gives an instrumental demonstration of neo-angiogenesis. The limits of the study are the lack of randomization, which we judged unethical for this kind of end-stage disease, and the low number of patients, mainly due to the restrictive inclusion and exclusion criteria. Goals for future studies are to enrol a major number of patients including also less advanced stages of PAD, and to consider other powerful stem cell sources as cord blood derived or mesenchymal stem cells.

Additional files

Additional file 1: Figure S1. The procedure of implant through multiple intramuscular 1 ml injection of CD133+ cells suspension.

Additional file 2: Figure S2. The complete healing of a deep and painful ischemic lesion with bone exposure in patient 1. Beside the corresponding change in RBV and RBF measurements.

Authors' contributions

Concept and design: CP, VA, CDF, AB. Supervision: VA, CP. CEUS: FC, FA. Cell management: CP, CDF, GV. Patient management: VA, AB, AM, MP, FR. Data collection: VA, CP, AB, FR, FC, FA,GV, MP, AM. Manuscript draft: all the authors. Manuscript revision and approbation: all the authors. Statistical analysis: CT.

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Competing interests

The authors declare that they have no competing interests.

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Spatio-temporal correlation between admissions for ruptured abdominal aortic aneurysms and levels of atmospheric pollution in Italy

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ABSTRACT

Aims: The aim of our study was to determine a correlation between rates and number of patients admitted with ruptured abdominal aortic aneurysms (rAAA) in Italian regions with different levels of atmospheric pollution.
Methods: We analyzed a possible correlation between the number and rate (ruptured versus not ruptured) of patients with rAAA admitted in eight Italian regions with different levels of atmospheric pollution.
Results: Number and rates of patients with rAAA were statistically correlated with levels of air pollution and low air temperature (RR = 1.90, 95% CI: 1.42, 2.1.0) ($p<0.01$). Even if low temperatures amplified the correlation between admissions for rAAA and PMs exposure, also during Summer and Spring there were sudden increases of the number of admissions for rAAA patients in periods with higher air pollution. The regions with high levels of atmospheric pollution had higher rates of admissions of patients with rAAA in comparison with regions with low level of air pollution. However, there was no difference between regions with low and very low level of atmospheric pollution. Mean age, sex distribution, exposure to established risk factors were similar for the population of the eight analyzed Italian regions.
Conclusions: The findings of this study highlight the potential to reduce AAA related mortality and burden by addressing the negative effects of exposure to high levels of atmospheric pollution. The possibility of a dose-dependent effect of atmospheric pollution on the cardiovascular system opens research initiatives and discussions about when and how to modulate interventions to reduce atmospheric pollutants.

Introduction

Epidemiological analyses support the hypothesis that sudden increase of Particulate Matters (PM) in the atmosphere is a risk factor for cardiovascular diseases.[1–6] Conceptually, a condition of systemic inflammation related with sudden increase of atmospheric pollution may promote degeneration of the wall of a pre-existing Abdominal Aortic Aneurysm (AAA) through multiple mechanisms.

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We correlated admissions for ruptured AAA (rAAA) and atmospheric levels of air pollution in Italy.

Material and methods

1 We analyzed a possible correlation between the number and rate (ruptured versus not ruptured) of patients with AAA admitted to the Hospital San Matteo during a 7-year period (January 2012-December 2018) and trends of atmospheric levels of pollution. The three most common pollutants, (Particulate Matter PM2.5, PM10, CO) were analyzed. PM2.5 and PM10 represent more than 80% of the atmospheric PMs in Pavia. Pavia (Lombardy) has high levels of air pollution, among the highest in Europe (Figs. 1 and 2).
2 We also analyzed number and rates of hospital admissions for patients with rAAA in Italy from January 2015 to December 2019, before the COVID19 pandemic. We correlated analyzed prevalence of rAAA, with simultaneous changes of atmospheric levels of PM2.5 and other seven established risk factor for cardiovascular diseases.[7–11]
3 We determined number and rate of patients who were admitted and had surgery for rAAA during the year 2021 in 32 Italian hospitals located in Italian regions with different levels of air pollution as reported by the Italian Agency AGENAS.[12] We randomly selected 16 hospitals located in three regions with higher air pollution (Lombardy, Veneto, Emilia-Romagna) and 16 hospitals located in five regions with lower air pollution (Tuscany, Marches, Umbria, Abruzzo, Apulia) .

The analyzed hospitals have similar number of beds, number and training of surgeons, number of admission of patients with AAA (more than 40 /per year), and similar operative results. We included only "public hospitals" with level 3 (the highest level) emergency-trauma centers. All procedures in these public hospitals are supported by the National Health System. The population of the eight included regions has similar mean age and similar exposure to established risk factors (sex, age, smoking, high systolic blood pressure, type of diet).

IRB approval was not required for this study.

Air Quality

Mean air quality index in the last 10 years was obtained from data determined by satellites Joint Polar Satellite System (JPSS) and Geostationary Operational Environmental Satellites-R (GOES-R): the higher the score the higher the air pollution. Atmospheric levels of PM2.5 were obtained from the World Health Organization Air Pollution Database.[11] The mean annual registered air quality score was 90 in the province of Pavia. In the province of Pavia annual averaging was 31 microgr/m^3 for PM10 and 23.5 for PM2.5 with a surplus of 64 days/per year.

The mean score of air quality in the year 2021 was 85 for the three regions with higher pollution (Lombardy, Veneto, Emilia Romagna) and 38 in the five regions with lower air pollution (Tuscany, Marches, Umbria, Abruzzo, Apulia) ($p<0.001$). Several reasons explain the difference in air pollution. The three regions with increased air pollution have a statistically significant higher density of population (400 Inhabitants/Km^2 CI 95% 455, 380) in comparison with the five regions with lower air pollution (210 Inhabitants/Km^2 CI 95% 360, 240) ($p<0.0001$) and more diffuse industrial activity. However, regional mean personal income is similar. The analyzed eight regions have a population of 26 384 000 inhabitants (15 230 000 for the three regions with higher air pollution; 11154 000 for the five regions with lower air pollution).

Trends (2014-2019) of established risk factors for Cardiovascular Diseases in Italy

The prevalence in the Italian population of seven established risk factors for cardiovascular diseases (diabetes, obesity, tobacco

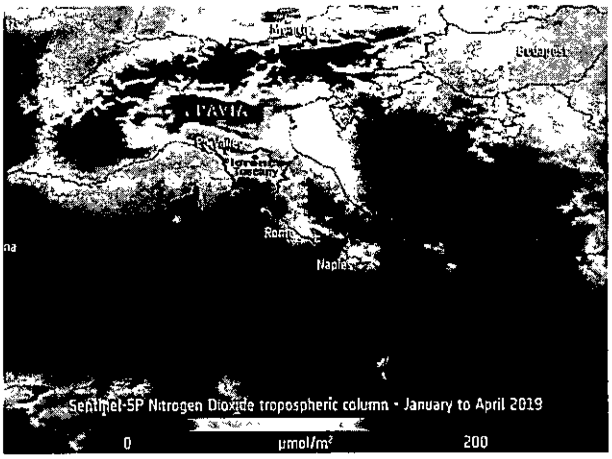

Fig 1. Nitrogen dioxide tropospheric columns in Italy. Nitrogen dioxide production is an index of "pollution". The region Lombardy (Milan-Pavia) has the highest air pollution in Italy and Europe[7,9].

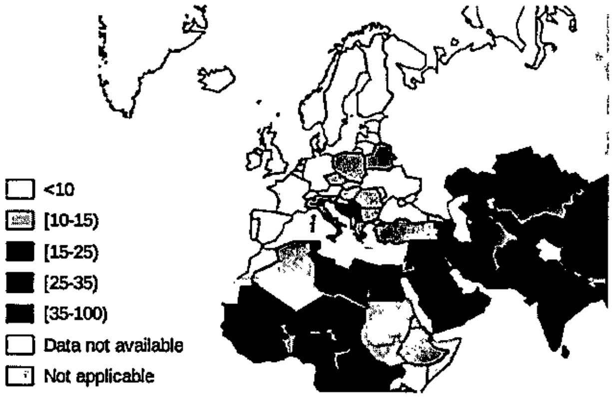

Fig 2. Annual mean levels (2019) of Atmospheric levels of Particulate Matters (PM)2.5 in Europe for cities (population weighted)[11].

smoking, arterial hypertension, non-HDL cholesterol, family income, educational attainment) were obtained from the European Health Interview System (EHIS)[13] (wave 2-2014; wave 3-2019). The EHIS is based on a scientifically organized and planned questionnaire with telephone interviews.

Statistical analysis

Continuous variables were compared using an unpaired Student's t-test or Mann–Whitney U test, as appropriate, and data were expressed as mean+-SD. Categorical data were evaluated using the chi-square test or Fisher exact test, as appropriate.

Results

Patients admitted with ruptured AAA in the province of Pavia

In a 7-year period (January 2012- December 2018), 777 patients with AAA were admitted to the Hospital San Matteo-Pavia: there were 120 patients with rAAA (15.4%). Number and rates of patients with rAAA were statistically correlated with levels of air pollution and low air temperature ($p<0.01$). PM2.5 and PM10 were associated with the highest risk of rAAA (RR = 1.90, 95% CI: 1.42, 2.1.0). Even during Summer and Spring there were sudden increases of the number of admissions for rAAA patients in periods with higher air pollution, despite increased air pollution (Fig 3). No correlation was found between the number and rate of patients admitted with rAAA and other climate variables.

In the years 2012, 2014 and 2016 atmospheric levels of PM2.5 increased, whereas in the years 2013, 2015, 2017, 2018 atmospheric levels of PM 2.5 slowly decreased.[9–12] In the years of increasing levels of PM 2.5 (2012,2014,2016) out of a total of 348 patents admitted and operated for AAA 67 patients (19.3%) had a rAAA; in the years during which atmospheric PMs decreased (2013,2015, 2017,2018) out 429 patients admitted and operated for AAA, 53 patients (12.4%) had a rAAA (12.4%) ($p<0.01$) (Fig 4).

Correlation between atmospheric levels of PM2.5 and hospital admissions for patients with ruptured AAA

An overall decrease of hospital admissions for patients with acute cardiovascular problems including ruptured AAA were registered simultaneously with reduced atmospheric levels of PM2.5 from 2015 to 2019 (Table 1 and 2). The reduction was statistically

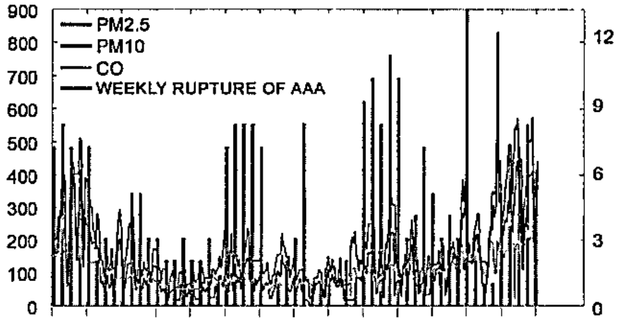

Fig 3. Correlation between levels of air pollutants and number of patients with ruptured AAA admitted and operated in the Hospital San Matteo-Pavia. On the left vertical axis the atmospheric levels of pollutants expressed as microgr/m^3; on the right vertical axis the number of patients with ruptured AAA admitted to the Hospital San Matteo each week.

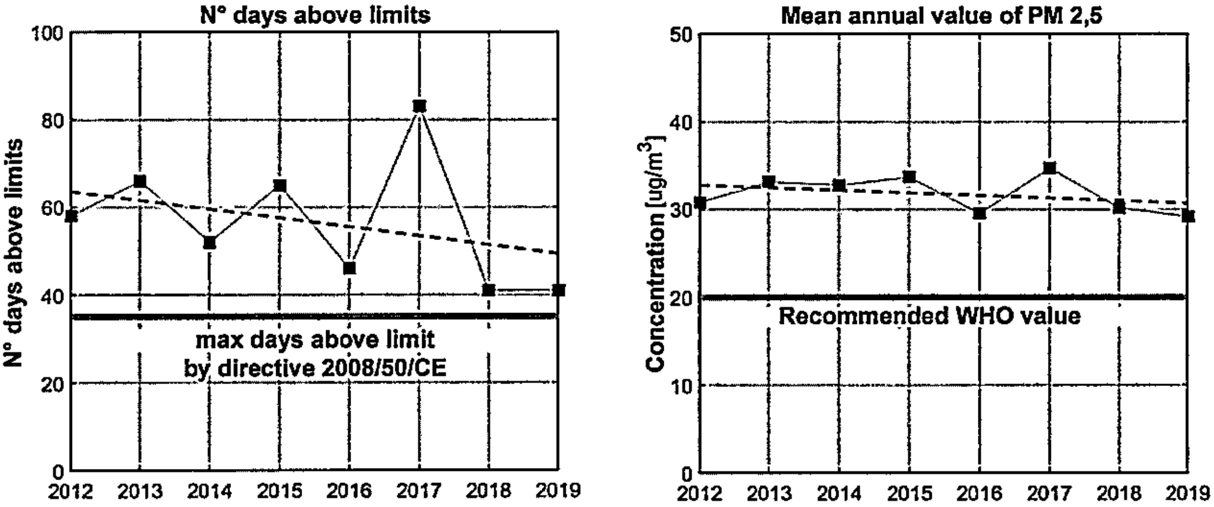

Fig 4. Changes of atmospheric levels of PM2.5 in Pavia. During the years when atmospheric levels of PM2.5 increased, there was an increased rate of patients admitted with ruptured AAA to the Hospital San Matteo-Pavia; whereas, in the years during which atmospheric levels of PM2.5 decreased there were reduced rates of patients admitted with ruptured AAA.

significant for regions with high levels of air pollution, but there was no difference for regions with lower levels of air pollution.

In the same period, the European Health Interview System (EHIS) (wave 2-2014; wave 3-2019) did not demonstrate significant changes for the Italian population, regarding the seven analyzed risk factors for cardiovascular diseases and mortality (Table 3).

Comparison between three regions with higher levels of air pollution and five regions with lower levels of air pollution in the year 2021

We included into the study 32 hospitals with similar characteristics. In the three regions with higher atmospheric pollution the rate of patients admitted and operated for rAAA was 14.2% of the total number of patients who had surgery for AAA (181/1271), whereas in the five regions with lower atmospheric pollution the rate of patents who had surgery for rAAA was 9.9% (136/1368) ($p<0.001$-Yates correction). Operative results were similar in all hospitals. There was no statistically significant difference in prevalence of patients admitted to hospital in regions with low and very low levels of atmospheric pollution.

Table 1
Hospital admissions in Italy for severe-acute cardiovascular problems and atmospheric levels of pm 2.5.

INDICATION FOR HOSPITAL ADMISSION	2015	2016	2017	2018	2019	% CHANGE FROM 2015 TO 2019 p LINEAR TREND FOR REDUCTION
ACUTE MYOCARDIAL ISCHEMIA/STEMI (%)	132896/ 57811 (43.5%)	131973/ 55199 (41.8%)	129763/ 53976 (41.6%)	124643/ 51827 (41.6%)	123336/ 51324 (41.6%)	-7.2%/ -11.2% P<0.05
CONGESTIVE HEART FAILURE	178828	174908	168318	159159	156487	-12.5% P<0.05
ISCHEMIC STROKE	91070	90516	88553	86022	83834	-7.9% P<0.05
RUPTURED ABDOMINAL AORTIC ANEURYSM	986	1041	1011	1014	971	-1.5% P<0.05 FROM 2016 TO 2019
DEEP VEIN THROMBOSIS AND/OR PULMONARY EMBOLISM	41595	40180	41443	42538	42550	+2.3% p=1.88
SEVERE LOWER LIMBS ISCHEMIA STAGE III-IV	27253	27527	26616	26013	26517	-2.7% P=1.56
ATMOSPHERIC LEVELS OF PM 2.5						
TOTAL	17.28 (17.00-17.54)	15.82 (15.59-16.07)	15.73 (15.5-15.97)	15.97 (15.75-16.19)	14.22 (13.99-14.44)	-17.7% p<0.05
URBAN	17.90	16.39	16.28	16.52	14.73	-17.7%
RURAL	14.84	13.6	13.59	13.82	12.26	-17.4%
CITIES	18.96	17.36	17.22	17.41	15.56	-17.9%
TOWNS	16.96	15.53	15.45	15.74	14.01	-17.4%

Table 2
Hospital admissions for patients with Abdominal Aortic Aneurysm in Italy.

HOSPITAL ADMISSIONS OF PATIENTS WITH RUPTURED ABDOMINAL AORTIC ANEURYSM						
Year	2015	2016	2017	2018	2019	% CHANGE FROM 2015 TO 2019
HOSPITAL ADMISSIONS OF PATIENTS WITH RUPTURED ABDOMINAL AORTIC ANEURYSM						
TOTAL NUMBER	986	1041	1011	1014	971	-3.5%
% OF TOTAL NUMBER OF AAA	9.7%	10.3%	10.0%	9.9%	9.6%	-4%
HOSPTAL ADMISSIONS OF PATIENTS WITH NOT RUPTURED ABDOMINAL AORTIC ANEURYSM						
TOTAL NUMBER	9136	9059	9099	9186	9060	-0.8%
%TOTAL NUMBER OF AAA	90.3%	89.7%	90.0%	90.1%	90.4%	+4%

Table 3
Prevalence of risk factors for cardiovascular diseases in 2014(European Health Interview System Wave 2) and 2019 (European Health Interview System Wave 3) in Italy.

ANALYZED FACTORS	2014-2015	2019
Mean Annual Temperature (°C)	13.2	13.4
Mean Annual Temperature Cities (°C)	15.7	16.0
Total Population (x1000)	60796	59817
Mean Age Italian Population	44.2 years	45.5 years
% Persons 65 years or more	21.4%	22.9%
Number of persons 65 years or more (x1000)	13219	13693
Male/Female (%)	48.5/51.5 %	48.7/51.3%
People with at least a college degree (% people 25-64 years)	60.0%	62.2%
Persons with University degree (% people 25-64 years)	17.2%	19.6%
Gross Domestic Product Pro Capita (US Dollars)	33042	33674
% Obesity	10.5%	11.4%
% Diabetes	6.7%	6.5%
%Arterial Hypertension	20.6%	20.4%
% Daily Smokers All Ages	17.8%	17.3%
%Daily Smokers 65 years and more	8.9%	9.4%
%High levels of Cholesterol	24.2%	25.3%

Discussion

Decreased incidence of mortality for aortic aneurysm in high-income countries and increased incidence in low-income countries were evident from previous studies which analyzed GBD data from 1990 to 2017.[5,6] Conceptually, global analyses have several limitations because of interferences and amplifications between several risk factors, varying from country to country. The analysis of global data implies modeling strategies and assumptions to overcome the characteristics of different regions, implying potential statistical biases. We analyzed only data of eight Italian regions with a total population of 26 384 000, with the ambition to overcome significant and often unavoidable differences in data collection, cultural level, tradition, medical education and structure of the health system which conceptually should be not very different from region to region in Italy. Health system, exposure to established risk factors, mean age are similar in the 8 analyzed Italian regions.

We found a statistically significant correlation between atmospheric levels of PM2.5 and PM10 and increased number and rates of admissions of patients with rAAA in regions with high level of air pollution.

Increased levels of air pollution may promote degeneration of the wall of AAA with possibility of sudden rupture through direct and indirect actions. Systemic levels of IL-1, IL-6 and TNF alfa increase as consequence of high air levels of PM10 and PM2.5.[13–17] they may activate metallic proteinases with digestion of the extracellular matrix of the AAA wall.

Experimental and clinical studies show that high levels of atmospheric of PM10 and PM2.5 promote a pro-thrombotic status with the possibility of progression of the intra-luminal thrombosis associated with aortic aneurysms, which is often associated with the site of rupture.[18–23].

In regions with higher levels of air pollution, we found decrease of number and rates of admissions for patients with rAAA in the years during which the levels of atmospheric PM2.5 diminished.

Several other hypotheses are supported by the findings of our study: the possibility exists that generic anti-inflammatory agents may reduce the negative effects of increased atmospheric pollution, limiting the negative actions of a condition of chronic inflammation related to the increased levels of inflammatory cytokines.

The findings of this study highlight the potential to reduce AAA related mortality and burden in regions with high levels of pollution, by addressing the negative effects of atmospheric pollution exposure through a valid communication.[24–27].

Expenditure related with a well-organized information about risk factors (including air pollution) has the potential to reduce mortality and burden, with diminished total health expenses.[20,28–34].

A final fundamental consideration relates to a possible dose-dependent effect of the level of atmospheric pollution. Recent epidemiological studies showed reduced prevalence of stroke associated with lowering high levels of atmospheric pollution; however, further decrease of atmospheric levels of air pollution had no effect on cardiovascular mortality.[35]

Thus, it is important to determine, if possible, levels of air pollution which represent a serious risk factor for health., and the eventual factors aggravating the effects of high levels of atmospheric pollution, like very high or very low temperature, smoking, diet, air humidity.

These questions are of fundamental importance, trying to find an appropriate balance between level of industrialization and health of the general population, taking in mind that in most countries the Health System itself is supported by national funds provided by the industrial activity .

Study Limitations

The findings of our study cannot differentiate between direct and indirect effects of elevated air pollution on the possibility of rupture of an aortic aneurysm. Atmospheric pollution may determine direct and indirect effects. Patients may change several life-style attitudes, such as increased smoking and high caloric diet, reduced physical activity and outdoor living in periods of higher atmospheric pollution. Furthermore, sudden increase of air pollution may lead to autonomic unbalance and vasoconstriction with consequent increased arterial blood pressure.[21–23,36,37] Another limitation related with the number and rate of patients with rAAA admitted to hospitals; a significant number of patients with rAAA has not the possibility to reach the hospital.

Data availability statement

All data are available upon request from A Bozzani and A Sterpetti

CRediT authorship contribution statement

Antonio Bozzani: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **Sara Cutti:** Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **Luca Di Marzo:** Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **Raimondo Gabriele:** Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **Antonio V Sterpetti:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Trends (2020–2022) toward Reduced Prevalence of Postcoronavirus Disease Syndrome and Improved Quality of Life for Hospitalized Coronavirus Disease 2019 Patients with Severe Infection and Venous Thromboembolism

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic seems to be at its end. During the first outbreak, alfa was the dominant variant, and in the two following years, delta was the dominant variant. Questions remain about the prevalence and severity of post-COVID syndrome (PCS). We compared the medium-term outcomes of a selected group of patients considered at high risk for PCS: hospitalized patients with severe COVID-19 infection who presented clinical evidence of the acute onset of venous thromboembolism. Weighted Cox regression was used to estimate the adjusted hazard ratios for the risk of early and medium-term complications and quality of life (QoL) in COVID-19 patients developing acute venous thrombo-embolism, according to the period of admission to the hospital. The primary outcome was the modification of QoL at a median follow-up of 24 months in patients hospitalized for COVID-19. The secondary outcome was the modification of QoL related to COVID-19 severity. The absolute risk of mortality for hospitalized COVID-19 patients was higher during the first outbreak (risk difference, 19% [95% confidence interval [CI], 16–22%]). Patients with acute onset of thromboembolism during the first outbreak had increased mortality, hospital stay, and need for intensive care unit treatment ($p < 0.01$). In patients who suffered from severe COVID-19 infection and thromboembolism in the following 2 years, symptoms during follow-up were less common and milder (risk difference 45% [95% CI, 40–52%]. In total, 19 patients were alive at 24 months follow-up: 12 patients (63%) reported important physical symptoms and 10 patients (52%) relevant emotional/mental symptoms. All patients reported reduced QoL in comparison with the preinfection time; in 15 patients

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(79%), the reduced QoL limited significantly their social and work activities. All patients reported permanent worsening of QoL after discharge from the hospital. Comparing the three different February to April interval years (2020, 2021, and 2022), patients reported a somewhat worse perception of health condition in comparison with the preinfection time, respectively, in 100, 79, and 56% respectively. The findings of our study show reduced prevalence and severity of PCS in the last 2 years. Less virulent variants, herd immunity, and vaccination may played a significant role.

The term postcornavirus disease (COVID) syndrome (PCS) (or long COVID) describes a condition characterized by the persistence of symptoms for at least 12 weeks after the onset of COVID-19 and its clinical resolution.[1–3] The general recurrent symptoms include fatigue, breathlessness, headache, loss of memory, and impaired concentration. Cardiovascular involvement is common.[4] The problem of PCS has been at the center of attention because of the relatively high prevalence after the first outbreak of the pandemic. The expected prevalence of post-COVID symptoms was around one-third of cases of the entire COVID-19 population infected during the first outbreak. The burden is such that it has led to the activation of PCS outpatient clinics. Analyzing the 1-year clinical outcome of more than 150,000 patients infected with COVID-19 during the first outbreak (March–May 2020), it was found that in the year after recovering from the infection, patients had higher risk of heart rhythm disorders, cardiomyopathy, blood clots, strokes, myocardial infarction, and heart failure in comparison with the matched general population.[5] These problems, even if less frequent than during active COVID-19, occurred among those who were not hospitalized, presuming then a mild form of infection.

We analyzed the early and medium-term occurrence of PCS in patients considered at high risk to develop the syndrome with the aim to determine a possible decrease in the prevalence and severity of the syndrome. PCS seems to be more common in patients with severe COVID-19 infection requiring oxygen therapy, who present a genetic predisposition including inflammatory and thrombophilia pathways.[6–8] For this reason, we included in the study hospitalized patients with severe COVID-19 requiring oxygen therapy, who presented severe hemostatic changes and clinical evidence of acute venous thromboembolism (VTE) during the first outbreak of the pandemic and during the outbreaks occurring in the same months of the following 2 years.

Outcomes of the study. The primary outcome was the modification of quality of life (QoL) at median follow-up in patients hospitalized for COVID-19. The secondary outcome was the modification of QoL related to vaccination.

Material and Methods

Study Design

Data of patients admitted to the San Matteo Hospital in Pavia (Lombardy-Italy) for severe COVID-19 and who developed acute VTE were prospectively collected and retrospectively analyzed. Three pandemic outbreak periods were examined: February to April 2020 (vaccine not available); February to April 2021 (vaccine available but only selected people received complete vaccination); and February to April 2022 (vaccine available and more than 85% of the population older than 12 years in the province of Pavia received complete vaccination). All patients gave written consent. The study was approved by the local ethical committee of Fondazione IRCCS Policlinico San Matteo of Pavia, and we conducted our study in compliance with the principles of the Declaration of Helsinki. Analyzed outcomes were survival, cardiovascular events, and physical and cognitive symptoms. They were measured with personal interviews with the patients and their family members.

Inclusion Criteria. Patients at High Risk to Develop Long Coronavirus Disease Symptoms

In the study, we included consecutive patients with COVID-19 admitted to the hospital with a severe form of infection, defined as requiring oxygen therapy support, both invasive and not invasive, hemostatic abnormalities, and who also suffered acute VTE during the infection[9,10] This group of patients was chosen because of the presence of several established risk factors for prevalence and severity of PCS. The patients were further divided into two subgroups: vaccinated and nonvaccinated, as a surrogate marker for COVID-19 severity.

Therapy during Hospitalization and after Discharge from Hospital

All patients received at admission prophylactic heparin and oxygen. Antibiotics and steroids were prescribed according to the evolution of the infection. Once a diagnosis of acute VTE was made, patients received therapeutic dose heparin. After discharge, oral anticoagulation was started with direct-acting oral anticoagulants or vitamin K antagonist, with the advice to continue for at least 6 months. This therapy was continued for more than 6 months in half of the patients included in the study.

Assessment of Quality of Life and Symptoms after Discharge from Hospital

The assessment was based on the Short Form Health Survey—36 (SF-36): the 36 items of the test are a measure of health-related quality-of-life (QoL) based on standardized questions.[11] The SF-36 questionnaire covers eight health domains:

physical functioning (10 items), bodily pain (2 items), role limitations due to physical health problems (4 items), role limitations due to personal or emotional problems (4 items), emotional well-being (5 items), social functioning (2 items), energy/fatigue (4 items), and general health perceptions (5 items). Scores for each domain range from 0 to 100, with a higher score defining a more favorable health state. The ability to return to work was assessed by questions with multiple options regarding the patient's level of recovery (from full recovery [working as before admission], to incapacity [completely stopped working because of the consequences of the critical illness episode]). Follow-up, complete for all patients, was 24 months for patients admitted during the first outbreak, 12 months for COVID-19 patients hospitalized in the outbreak February to April 2021, and 6 months for those hospitalized in the outbreak February to April 2022.

Statistical Analysis

We used the Statistical Package for Social Sciences software version 14.0 (SPSS Inc, Chicago, IL) for Windows to prepare the database and to perform descriptive analysis. Categorical variables are expressed as frequencies and percentages. Continuous variables with normal distribution are expressed as mean and standard deviation and those with skewed distribution as median and interquartile range. The Student's *t*-test and the chi-square test were used where appropriate.

Logistic regression was performed with combined mortality, morbidity, and QoL as independent variables and age, sex, Charlson Comorbidity Index, comorbidities, complete vaccination, and period of infection as covariates. The correlations between different risk factors were evaluated by the Spearman correlation test.

Outcomes

Primary outcomes included the proportion of patients with worsening of QoL at the median follow-up in the three cohorts.

Secondary outcomes included the proportion of patients with worsening of QoL at the median follow-up in patients vaccinated and nonvaccinated.

Results

During the three outbreak periods, 69 (3% of total admissions) patients hospitalized for severe COVID-19 infection developed acute VTE. Fifteen patients died during hospitalization; 54 patients were discharged with normalization of laboratory tests and clinical absence of infection (no fever and dyspnea, normalization of gas analysis and of hemostatic parameters) and clinical and duplex evidence of VTE resolution (**►Table 1**).

Table 1 Hospitalized COVID-19 patients during three different outbreak periods. Vaccination status and acute venous thromboembolism

Analyzed outbreak period	February–April 2020	February–April 2021	February–April 2022
Hospitalized COVID-19 patients	1,183	704	409
In-hospital mortality	34.7%	15.1%	14.5%
Overall mortality in the province of Pavia in the same months	3,551	1,965	1,853
Percentage increase of the overall mortality in the same months in comparison with the mean mortality in the period 2015–2019 (1,776 patients)[a]	+100%	+10.6%	+4.3%
Complete vaccination in the general population of the province.	0	50% of people older than 80 years and at risk (health care and school personnel)	85% of people older than 12 years of age
COVID-19 hospitalized patients with complete vaccination, *n*	0	8	301
Predominant COVID-19 variant	Alfa	Delta	Delta
Clinical evidence of acute onset of VTE	32	26	11
Acute onset of VTE in nonvaccinated patients	32	26	4
Acute onset of VTE in patients with complete vaccination	0/0	0/8	7/301
In-hospital mortality of patients with acute onset of VTE and no vaccination	9/32	4/26	2/4
6-mo-mortality of patients with acute onset of VTE and no vaccination	3/23	3/22	0/2
In hospital and 6 mo-mortality of patients with acute onset of VTE and complete vaccination	0/0	0/0	0/7

Abbreviations: COVID-19, coronavirus disease 2019; VTE, venous thromboembolism.
[a]The mean mortality of 2015–2019 years was calculated for only each February–April period in overall hospitalized patients.

Clinical Outcomes for Hospitalized Coronavirus Disease 2019 Patients Who Developed Acute Venous Thromboembolism during the First Outbreak (Vaccine Not Available)

Thirty-two patients developed clinical evidence of acute VTE during the infection confirmed by duplex scanning (►Tables 1 and 2). In total, 9 of the 32 patients died due to multiple organ failure. Fifteen of the twenty-three patients who survived were treated in the intensive care unit (ICU). During a 24-month follow-up, 4 of the 23 discharged patients died. Three patients died within 6 months from hospital discharge.

Clinical Outcomes for Hospitalized Coronavirus Disease 2019 Patients who Developed Acute Venous Thromboembolism during the Second Outbreak (Vaccine Available)

Twenty-six patients developed clinical evidence of acute VTE during the infection confirmed by duplex scanning and only 1 (4%) was vaccinated. Seven patients (27%) were treated in the ICU and four (15%) died due to multiple organ failure. During the 12-month follow-up, 3 of the 22 discharged patients died, all within 6 months from hospital discharge.

Clinical Outcomes for Hospitalized Coronavirus Disease 2019 Patients who Developed Acute Venous Thromboembolism during the Third Outbreak (Vaccine Available)

Eleven patients developed clinical evidence of acute VTE during the infection confirmed by duplex scanning and seven (64%) were vaccinated. Only one patient (9%) was treated in the ICU with no intrahospital death. During the 6 months of follow-up, 2 of the 11 discharged patients died.

Quality of Life at 24 Months for Survivors after the First Outbreak (February to April 2020)

►Table 3 shows the QoL of the 19 patients who were alive after the first outbreak, when the vaccine was unavailable, and with 24 months follow-up. Important physical symptoms were reported by 12 patients (12/19 = 63%) and relevant emotional/mental symptoms by 10 patients (10/19 = 52%). All patients reported reduced QoL in comparison with the preinfection time; in 15 out of the 19 patients (79%), the reduced QoL limited significantly their social and work activities. All patients reported permanent worsening of QoL after discharge from hospital. Two years after discharge from hospital five (5/19 = 26%) of the survivors reported being frail; ten (52%) reported experiencing fatigue. Joint pain and stiffness were the most common symptoms. All patients reported symptoms of anxiety and emotional stress. In five patients (26%), these were so intense to limit significantly their social and work activities. Physical and emotional symptoms were more common in patients older than 65 years of age. In patients younger than 55 years of age, symptoms were less evident without interfering significantly with their social and work activities.

Quality of Life at 12 and 6 Months for Survivors after the Second and Third Outbreak, Respectively (February–April 2021; February–April 2022)

During the two selected outbreak periods, the vaccination status of the general population was different (►Table 1). The number of hospitalized COVID-19 patients ($n = 37$) diminished considerably ($p < 0.001$) with significantly reduced overall mortality.

Table 2 Clinical characteristics of hospitalized COVID-19 patients who had clinical evidence of venous thromboembolism in the three analyzed outbreak periods

Analyzed outbreak period	March–April 2020	February–April 2021	February–April 2022
Patients with VTE	32	26	11
Age, mean, SD, range	62.3 ± 11.2 (30–94)	72.5 ± 8.7 (53–86)	72.5 ± 8.9 (55–91)
Males/females	24/8	17/9	6/5
Intensive care unit	23	7	1
Vaccinated, *n* (%)	0 (0)	1 (4%)	7 (64%)
Mortality, nonvaccinated, *n* (%)	9 (28%)	4 (15%)	2 (29%)
Mortality, vaccinated	0 (0)	0 (0)	0 (0)
Comorbidities, mean	2.0	2.2	2.2
Smoking	14 (44%)	8 (31%)	5 (45%)
Arterial hypertension	18 (56%)	11 (42%)	5 (45%)
Coronary artery disease	6 (19%)	5 (19%)	2 (18%)
Chronic obstructive pulmonary disease	16 (50%)	6 (23%)	3 (27%)
Diabetes	4 (12%)	4 (15%)	4 (36%)
Renal failure (serum creatinine >1.5 mg/dL)	2 (6%)	6 (23%)	2 (18%)
Previous diagnosis of cancer	1 (3%)	3 (12%)	1 (9%)
Evidence of pulmonary embolism	8 (25%)	12 (46%)	3 (27%)

Abbreviations: COVID-19, coronavirus disease 2019; SD, standard deviation; VTE, venous thromboembolism.

Table 3 Assessment of health-related quality-of-life for 19 survivors who developed acute venous thromboembolism during the first outbreak 24 months after hospitalization[a](scores range from 0 to 100, with a higher score defining a more favorable health state)

	Mean; SD (range)
1-Physical functioning (10 items)	70; ± 13.9 (45–90)
2-Bodily pain (2 items)	75; ± 0 (50–100)
3-Role limitations due to physical health problems (4 items)	78; ± 18.4 (67–100)
4-Role limitations due to personal or emotional problems (4 items)	74; ± 0 (67–100)
5-Emotional well-being (5 items)	76.5; ± 7.9 (60–84)
6-Social functioning (2 items)	64.5; ± 0 (50–87.5)
7-Energy/fatigue (4 items)	65; ± 9.9 (60–80)
8-General health perceptions (5 items)	66, ± 19.5 (40–90)
9-Health status change in comparison with the preinfection time	46; ± 22.4 (25–75)
Overall health condition in comparison with the preinfection time	Somewhat worse 19/19

Abbreviation: SD, standard deviation.
[a]Based on standardized questions by Short Form Health Survey-SF-36[11] Scores range from 0 to 100, with a higher score defining a more favorable health state.

Overall QoL at 6 and 12 months was improved in comparison with patients infected during the first outbreak (►Table 4). There was no significant decrease of QoL in vaccinated patients at 6 and 12 months from discharge. Patients who were not vaccinated presented reduced QoL in comparison with vaccinated patients.

Primary Outcome

In total, 79% of the patients who survived after the first outbreak had reduced QoL limiting significantly their social and work activities and after 2 years 52% still reported experiencing fatigue. Sixty-two percent of the patients who survived after the second outbreak had reduced QoL limiting significantly their social and work activities and after 1 year 39% still reported experiencing fatigue. Thirty-one percent of the patients who survived after the third outbreak had reduced QoL limiting significantly their social and work activities and after 6 months just twelve percent still reported experiencing fatigue.

Secondary Outcome

Vaccinated patients (none in the first outbreak, 4% in the second and 64% in the third) had significantly shorter hospital stay and significantly reduced alterations of the

Table 4 Six months assessment of health-related quality-of-life for 48 hospitalized COVID-19 survivors who developed acute venous thromboembolism during the first outbreak and during the outbreaks of the following 2 years

	February–April 2020	February–April 2021	February–April 2022
Patients discharged from hospital with resolution infection, *n*	23	22	11
Patients who died within 6 mo from discharge, *n*	3	3	2
Patients available for assessment, *n*	20	19	9
6 mo mean score—Scores range from 0 to 100, with a higher score defining a more favorable health state (based on standardized questions Short Form Health Survey-SF-36[15])			
1-Physical functioning	68	74	76
2-Bodily pain	66		88
3-Role limitations due to physical health problems	70	83	92
4-Role limitations for personal-emotional problems	65	84	89
5-Emotional well-being	68	74	75.5
6-Social functioning	60	70	76.5
7-Energy/fatigue	58	73	75.5
8-General health perception	60	70	79
9-Perception of health condition in comparison with the pre-infection time	42 (somewhat worse 20/20)	43.5 (somewhat worse 15/19)	48 (somewhat worse 5/9)

Abbreviation: COVID-19, coronavirus disease 2019.

hemostatic parameters ($p < 0.01$), with no mortality. QoL parameters improved in vaccinated population. The mean increase of QoL parameters between first and second outbreak, the second and the third, and the first and the third was, respectively, 15.8% ($p = 0.0005$), 8.3% ($p = 0.002$), and 25.3% ($p = 0.0001$)

Risk Factors for Reduced Quality of Life

In univariable analysis, several other risk factors were associated with reduced QoL (time between initial symptoms and admission to the hospital; longer hospital stay; need for ICU treatment; and comorbidities); all these risk factors were related to the first outbreak and with the COVID-19 alfa variant. Multivariable analysis showed that the COVID-19 alfa variant as an independent factor for increased mortality and reduced QoL ($p < 0.001$).

The results of the Spearman correlation analyses showed a high correlation between alfa variant infection, longer hospital stay, need for ICU treatment, increased mortality, and reduced QoL ($r = 0.91$). Multivariable analysis showed complete vaccination as an independent factor correlated with reduced mortality and better QoL ($p < 0.05$).

Discussion

The pathogenesis of PCS is unknown, and we are not aware of any other study investigating the same type of cohorts in three different years. The wide heterogeneity of the symptoms supports the hypothesis of a multisystem disorder.[1,2,12] A direct role of the severe acute respiratory coronavirus 2 (SARS-CoV-2), and its possible persistence has been proposed but there is no direct evidence of viral persistence with replication properties. The possibility exists that fragments of the viral genome or viral antigens, lacking infectious capacity, persist over time. However, it is difficult to determine the correlation between the persistence of fragments of the viral genome and clinical manifestations of the PCS and if this possibility is related to specific variants of SARS-CoV-2.[2,3]

In our study, we analyzed the occurrence and severity of PCS in patients traditionally considered at high risk of developing PCS.[13,14] The occurrence of acute onset of VTE for hospitalized COVID-19 patients has been correlated with the severity of the infection and worse clinical outcomes with high prevalence of PCS and reduced QoL after resolution of the infection.[14–18]

Hospitalization per se implies significant medium- and long-term complications, namely when ICU treatment is required.[6,7] Similarly to other studies,[16,17] we found a significant deterioration of quality life in patients who developed VTE during COVID-19 infection in the first outbreak. The reduced QoL and symptoms referable to PCS persisted for up to 24 months from resolution of the infection and discharge from hospital, without evidence for improvement. Only people younger than 55 years reported recovery of the emotional state and also being able to return to work.

In the subsequent two outbreaks, the prevalence of symptoms referable to PCS was significantly lower both after 6 and 12 months, with a trend toward progressive improvement.

In our analysis, vaccinated patients who developed acute VTE during the infection had better early clinical outcomes. Vaccination seems to reduce also the medium-term complications of COVID-19 infection. Azzolini et al[15] found a lower incidence of symptoms of long COVID-19 in not hospitalized asymptomatic health workers who were vaccinated, in comparison with those who were not vaccinated. Several reports[16–18] have underlined the trend toward decreased prevalence and severity of PCS and the positive effect of previous vaccination.[19–21] Timely aggressive therapy seems to be a cornerstone in this complex clinical setting. During the first outbreak, when vaccines were not available and the virulence of the disease was not well known, there was generally a delay in starting antiviral and anti-inflammatory treatment.

The Emergency Committee of the World Health Organization declared COVID-19 over (May 4th, 2023) as a global health emergency on the basis of careful analysis of data and said the emergency status could be reinstated if the situation changed.[22,23] In this evolving situation, it is fundamental to maintain and sustain international cooperation for data collection, variants testing and vaccination in selected groups of patients. For those stratified in a high-priority group, including older adults, people with underlying conditions or who are immune compromised, and frontline health care workers, Strategic Advisory Group of Experts on Immunization (SAGE), part of the World Health Organization recommends an additional booster 6 or 12 months after the last dose. In addition, the roadmap suggests that pregnant people obtain another booster dose if they received their last dose more than 6 months before. SAGE does not recommend routine use of additional boosters for healthy adults younger than 50 to 60 years, although their use is safe. Moreover, although primary and booster doses are safe and effective for healthy children between the age of 6 months and 17 years, the new guidance suggests that countries consider their disease burden, cost-effectiveness, as well as other health priorities when choosing whether to vaccinate this group.

Study Limitations

Despite some interesting findings, this study has some limitations. First of all the small sample size in each of the three cohorts. Second, the heterogeneity of the sample in terms of vaccination status, severity of COVID-19 disease, and regimen of anticoagulation. Third, we did not use the Long COVID Symptom and Impact Tool.[24] Nevertheless, all the patients in the sample were consecutive, and a consistent QoL tool scale has been used.

Conclusion

It is difficult to determine if the reduced QoL after apparent recovery from COVID-19 infection is the consequence of the initial severe infection or if it depends on the effects of chronic changes of the endothelial barrier determined by a specific SARS-CoV-2 variant.

Our study supports the concept that PCS was mainly related to the high virulence of the first SARS-CoV-2 variant and that vaccination was effective in reducing early and medium-term complications.

Data Availability
Data are available on request.

Conflict of Interest
None declared.

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Heterogeneous Characteristics of Patients with Inflammatory Abdominal Aortic Aneurysm. Systematic Review of Therapeutic Solutions

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Background: Endovascular repair of inflammatory abdominal aortic aneurysms (IAAAs) has emerged as an alternative to open surgery, but direct comparisons are limited. The aim of the study was to compare clinical outcomes of endovascular and open repair for IAAA according with specific clinical characteristics.

Methods: We performed a literature review of reports describing patients who had open or endovascular repair for IAAA. A literature search was performed in June 2022 by 2 investigators who conducted a review of papers reported in PubMed, Embase, MEDLINE, and Cochrane Database. The strings "Inflammatory aneurysm" and "Abdominal Aortic Aneurysms" were used. There was no language restriction and screened reports were published from March 1972 to December 2021. We identified 2,062 patients who had open (1,586) or endovascular repair (476) for IAAA. Primary outcomes were operative mortality and morbidity. Secondary outcomes were complications during follow-up (mean follow-up: 48 months). Propensity score matching was performed between patients who had open or endovascular surgery.

Results: In Western countries, propensity-weighted postoperative mortality (in-hospital) (1.5% endovascular vs. 6% open) and morbidity rates (6% vs. 18%) were significantly lower in patients who had endovascular repair ($P < 0.0001$); patients with larger aneurysm (more than 7 cm diameter), signs of active inflammation, and retroperitoneal rupture of the aneurysm had better outcomes after endovascular repair than after open surgery. Hydronephrosis was present in 20% of the patients. Hydronephrosis regressed in most patients when signs of active inflammation were present suggesting an acute onset of the hydronephrosis itself (fever, elevated serum C Reactive Protein) either after endovascular or open surgery. Long-standing hydronephrosis as suggested by the absence of signs of active inflammation rarely regressed after endovascular surgery despite associated steroid therapy. During a mean follow-up of 48 months, propensity-weighted graft-related complications were more common in patients who had endovascular repair (20% vs. 8%). For patients from Asia, short-term and medium-term results were similar after open and endovascular repair. IAAAs related with aortitis were more common in Asia. In Western countries, IAAAs were commonly associated with atherosclerosis.

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Author Contributions: Antonio Sterpetti conceived the research and wrote the manuscript. Umberto Costi, Maria Vittoria Carati, Luca Di Marzo, and Giuseppe D'ermo collected data from literature. Antonio Bozzani, Franco Ragni, and Vittorio Arici gave suggestions and organized the research.

The registration number at PROSPERO was CRD 4201808633.

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Conclusions: Patients with IAAA represent a heterogeneous population, suggesting biological differences from continent to continent; conservative therapy and endovascular or open surgery should be chosen according to the patient clinical condition. Endovascular repair presents advantages in patients with signs of active inflammation and contained rupture of the IAAA and larger aneurysms. Hydronephrosis, without signs of active inflammation, rarely regresses after endovascular repair associated with steroid therapy. Further studies are needed to establish the long-term results of endovascular repair.

De Weerd et al.[1] in 1955 reported on a 45-year-old patient with bilateral hydronephrosis. At the operation, both ureters were encased in a thick, whitish, fibrotic reaction, starting from an aneurysm of the abdominal aorta. Bilateral ureterolysis was performed with normalization of renal function. The aneurysm was left in place. The same year Shumacker and Garrett[2] performed a successful resection of an inflammatory abdominal aortic aneurysm (IAAA), with bilateral ureterolysis. The postoperative course was uneventful with return of a regular renal function. Walker et al.[3] reviewed the clinical outcome of 187 patients who had resection of an abdominal aortic aneurysm (AAA): in 19 patients (10%) the aneurysm was surrounded by a "thick, whitish fibrosis". They used the term "inflammatory aneurysm", noting the higher surgical mortality (26%) for these patients. Crawford et al.[4] defined some of the operative principles to prevent complications in surgery for IAAA, including minimal dissection of the aneurysm: Open surgery for IAAA is complications prone for the peri-aneurysmal fibrosis involving the adjacent structures (Figs. 1 and 2).[5,6] Endovascular repair offers several advantages, avoiding a complex dissection with the possibility of injuries to the duodenum, small bowel, and vena cava. Concerns remain about the medium-term and long-term results of endovascular surgery in this clinical setting. The aim of this study was to analyze the results of open and endovascular surgery for patients with IAAA.

MATERIALS AND METHODS

The methods used for the study and inclusion criteria were based on PRISMA and AMSTAR recommendations. A literature search was performed in June 2022 by 2 investigators who conducted a review of papers reported in PubMed, Embase, MEDLINE, and Cochrane Database. The strings "Inflammatory aneurysm" and "Abdominal Aortic Aneurysms" were used. There was no language restriction and screened reports were published from March 1972 to December 2021 (Supplement). Papers reporting patients with a follow-up less than 6 months were not included. Data extraction was performed by 2 reviewers independently; a third reviewer was involved to solve any question in interpreting data. The primary outcomes were operative mortality and morbidity. Secondary outcomes were complications related to therapy and survival. Data were analyzed according to the geographical areas. The presence of an IAAA was defined for a significant peri-aneurysmal fibrosis at computed tomography (CT) scan or at operation. Patients with Beçhet disease and AAA were considered separately. The registration number at PROSPERO was CRD4201808633. This systematic review was approved by the Council of our Department and from the Ethics Committee of our University and Hospital. Being a systematic review of already published data, written consent was not required.

Quality Assessment

Two independent reviewers assessed the quality and risks of biases of the analyzed studies by using the Newcastle-Ottawa scale. Papers with a score more than 6 were considered of good quality (scale 0 to 9).

Geographical Regions

Results were analyzed by an overall point of view as well as according to specific geographical areas: (1) USA-Canada-Europe, (2) North Africa and Middle East, (3) India-Pakistan, (4) Japan-China-South Korea, and (5) Mexico-Central and South America. USA, Canada, and Europe were considered together for similar clinical characteristics of the patients and similar operative results.

Statistical Analysis

Interstudy heterogeneity was assessed by I^2 statistics as a measure describing degree of heterogeneity. I^2 results less than 50% were considered as low heterogeneity; I^2 more than 50% were considered with high heterogeneity. Comparisons were made by Chi-square test and Student's *t*-test where appropriate. Log-rank test was used to compare actuarial

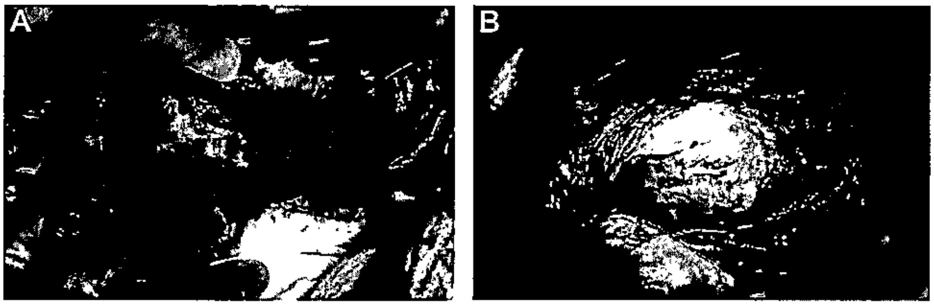

Fig. 1. **(A–B)** Intraoperative view of inflammatory abdominal aortic aneurysm: The dissection is kept to a minimum to avoid injuries to the adjacent structures.

survival rates after surgery between selected groups of patients. Multivariate analysis was not possible because of incomplete data in the majority of the study.

Propensity Score Matching

Results were compared for selected patients who had open surgery or endovascular surgery in USA-Canada-Europe. Two hundred patients who had open surgery were compared to 100 patents who had endovascular surgery. Patients were selected by random sampling within strata: all observations were ranked on their propensity score, and the data were then divided into quantiles of the propensity score. Within each stratum, equal sample sizes in the treatment and control groups were selected. Matching within calipers was proposed to protect against a treated and control observation not similar to each other in their propensity score. For covariate balance, we used the standardized differences after weighting. These were all <0.1, indicating adequate balancing by the propensity score model. Patients were matched on characteristics that predict receipt of 1 treatment strategy over another. Analyzed preoperative clinical characteristics of the patients were age, gender, symptoms if present (fever, abdominal pain, and weight loss), general clinical conditions, comorbidities, associated autoimmune diseases, and previous cardiovascular events. Other included variables were maximum transverse diameter of the AAA, intact or ruptured aneurysm (free or contained rupture), and presence of aneurysms in other arterial segments.

For covariate balance, we used the standardized differences after weighting. These were all <0.1, indicating adequate balancing by the propensity score model. We used weighted Cox regression to compare overall survival and overall disease-free survival.

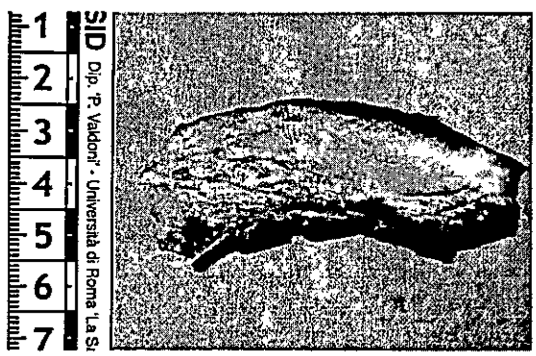

Fig. 2. Aneurysmal wall of an IAAA.

Definition of Complications

The postoperative morbidity (in-hospital) was recorded as a total percentage and based on the presence of significant complications according to the Clavien-Dindo Classification (Class III-IV-V).[7] If the Clavien-Dindo Classification was not mentioned in the reports, grades were assigned based on the information provided. We also considered as major complications all negative events which required a new intervention either after open or endovascular repair.

RESULTS

Two thousand and six hundred articles were screened: 94 papers were included in the analysis (Supplement Methods). There was no randomized study. Most studies were retrospective. Few prospective studies (10 papers) were included, but details about the organization of the study were not clearly reported. The average Newcastle Ottawa

Table I. Comparison between the overall results of open and endovascular surgery for IAAA in USA-Canada-Europe

Early and late results	Open repair (1,276 patients)	Endovascular surgery (166 patients)
Operative mortality (30 days)	6.8%	1.8%
Operative morbidity (30 days)	25%	5%
Perianeurysmal fibrosis	(124 patients)	(55 patients)
Significant regression	73%	62%
Unchanged	26%	34%
Progression	1%	4%
Ureteral entrapment	(85 patients)	(32 patients)
Significant regression	69%	44%
Unchanged	22%	44%
Progression	9%	12%

score was low. Study heterogeneity ranged from 30% to 60%, with an average of 46%. A total of 2,054 patients were collected: 1,578 had open surgery (only 1,394 are included because 184 patients had incomplete information or very short follow-up) and 476 had endovascular surgery. Postoperative mortality ranged from 20% to 0% and morbidity rates from 50% to 10%. We considered separately patients from different continents because of a significant difference in results of open and endovascular surgery and specific clinical characteristics suggesting various etiologies and pathophysiology of the IAAA.

USA-Canada-Europe

Open surgery—clinical characteristics. Overall, 1,276 patients with intraoperatively defined IAAA were considered for the analysis. Twenty of these patients had associated autoimmune disease (1.6%), but histology did not show a significant difference from patients with IAAA and no associated autoimmune disease. Three patients had Takayasu disease; histology confirmed the nature of the aneurysm. The clinical characteristics of 200 patients with IAAA were compared with those of 200 patients with simple atherosclerotic-degenerative aneurysm. Patients with inflammatory AAA complained more often from pain ($P < 0.001$) and they had increased serum inflammatory markers (C-reactive protein) ($P < 0.001$). Comorbidities, age, and sex distribution were similar between patients with IAAA and simple atherosclerotic-degenerative aneurysm. IAAAs had lower prevalence of rupture (5%), and the rupture was generally contained into the retro-aortic space ($P < 0.0001$).[7–18]

Open surgery—results. Tables I and II show the operative mortality and morbidity. There was a significant improvement in results after the year 1985, when the operative details of minimal aneurysm dissection were popularized, and after the year 2008, when endovascular surgery started to be accepted and performed in patients with IAAA (Table III). Reports from the same centers showed improved results in time ($P < 0.0001$), namely after the introduction of endovascular surgery.[7–13] Five papers compared the results for patients with IAAA with those for patients with simple atherosclerotic-degenerative aneurysm and no statistically significant difference was found for the low number of observations.[14–18] However, aggregated data of the 5 papers show a significant increased operative mortality (7% vs. 2%) and postoperative morbidity (25% vs. 15%) in patients with IAAA in comparison with patients with simple AAA ($P < 0.0001$). Peri-aneurismal fibrosis regressed in 73% of the patients in whom serial postoperative CT scans were performed (Table I).

Endovascular Surgery—Clinical Characteristics

One hundred and sixty six patients who had endovascular repair for IAAA were collected. The aneurysm was defined for the increased thickness of the peri-aneurysmal tissue at CT scan. The incidence of associated hydronephrosis (22%) was similar with that of patients with IAAA who had open surgery.

Endovascular Surgery—Results

Table I shows the results of endovascular surgery compared with those of open surgery. Ten patients had endovascular surgery, after open surgery was abandoned for difficulties in the dissection. Operative mortality and morbidity rates were significantly lower than those after open surgery. One hundred

Table II. Results of open surgery for inflammatory abdominal aortic aneurysms

Author	Type of study	*N* patients	Analyzed years	Postop mortality	morbidity
Paravastu et al.[7]	Systematic Review	999	1972–2008	6.9%	NA
Kakkos et al.[13]	Systematic Review	459	1972–1999	9.8%	NA
Kakkos et al.[13]	Systematic Review	300	1999–2013	4%	NA
Current Review	Systematic Review	205	1972–1984	12%	30%
Current Review	Systematic Review	350	1985–1994	7.5%	20%
Current Review	Systematic Review	580	1995–2007	6.2%	15%
Current Review	Systematic Review	443	2008–2019	3%	10%

Table III. Overall results of open and endovascular surgery for IAAA performed in the same period in the same centers in the last 10 years

Authors year publication		Mortality EVAR[a]	Mortality open	Overall mortality (30 days from Surgery)
Coppi et al.[19]	2010	0/9 (0%)	?/9	?
Stone et al.[10]	2012	0/10 (0%)	1/59 (1.6%)	1/69 (1%)
Zhang et al.[20]	2014	0/8 (0%)	0/5 (0%)	0/13 (0%)
Kakkos et al.[13]	2015	0/9 (0%)	0/10 (0%)	0/19 (0%)
Kasashima at al[21]	2017	0/17 (0%)	0/23 (0%)	0/40 (0%)
Georgakarakos et al.[22]	2017	0/1 (0%)	0/1 (0%)	0/2 (0%)
Duques Santos et al.[23]	2018	0/5 (0%)	1/29 (3.4%)	1/34 (2.9%)
Total		0/59 (0%)	2/128 (1.5%)	2/187 (1.0%)

[a]30-days mortality.

patients who had endovascular surgery were compared with 200 patients who had open surgery by propensity score matching 1 to 2. Operative mortality and morbidity were significantly lower for patients who had endovascular repair in comparison with patients who had open surgery (endovascular repair operative mortality 1.5% and operative morbidity 6%; open surgery operative mortality 6% and operative morbidity 18%; $P < 0.001$). This difference was more evident in patients who were operated upon in emergency conditions, in patients who had clinical (fever-abdominal pain and tenderness) and serologic signs (increased serum C-reactive protein) of active inflammation and in patients with an aneurysm with transverse diameter larger than 7 cm ($P < 0.001$). Endovascular surgery resulted in a lower rate and speed for regression of peri-aneurismal fibrosis. During a mean follow-up of 48 months, reinterventions were more common in patients who had endovascular repair (20% vs. 8%) ($P < 0.0001$). After the introduction of new graft materials and the routine use of steroids, immediately before and after endovascular surgery, worsening of the peri-aneurismal fibrosis was seldom reported. Hydronephrosis, when present, regressed more frequently when associated with clinical and/or hematological sings of inflammation (12/13). In patients with no evidence of clinical and/or hematological signs of acute inflammation, hydronephrosis rarely regressed (3/19).

Asian Countries

Open surgery—clinical characteristics. Overall, 124 patients who underwent open surgery were collected. Seventeen patients had IG4-related disease, 4 patients IG4 not related chronic periaortitis, and 1 patient Takayasu disease. The remaining 102 were defined as having atherosclerotic-degenerative AAA; however, patients with atherosclerotic-degenerative disease had lower prevalence of associated disease in comparison with patients with atherosclerotic IAAA from USA-Canada and Europe, suggesting the possibility of a less virulent form of atherosclerosis. This was indirectly confirmed by the higher 5-year actuarial survival rate (78% vs. 70%, $P < 0.001$).

Open surgery—results. There was only one postoperative mortality (1/124 = 0.8%). Reported postoperative complication rate was less than 5%. Postoperative mortality and morbidity were significantly lower in comparison with patients operated upon in USA-Canada-Europe ($P < 0.001$). Mean follow-up was 48 months. Four patients had an anastomotic pseudoaneurysm and 1 patient an aorto-enteric fistula.

Endovascular surgery—clinical characteristics. Three hundred nine patients with inflammatory aneurysm were reported: 278 were extracted from the Japan National Statistics.[24]

Thirty one patients were reported in single-institution studies. There were 2 cases of postoperative mortality (2/309 = 0.6%). During a mean follow-up of 28 months, there were 3 patients with graft rupture (3/309 = 1%). Early results after endovascular repair were similar with those after open surgery. Reintervention rates were also similar after open and endovascular surgery. Worsening of peri-aneurysmal fibrosis was reported in 9 of 10 patients with IG4-related disease; none of those patients had associated steroid therapy.[21,25]

We were able to find only 2 reports of 2 young patients (aged 38 and 39 years; 1 male; 1 female) who underwent successful open resection for a Takayasu-related IAAA.[26–33]

North Africa-Middle East

The possibility of abdominal aneurysm or pseudoaneurysm related with Beçhet disease was high in these regions, with a higher prevalence in young males (average age: 35 years). There was an increasing use of endovascular surgery, with improved results in comparison with open surgery.[34–36] We found only 1 report from Turkey which described the clinical outcome of 17 patients after open surgery for repair of IAAA probably atherosclerotic in nature.[16] The postoperative mortality was 11% (2/17) and complication rate was 29%, mainly related with renal failure.

DISCUSSION

Several theories have been proposed about the etiology of IAAA. Rose and Dent in 1981[35] demonstrated an inflammatory reaction in almost all AAAs: in 6 patients, the inflammatory reaction was severe. Other reports have hypothesized a major role of autoimmunity in the genesis of IAAA, extrapolating the etiological events associated with the formation of chronic aortitis to the development of IAAA in general.[36–39] The Society for Cardiovascular Pathology has provided guidelines to distinguish IAAA associated with severe atherosclerosis from those associated with aortitis and peri-aortitis.[40] The term Inflammatory Atherosclerotic Abdominal Aneurysms should be used to introduce a clear distinction between atherosclerosis-related IAAA and other forms of aortitis and peri-aortitis, which can result also in aneurysmal degeneration. Atherosclerosis-related IAAA shows severe atherosclerosis and excessive degree of adventitial inflammation, consisting mainly on lymphocytes and plasma cells. The thickness of the aortic wall should exceed 4 mm to make a diagnosis of IAAA. The presence in the adventitia of histological findings not typical for atherosclerosis (like granulomata, extensive IG4+) combined with no significant or mild atherosclerosis favors the diagnosis of peri-aortitis.[40] In our review, we found a significant difference in the distribution and etiology of IAAA. Atherosclerotic IAAA was the most common form in USA-Canada and Europe; in Asia, there was a significant prevalence of IAAA related with aortitis. CT scan shows in IAAA related with aortitis a homogeneous distribution of the peri-aneurysmal fibrosis, involving also the posterior wall. In patients with atherosclerotic-related IAAA, the peri-aneurysmal fibrosis is confined to the anterior and lateral walls.

Patients from Asia with atherosclerotic IAAA had less comorbidities, better operative results, and survival rates. These findings support the hypothesis of different forms of atherosclerosis between Western and Eastern countries. Moreover, patients with Takayasu disease had different characteristics when comparing patients from Asia, with a high prevalence of AAA, with those from Mexico and South America in whom associated AAA was uncommon.

Endovascular surgery resulted in reduced mortality and morbidity in comparison with open surgery in patients with contained retro-aortic rupture, evidence of active inflammation (either clinically—abdominal pain, fever, weight loss—or based on serologic inflammatory markers), and with larger aneurysms in USA-Canada-Europe. In an average follow-up of 48 months, complications and reinterventions were higher after endovascular repair than after open surgery in USA-Canada-Europe, but not in East Asia. Regression of peri-aneurismal fibrosis was more common and faster after open surgery. Regression of hydronephrosis related to IAAA was more common in patients with active, recent-onset inflammation either after open or endovascular surgery. The absence of active inflammation, presuming a chronic inflammation with long-standing peri-aortic fibrosis, was associated with reduced rates of regression of the hydronephrosis, especially after endovascular surgery.[7,13,41–44]

These findings represent the theoretical basis for an aggressive medical and surgical therapeutic approach in patients with IAAA and clinical and serologic evidence of active inflammation before chronic fibrosis supervenes. In presence of markers

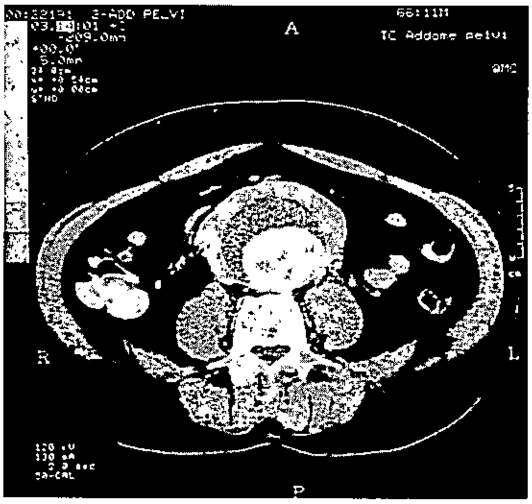

Fig. 3. CT scan of a patient with an atherosclerotic IAAA. The peri-aneurysmal fibrosis is present only in the anterior and lateral segments.

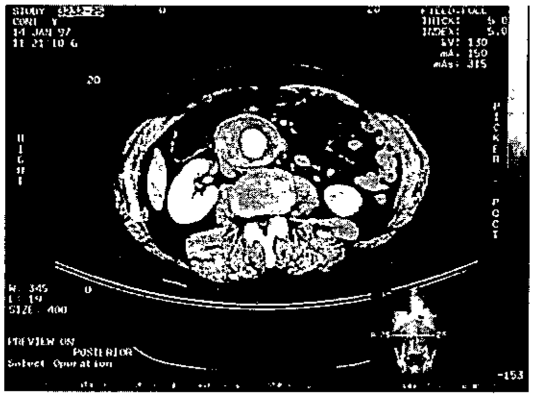

Fig. 4. CT scan of a patient with an IAAA related with aortitis. The peri-aneurysmal fibrosis involves also the posterior segment.

for active inflammation, endovascular surgery associated with steroids represents a valid therapeutic approach. Short course of steroids followed by open surgery may be a realistic alternative. In patients with IAAA and no signs of active inflammation, the presence of hydronephrosis should be considered related with chronic fibrosis. In this clinical setting, regression of the hydronephrosis is uncommon after endovascular surgery, even if combined with steroid therapy. Open IAAA repair and ureterolysis may be a more appropriate solution: steroid therapy may help to prevent recurrent ureteric obstruction.

CONCLUSION

Patients with IAAA represent a significant heterogeneous group. Conservative treatment in older patients, with reduced life expectancy, with smaller aneurysm (<5 cm in maximum transverse diameter), without associated hydronephrosis, is an acceptable therapeutic option.[45–47] Endovascular surgery associated with steroids is followed by good clinical outcomes, with significantly reduced operative mortality and morbidity in comparison with open surgery, and it should be considered the optimal treatment for patients with contained rupture, active inflammation, and larger aneurysms.[48,49] The initial concerns that endovascular surgery might lead to worsening of the peri-aneurysmal inflammation seem to reduce because the evidence of improved early result of endovascular surgery with lower perioperative complications and the reduced incidence of the problem for new graft materials and diffusion of associated steroids therapy. Open surgery in patients with longer life expectancy, with chronic inflammatory conditions, and hydronephrosis represents a valid choice for the higher possibility of hydronephrosis regression in comparison with endovascular repair.

The therapeutic approach in patients with IAAA should be chosen according to the specific clinical characteristics and expectations of each single patient[50–52] (Figs. 3 and 4). Conservative medical treatment and open or endovascular surgery should be considered valid complementary options. Table III shows the improved results reported in centers where endovascular or open repair were selected according to the characteristics of the patients.

Limitations

Our review implies several possible biases: retrospective nature of most studies, incomplete and not uniform reported data, and low quality of papers by New Castle grading.

The definition of an IAAA was approximate and not uniform and information about clinical presentation (elective and emergency) was not reported in several papers. Despite these limitations, the review offers an overall view of the current controversies about the proper treatment of patients with IAAA and underlines the importance of personalized therapy in treating this heterogeneous group of patients.[53,54] Patients with IAAA have been often classified as a homogeneous group of patients; general guidelines for treatment are not appropriate, without considering the specific conditions and needs of each singe patient.

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Prevalence and Complications of Aberrant Subclavian Artery in Patients With Heritable and Nonheritable Arteriopathies

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ABSTRACT

BACKGROUND An aberrant subclavian artery (ASA) (or lusoria) is the most common congenital anomaly of the aortic arch (0.5%-2.2%; female-to-male ratio 2:1 to 3:1). ASA can become aneurysmal and result in dissection, involving Kommerell's diverticulum when present and the aorta. Data of its significance in genetic arteriopathies are not available.

OBJECTIVES The purpose of this study was to assess the prevalence and complications of ASA in gene-positive and -negative nonatherosclerotic arteriopathies.

MATERIALS The series includes 1,418 consecutive patients with gene-positive (n = 854) and gene-negative arteriopathies (n = 564) diagnosed as part of institutional work-up for nonatherosclerotic syndromic and nonsyndromic arteriopathies. Comprehensive evaluation includes genetic counseling, next-generation sequencing multigene testing, cardiovascular and multidisciplinary assessment, and whole-body computed tomography angiography.

RESULTS ASA was found in 34 of 1,418 cases (2.4%), with a similar prevalence in gene-positive (n = 21 of 854, 2.5%) and gene-negative (n = 13 of 564, 2.3%) arteriopathies. Of the former 21 patients, 14 had Marfan syndrome, 5 had Loeys-Dietz syndrome, 1 had type-IV Ehlers-Danlos syndrome, and 1 had periventricular heterotopia type 1. ASA did not segregate with genetic defects. Dissection occurred in 5 of 21 patients with genetic arteriopathies (23.8%; 2 Marfan syndrome and 3 Loeys-Dietz syndrome), all with associated Kommerell's diverticulum. No dissections occurred in gene-negative patients. At baseline, none of the 5 patients with ASA dissection fulfilled criteria for elective repair according to guidelines.

CONCLUSIONS The risk of complications of ASA is higher in patients with genetic arteriopathies and is difficult to predict. In these diseases, imaging of the supra-aortic trunks should enter baseline investigations. Determination of precise indications for repair can prevent unexpected acute events such as those described. (J Am Coll Cardiol 2023;81:979-991)

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ABBREVIATIONS AND ACRONYMS

ALSA = aberrant left subclavian artery

ARSA = aberrant right subclavian artery

ASA = aberrant subclavian artery

CTA = computed tomography angiography

EDS = Ehlers Danlos Syndrome

KD = Kommerell's diverticulum

LAD = Left anterior descending artery

LDS = Loeys-Dietz Syndrome

MFS = Marfan syndrome

The lusoria artery is the most common embryologic anomaly of the aortic arch in which an aberrant subclavian artery (ASA), either aberrant right subclavian artery (ARSA) or aberrant left subclavian artery (ALSA), originates as the last vessel off of the aortic arch and crosses the midline, behind the esophagus and the trachea in 80% of cases.[1,2] The ASA originates during embryologic development of the aortic arch in which the left and right subclavian and carotid arteries, respectively, stem from a 2-sided (right and left) aortic arch.[2] ASA is classified as a congenital vascular abnormality and is currently considered predictive for chromosomal diseases such as trisomy 21,[3] as well as other congenital disorders.[4]

The prevalence of ASA in the general population ranges from 0.5% to 2.2%, with a female to male ratio of 2:1 to 3:1.[5-8] ASA originates from an enlargement of the aortic arch termed Kommerell's diverticulum (KD) in 60% to 82% of cases[5] and can be associated with other vascular abnormalities such as truncus bicaroticus (up to 38%)[9] and right-sided aortic arch (9.2%).[10]

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ASA is asymptomatic in most cases (60%-80%). However, dysphagia (often for solids caused by mechanical obstruction) is reported in up to 30% of cases and can be the first clinical manifestation that leads to its detection. Other less common complaints include coughing, thoracic pain, or Horner's syndrome.[11,12] As with any other artery, ASA can dilate and result in life-threatening dissections that can affect only the aberrant vessel or extend to the KD, when present, and the aorta. Dissection can occur spontaneously or be iatrogenic, often in the setting of a radial approach during coronary angiography and PCI.[10,13,14] Although there is no known association between ASA and heritable connective tissue diseases, the risk of dilation and dissection could be higher in patients affected by these disorders. At present, the prevalence and complications of ASA in heritable arteriopathies are unknown and reports of ASA dissection in these diseases are anecdotal.[15,16] Whether the inherent weakness of the arterial wall could contribute to complications such as dilation and dissection is not certain. In this series, we describe the prevalence of ASA and associated dissection in a consecutive series of adult patients with nonatherosclerotic gene-positive and -negative arteriopathies who have undergone whole body computed tomography angiography (CTA).

METHODS

This is a retrospective single-center study performed in context of the institutional evaluation of heritable arteriopathies approved by the local ethics committee. We use the term "heritable arteriopathies" rather than "heritable aortopathies" to include genetic diseases with recurrent extra-aortic aneurysms/dissections such as vascular Ehlers-Danlos syndrome (EDS). According to institutional assessment, all patients underwent multidisciplinary evaluations for both syndromic and nonsyndromic disorders. The initial multidisciplinary evaluation included a genetic visit and counseling with genetic testing, cardiology visit, noninvasive imaging with 2-dimensional transthoracic echocardiography (2DTTE), ultrasound-based evaluation of peripheral arteries, and ophthalmologic and orthopedic review. Additional multidisciplinary evaluation was performed on the basis of clinical indications. Parallel clinical family screening (of at least first-degree relatives) was performed (clinical genetic visit, baseline ECG, 2DTTE, and multidisciplinary evaluations), irrespective of genetic testing results, as per protocol for heritable arteriopathies.

The inclusion criteria for this study were available CTA and next-generation sequencing (NGS)–based multigene panels testing from 2011 to December 2021. The number of patients excluded from this series and the reasons for exclusion are detailed in Supplemental Figure 1.

COMPUTED TOMOGRAPHY ANGIOGRAPHY. CTA is considered the modality of choice for imaging of the aorta.[17,18] ECG-gated contrast (Iomeprol 400)-enhanced whole body CTA was performed in the context of the following indications: episodes of thoracic pain; procedural planning before aortic or

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nonaortic surgery or vascular interventional procedures; prior aortic and extra-aortic arterial dissections requiring surveillance imaging; rapidly progressing aortic or extra-aortic aneurysms as seen with ultrasound-based imaging; known or suspected aortic and/or medium-caliber arterial dilation or dissection with and without a family history of arteriopathy; and aneurysms and arteriovenous malformations with and without phenotypic traits known to be associated with heritable arteriopathies.

ASA AND KD MEASUREMENTS. As suggested by Tanaka et al[19] and acknowledged in the EACTS and ESVS recommendations,[18] KD was measured from the wall next to the trachea to the opposite aortic wall or from the tip of the diverticulum to the opposite aortic wall. The ASA diameter was measured at the level of the orifice, and, in the case of diameter asymmetry, at multiple levels along the vessel length.

GENETIC TESTING. After genetic counseling and clinical evaluation, patients signed the institutional informed consent form for genetic testing. DNA testing was performed in all probands by a first-line NGS sequencing (Illumina MiSeq) using Trusight Cardio Sequencing panel (Illumina). In patients with negative genetic testing results who manifested characteristic phenotypic traits or had a family history suggestive of genetic disease, we used a second customized panel also including candidate genes that are not present in Trusight Cardio Sequencing panel (Supplemental Table 1). Trusight One (Illumina) (n = 15) and CCP17 (Agilent) (n = 8) clinical exomes NGS in adults were performed in selected cases with negative NGS analysis of the multigene panels with traits or family history strongly suggesting a genetic disease. The NGS data analysis for the identification of single nucleotide variants, insertion-deletion mutations, and copy number variations was performed using an institutional pipeline validated for diagnostic purposes. Copy number variations were confirmed with Multiplex Ligation-dependent Probe Amplification. All variants were classified according to American College of Medical Genetics and Genomics criteria[20] (recently modified for *FBN1* gene[21]) and confirmed with Sanger sequencing (ABI 3130xl).

DATA ANALYSIS. For statistical analysis, we grouped patients according to a positive genetic test (pathogenic [P] and likely pathogenic [LP] variants in disease genes as per American College of Medical Genetics and Genomics criteria) and nonactionable results of a genetic test (variants of uncertain significance [VUS], likely benign [LB], and benign [B] genetic variants). Continuous variables were tested for normal distribution and presented as mean ± SD for the major groups of gene-positive and -negative diseases. Categorical variables are presented as absolute numbers (n) and frequencies (%) and compared using the chi-square test or Fisher exact test if applicable. Statistical significance was defined as $P < 0.05$.

RESULTS

PREVALENCE OF ASA. The CTA series comprises 1,418 patients (mean age at first CTA 43 ± 15 years), including 843 men (age 43 ± 16 years) and 575 women (age 43 ± 14 years). Disease-causing genes were positive (LP-P variants) in 854 patients (60%) and negative (VUS and LB-B variants) in 564 patients (40%) (Supplemental Table 2). Patients with Marfan syndrome (MFS) who were carriers of LP-P *FBN1* variants were largely prevalent in the overall series (39%) and in the gene-positive series (519 of 854, 61%), followed by patients with Loeys-Dietz syndrome (LDS) 1-5 (158 of 854, 19%), vascular EDS (88 of 854, 10%), and ACTA2-arteriopathies (35 of 854, 4%). Other less common genes (n = 54, 6%) are listed in Supplemental Table 3. The MFS series included 6 pairs of homozygous twins.

Of the 1,418 cases, 34 demonstrated ASA (2.4%) (**Tables 1 and 2**), of which 24 of 34 (70%) were women. The mean baseline ASA diameter was 12.55 ± 4.3 mm (median 11 mm; IQR: 10-13 mm) (men 12 mm; women 12.7 mm). Serial CT in 23 patients at a median of 5 years from the baseline evaluation showed nonsignificant increase in the diameter of the lusoria artery in the 18 uncomplicated ASA (Supplemental Table 4). The ASA coursed posterior to the trachea and esophagus in all cases. A right-sided aortic arch was present in 5 patients (with related ALSA), including 1 in the gene-negative group and 4 in the gene-positive group, all with MFS.

Of the 34 patients, 12 (35%) showed truncus bicaroticus as an associated variant of supra-aortic trunks. The 34 patients were asymptomatic at baseline evaluation, although 24 (70.5%) demonstrated aortic aneurysm (z-score >2.5) in at least 1 aortic segment, and 3 (8.8%) had undergone elective aortic surgery before being referred to our center. The remaining 7 patients had extra-aortic aneurysm/dissection, including 1 in the context of PHACES Syndrome. KD was present in 13 of 21 patients (62%) in the gene-positive group vs 3 of 13 patients (23%) in the gene-negative group.

ASA COMPLICATIONS. Of the 34 patients, 29 had ARSA and 5 had ALSA. Five (14.7%), all with ARSA and all women, developed aneurysm and dissection of the lusoria artery, including 2 homozygous twins with *FBN1*-positive MFS and 3 unrelated patients

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TABLE 1 Gene-Positive (ACMG Class LP-P) Patients With ARSA

				Genetics		Aortic Diameters (mm)							ASA Right (R), Left (L)		
N	Sex	BSA	Age First CT	Gene	ACMG	Root	STJ	Asc	Arch	Desc	Aortic Arch Side	Number of SAT (Variant)	Kommerell Y/N (mm)	Lusoria Diam (mm)	TAA Y/N (Tract)
1	F	1.59	34	*COL3A1 c.1347+1G>T (de novo)*	P	28	26	28	25	18	L	4	N	9.5 (R)	N
2	F	1.62	41	*FBN1 p.Tyr1311Cys (F-AD)*	P	36	28	24	21	34	R	4	Y (24)	12 (L)	Y (Root)
3	F	1.98	43	*FBN1 p.Ile1076fs (F-AD)*	P	51	34	30	28	51	R	4	Y (23)	12 (L)	Y (Root)
4	**F**	**1.54**	**47**	***FBN1 p.Ser901Ter (de novo)***	**P**	**36**	**31**	**20**	**29**	**23**	**L**	**3 (TB)**	**Y (26)**	**21 (R)**	**Y (Root)**
5	**F**	**1.74**	**45**	***FBN1 p.Ser901Ter (de novo)***	**P**	**44**	**36**	**30**	**25**	**26**	**L**	**3 (TB)**	**Y (26)**	**19 (R)**	**Y (Root)**
6	M	2.10	49	*FBN1 p.Cys504Ser (de novo)*	P	47	43	38	35	28	L	3 (TB)	N	12.5 (R)	Y (Root)
7	F	1.51	50	*FBN1 p.Gly343Arg (F-AD)*	P	33	24	23	26	33	R	4	Y (22)	7 (L)	Y (Desc)
8	M	1.95	55	*FBN1 p.Cys2142Tyr (F-AD)*	P	40	35	35	33	37	R	4	Y (29)	13 (L)	Y (Root)
9	F	1.66	38	*FBN1 p.Cys2500Arg (F-AD)*	P	44	36	33	31	22	L	2 (TB)	N	9.5 (R)	Y (Root)
10	F	2.10	44	*FBN1 p.Cys570Tyr (F-AD)*	P	42	32	33	29	23	L	3 (TB)	N	11 (R)	Y (Root)
11	M	2.25	26	*FBN1 p.Arg2414Ter (F-AD)*	P	40	34	29	27	21	L	3 (TB)	Y (15)	11 (R)	Y (Root)
12	F	1.41	43	*FBN1 p.Cys1928Ser (F-AD)*	P	*Pr*	*Pr*	25	21	20	L	4	Y (24)	10 (R)	Y (Bentall)
13	M	2.13	55	*FBN1 p.Gly2279Glu (F-AD)*[a]	P	44	38	36	32	28	L	3 (TB)	Y (23)	13 (R)	Y (Root)
14	M	2.00	32	*FBN1 p.Val372fs (F-AD)*	P	*Pr*	*Pr*	*Pr*	35	27	L	4	N	13 (R)	Y (Bentall)
15	F	1.74	20	*FBN1 p.Arg566Ter (F-AD)*	P	40	26	25	24	18	L	3 (TB)	N	11 (R)	Y (Root)
16	F	1.79	25	*FLNA p.Trp636Leu (de novo)*	P	49	45	49	34	27	L	4	N	13 (R)	Y (Asc)
17	**F**	**1.86**	**28**	***SMAD3 p.Cys421Tyr (F-AD)***	**LP**	**47**	**40**	**27**	**23**	**20**	**L**	**4**	**Y (30)**	**21 (R)**	**Y (Root)**
18	F	1.95	34	*TGFBR2 p.His362Leu (F-AD)*	P	*Pr*	*Pr*	26	25	21	L	4	Y (29)	12.5 (R)	Y (T.David)
19	**F**	**1.57**	**14**	***TGFBR2 p.Leu402Pro (de novo)***	**P**	**43**	**40**	**25**	**23**	**14**	**L**	**4**	**Y (10)**	**26 (R)**	**Y (Root)**
20	**F**	**1.46**	**49**	***TGFBR1 p.Ser236Phe (de novo)***	**LP**	**41**	**29**	**35**	**30**	**32.5**	**L**	**3 (TB)**	**Y (21)**	**18 (R)**	**Y (Root)**
21	M	1.86	52	*TGFB3 p.Glu216Gly (F-AD)*[b]	LP	40	27	27	25	22	L	5	N	10.5 (R)	Y (Root)

Cases in **bold** indicate aberrant right subclavian artery (ARSA) dissection. [a]Lusoria is absent in his homozygous twin (**Central Illustration**). [b]Retrognatia, exotropia, bifid uvula, aortic root dilation, mitral valve prolapse, pectus excavatum, kyphoscoliosis, arachnodactyly, pes planus.

AAA = abdominal aortic aneurysm; Arch = aortic arch; Arch side = aortic arch position (R = right, L = left); Asc = ascending aorta; BSA = body surface area (sqm); Desc = descending aorta; Diam = diameter (mm); Diam max = maximum diameter (mm) of the aortic aneurysm; Kommerell = presence of Kommerell (Y = presence, N = absence) diverticulum and the diverticulum diameter (mm); LP = likely pathogenic variant; P = pathogenic variant; PHACE/S = posterior fossa brain malformations, large facial hemangiomas, anatomical anomalies of the cerebral arteries, aortic coarctation and other cardiac anomalies, and eye abnormalities (when Sternal anomalies are also present the syndrome is referred to as PHACES); Pr = prosthetic; Root = aortic root; SAT = supra-aortic trunk; STJ = sinotubular junction; TAA = thoracic aortic aneurysm (Y = presence, N = absence); TB = truncus bicaroticus; Tract = aortic aneurismatic tract; VUS = variant of uncertain significance.

with LDS (**Figure 1**). Of the 15 gene-positive female patients, 10 had at least 1 pregnancy and none had peripartum complications (Supplemental Tables 5A and 5B).

ARSA DISSECTION IN MFS. A pair of homozygous twins were diagnosed with MFS at the age of 37 years (**Figure 1**). Their systemic scores were 10 and 11, respectively, and they were carriers of an *FBN1* [p.(Ser901*)] de novo variant (**Table 1**). Both had successful pregnancies and were unaware of their MFS diagnosis prepartum. For 10 years after their diagnosis, they remained asymptomatic and demonstrated the stability of the 2DTTE-measured aortic root, sinotubular junction (STJ), ascending aorta, arch, and descending aorta. An initial whole-body CTA at the age of 47 years showed stable aortic root diameters (44 mm in II:3 and 36 mm in II:4, pedigree A in **Figure 1**), coinciding with values measured on 2DTTE, but also demonstrated ARSA with KD, saccular aneurysm (thrombosed in one of the twins), and dissection of the mid to distal portion of the ARSA (**Figure 2**). The first event occurred in twin A II:3 (**Figure 1**) at the age of 48 years, when she had an unexpected cardiac arrest and was diagnosed with type A aortic dissection. The aortic root at time of emergency CTA measured 45 mm. She underwent an aortic root remodeling technique (Florida-Sleeve) and ascending aorta and proximal arch conduit. Two years later, in context of planning a repair of the KD and of the dilated arch, the patient underwent lusoria artery embolization with percutaneous placement of an Amplatzer II Vascular plug. The last CTA scan did not demonstrate further aortic growth.

The second twin (A II:4 in **Figure 1**) had very mild aortic root dilation at baseline and the same monitoring strategy as her sister. Her first CTA confirmed mild aortic root dilation (z-score[22] = 2.11) and demonstrated KD and ARSA with a saccular aneurysm and distal focal dissection. She underwent double-stent grafting at the age of 47 years. The post-procedure CTA demonstrated good results but also showed a bronchial artery saccular aneurysm (12 × 8 mm) that was absent in the prior CTA. The bronchial artery aneurysm was treated 2 months later with an endovascular embolization procedure that was complicated by bidirectional aortic dissection

TABLE 2 Gene-Negative (ACMG Class B, LB, VUS) Patients With ARSA

N	Sex	BSA	Age	Vascular Phenotype and Extravascular Traits	Aortic Diameters (mm) Root	STJ	Asc	Arch	Desc	Aortic Arch Side	SAT N (Variant)	ASA Right (R), Left (L) Kommerell Y/N (mm)	Lusoria Diam (mm)
22	M	2.29	48	Onset with AMI at 35 y; dilation of iliac arteries; arterial tortuosity.	34	32	32	32	26	L	4	Y (20)	9.8 (R)
23	M	1.82	45	Mild aortic coarctation (max prestenotic dilation 37 mm); BAV; dilation of superior mesenteric, right renal, left common iliac arteries, this latter with intimal flap.	37	28	27	41	37	L	4	Y (37)	14 (R)
24	F	1.63	32	LAD and splenic artery dilation; arterial tortuosity; right ICA dissection at 17. Hepatic angiomas. Varicocele. Lobeless ears; skin and skeletal traits suggestive for EDS.	29	27	28	27	17	L	4	N	9.5 (R)
25	M	1.83	47	MVP since age 20 y; mitral valve surgery. Tall stature, pectus excavatum, father and 2 paternal uncles with AAA; 1 paternal brother: sudden death at 20 y.	38	30	29	25	21	L	4	N	9.5 (R)
26	F	1.64	49	Skeletal traits (scoliosis, joint laxity); arterial tortuosity; suspected EDS-IV; negative functional studies of skin fibroblasts; Arnold-Chiari 1.	31	24	22.5	23	20	L	3 (TB)	N	10 (R)
27	F	1.70	42	TAA and MVP; father, paternal aunt and uncle: TAAD; 2 sisters: TAA; Liver cavernous angioma, 8 cm; left ICA aneurysm; MVP and TVP.	31	28	39	25	18	L	3 (TB)	N	13 (R)
28	F	1.82	60	F-TAA; sporadic BAV.	40	33	43	34	24	L	4	N	11 (R)
29	F	1.55	47	Right ICA dissection; TAA in 2 relatives.	34	29	33	25	18	L	3 (TB)	Y (14)	8 (R)
30	M	2.11	18	Syndromic; 46XY; Array CGH negative; suspected and excluded: Sotos, Fragile X; kinking of the right aortic arch with gothic shape.	31	25	23	22	20	R	3	N	11 (L)
31	F	1.58	64	F-TAAD (fatal TAAD: mother; TAA: brother); nonsyndromic TAA	37	34	43	31	28	L	4	N	10.5 (R)
32	F	1.44	60	F-TAA; separate origin of LAD and CX (no LMCA)	27	25	29	27	21	L	4	N	11 (R)
33	F	1.69	61	F-TAA; no BAV	44	25.5	27	27	22	L	4	N	9 (R)
34	F	1.80	26	PHACES syndrome; ICA dissection	24	22	22	19	16	L	4	N	10 (R)

ACMG = American College of Medical Genetics and Genomics; AMI = acute myocardial infarction; BAV = bicuspid aortic valve; CX = circumflex artery; DVT = deep vein thrombosis; EDS = Ehlers-Danlos syndrome; ICA = internal carotid artery; LAD = left anterior descending coronary artery; MVP = mitral valve prolapse; F-TAA = familial thoracic aortic aneurysm; TAAD = thoracic aortic aneurysm and dissection; other abbreviations as in Table 1.

involving the ascending aorta 7 cm distal to the aortic valve annulus, aortic arch, and descending aorta up to its intermediate-proximal tract (at the level of D6 vertebral body). She was medically managed. The last CTA, performed at the age of 51 years, showed no progression in size of the dissected and nondissected aortic segments. The 2 twins are mothers of 1 affected daughter and son, respectively, who did not show evidence of an ARSA on CTA.

ARSA DISSECTION IN LDS. ASA dissection occurred in 3 of 5 LDS patients with lusoria (**Table 1, Figure 1**).

LDS2. This patient was diagnosed with LDS2 and aortic root aneurysm (z-score[22] at baseline = 6) at the age of 4 years (**Figure 1B**). She underwent routine clinical and imaging surveillance and was treated with both beta-blockers and angiotensin-II receptor blockers for the following 10 years, with an associated very slow increase in aortic dimensions (z-score[22] from 6 to 8). At the age of 15 years, she experienced an episode of atypical chest pain and underwent whole-body CTA that showed ARSA (maximum diameter = 23 mm) and an aortic root diameter of 40 mm. Two years later (1 follow-up was missed because of the COVID-19 pandemic), she experienced thoracic and back pain, and urgent CTA demonstrated ARSA dissection (61 mm) and further growth of the aortic root (maximum diameter 43 mm, z-score[22] 9.6). The ARSA aneurysm was excluded with a balloon-expandable double stent graft (GORE VBX) with axillo-femoral through and through technique. The aortic root aneurysm was treated with Florida-Sleeve and ascending aorta prosthetic replacement. The last CTA 18 months later confirmed exclusion and shrinkage of the ARSA aneurysm (**Figure 3**).

LDS3. A 27-year-old woman and mother of a 5-year-old daughter was referred for aortic root dilation and was diagnosed with LDS3 (**Figure 1C**). Systematic monitoring was subsequently deferred because of patient preference. In the following 10 years, she underwent sporadic evaluation at a center close to her residency with reported stability of the aortic

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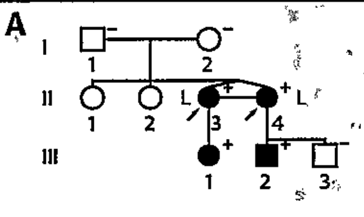
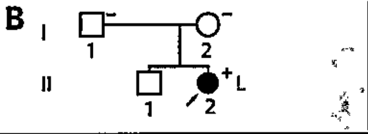
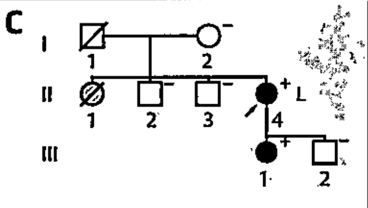
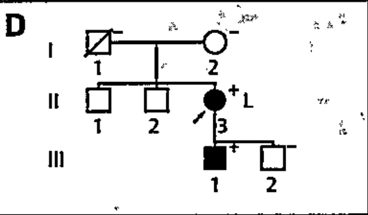
FIGURE 1 Dissected Lusoria: Pedigrees

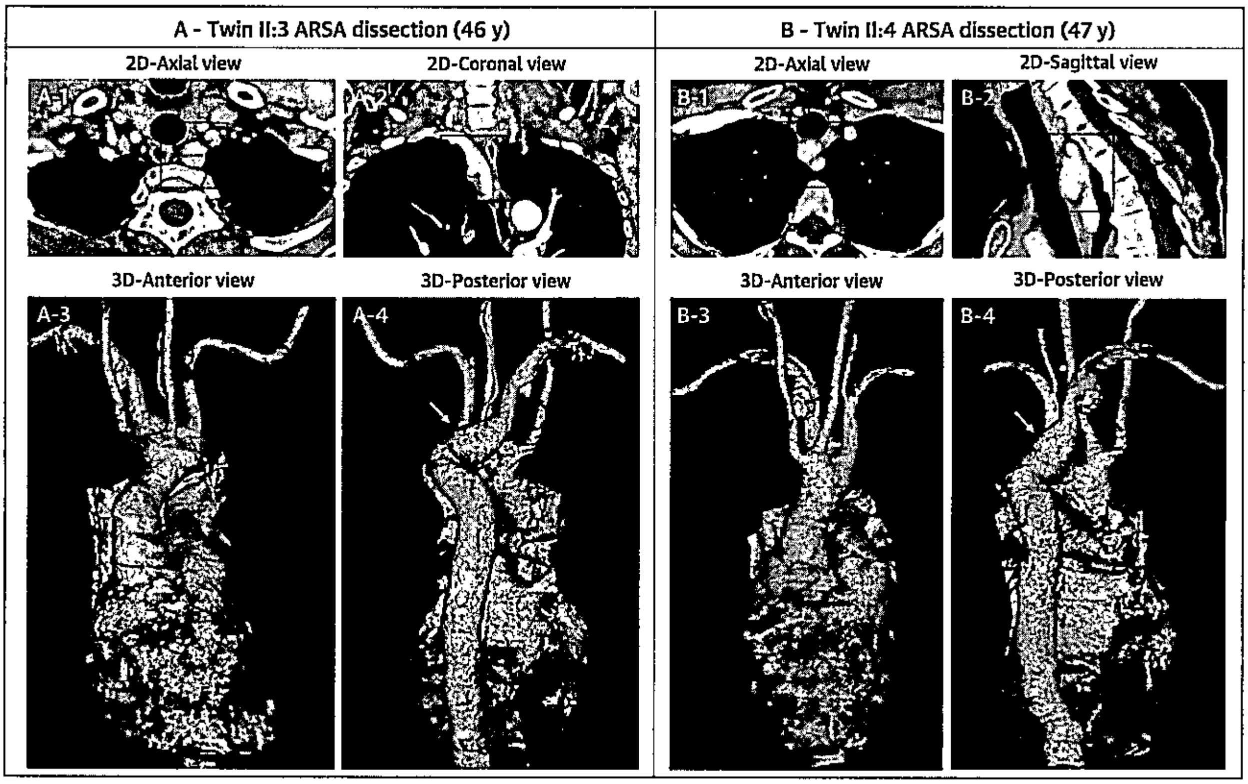
Pedigrees of the 5 Patients With Dissected Lusoria	Clinical Data
A 	I:1 - 82 y: no phenotype I:2 - 80 y: no phenotype II:1-2 - healthy, 40 and 38 y at baseline screening II:3 - MFS diagnosis at 37 y; systemic score = 11; (Case 5 in Table 1) II:4 - MFS diagnosis at 37 y; systemic score = 10; (Case 4 in Table 1) III:1 - MFS diagnosis at 11 y III:2 - MFS diagnosis at 7 y III:3 - baseline screening at 5 y
B 	I:1 - age at baseline: 45 y, healthy I:2 - age at baseline: 44 y, healthy II:1 - age at baseline: 10 y, healthy II:2 - 18 y; LDS2 diagnosis at 4 y; LDS1-like phenotype as in PMID:16928994; (Case 19 in Table 1)
C 	I:1 - death at 49 y, Non-Hodgkin Linfoma I:2 - age at baseline: 65 y, healthy II:1 - sudden death at 26 y; no autopsy; no genetic test II:2 - age at baseline: 28 y II:3 - age at baseline: 30 y II:4 - LDS3 diagnosis at 27 y; (Case 17 in Table 1) III:1 - LDS3 diagnosis at 5 y III:2 - age at baseline: 1 y
D 	I:1 - death at 73 y, lung cancer I:2 - 79 y, DM2, hypertension II:1 - 52 y, DM2 II:2 - 50 y, healthy II:3 - LDS1 onset at 41 y with acute TAAD; now, 49 y; (Case 20 in Table 1) III:1 - LDS1 diagnosis at 27 y; Aortic root z-score: 2.52 III: - 2 age at baseline: 24 y, healthy

The figure shows the pedigrees and main clinical traits of the 5 patients with dissected aberrant right subclavian artery.

root. At the age of 37 years, she presented with an anterior ST-segment elevation myocardial infarction caused by spontaneous coronary artery dissection of the proximal left anterior descending artery, which required percutaneous coronary intervention. The ST-segment elevation myocardial infarction was recognized 48 hours after the onset of symptoms and resulted in postischemic left ventricular dilation and dysfunction (ejection fraction 25%). She underwent implantable cardioverter-defibrillator (ICD) implantation for primary prevention. Her whole-body CTA demonstrated an ARSA (diameter 8 mm) with KD (diameter 20 mm) and a mildly dilated aortic root (41 mm) with preserved STJ (27 mm). CTA the following year showed stability of aortic and ARSA diameters while on treatment with beta-blockers and angiotensin-II receptor blockers. At the age of 40 years, she survived cardiac arrest after receiving 9 appropriate DC shocks. After angiographic exclusion of further coronary dissections, she was readdressed to our attention. CTA showed progression of the aortic root (47 mm) and STJ (40 mm) dimensions, and an ARSA dissection (diameter 21 mm), which extended to KD (**Figure 4**) with partial thrombosis of the false lumen at the level of KD (diameter 30 mm), and a circumferential thrombotic layer of about 10 mm. Given persistent severe heart failure with reduced ejection fraction (LVEF 20%-25% on guideline-directed medical therapy) and functional status led to discussions of heart transplantation (HTx). At the present time, after multidisciplinary team evaluation, the indications for HTx and repair of aortic aneurysm and lusoria continue to be debated.

LDS1. A 49-year-old woman was referred to the emergency department for acute chest and back pain at the age of 42 years (**Figure 1D**). CTA showed ARSA dissection extending to KD and the descending aorta, terminating at the level of the superior mesenteric artery (**Figure 5**). Aortic dimensions were not prohibitively enlarged, with a maximum descending aorta

FIGURE 2 Dissected Lusoria in Marfan Twins



(A) First computed tomography angiography in twin II:3 with Marfan syndrome showing aberrant right subclavian artery (ARSA) dissection **(A-1 and A-2, red squares)**. **(A-3 and A-4)** 3-dimensional (3D) anterior and posterior view of dissected ARSA **(red arrows)** and Kommerell's diverticulum **(blue arrow)**. **(B)** First computed tomography scan in twin II:4 with Marfan syndrome showing dissected ARSA **(B-1 and B-2, red squares)**. **(B-3 and B-4)** Anterior and posterior view of dissected ARSA **(red arrows)** and Kommerell's diverticulum **(blue arrow)**. 2D = 2-dimensional.

diameter of 32-33 mm. She was treated with guideline-directed medical therapy and underwent close imaging follow-up. CTA performed after 7 months demonstrated thrombosis of the false lumen and progressive enlargement of the descending aorta up to 51 mm. She underwent open repair of the descending aorta and ARSA resection with subclavian to carotid bypass grafting. After 7 years, because of massive hematemesis that led to hemorrhagic shock, she was diagnosed with an aortic-esophageal fistula and underwent emergency esophageal repair and placement of 3 aortic endoprostheses. One month later, she underwent thoracoabdominal aneurysmectomy with reimplantation of the superior mesenteric artery and celiac trunk, jejunostomy, removal of 3 aortic endoprosthesis, and esophageal suture reinforced with pedunculated muscle placement. One month later, because of infectious complications, esophageal stripping and mediastinal toilette were performed. She subsequently had stenosis of the superior mesenteric and celiac tripod that was treated with PTA.

DISCUSSION

The events described in this series were unexpected. Almost all of the patients were routinely monitored, and the size of ASA was not such to predict the observed complications.[18] According to the current recommendations, a subclavian artery >3 cm and/or KD >5.5 cm should be considered for repair (Class IIa, Level of Evidence: C), and symptomatic patients with aberrant subclavian artery and/or KD should be treated (Class I, Level of Evidence: C).[18] In our patients, both with complicated and uncomplicated presence of ASA, the diameters of both lusoria and KD as well as those of lusoria without KD were below the risk cutoff.

The lusoria diameters and the morphology of ARSA dissection differed in the 3 LDS cases, whereas the 2

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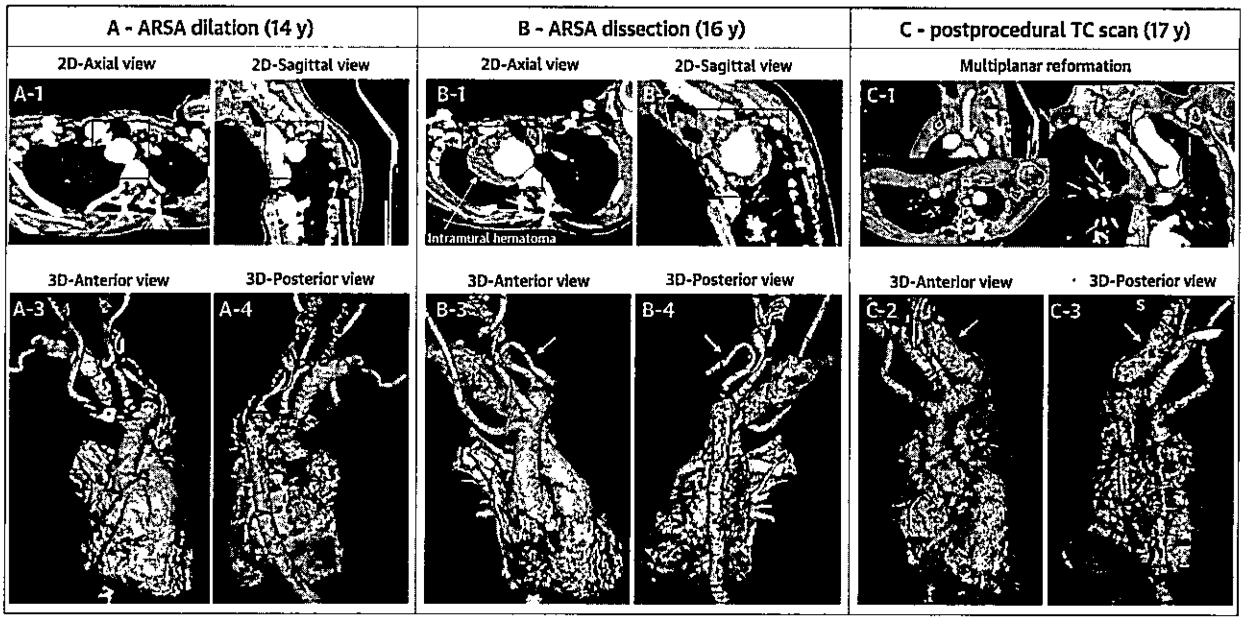
FIGURE 3 Dissected Lusoria in LDS2 Patient



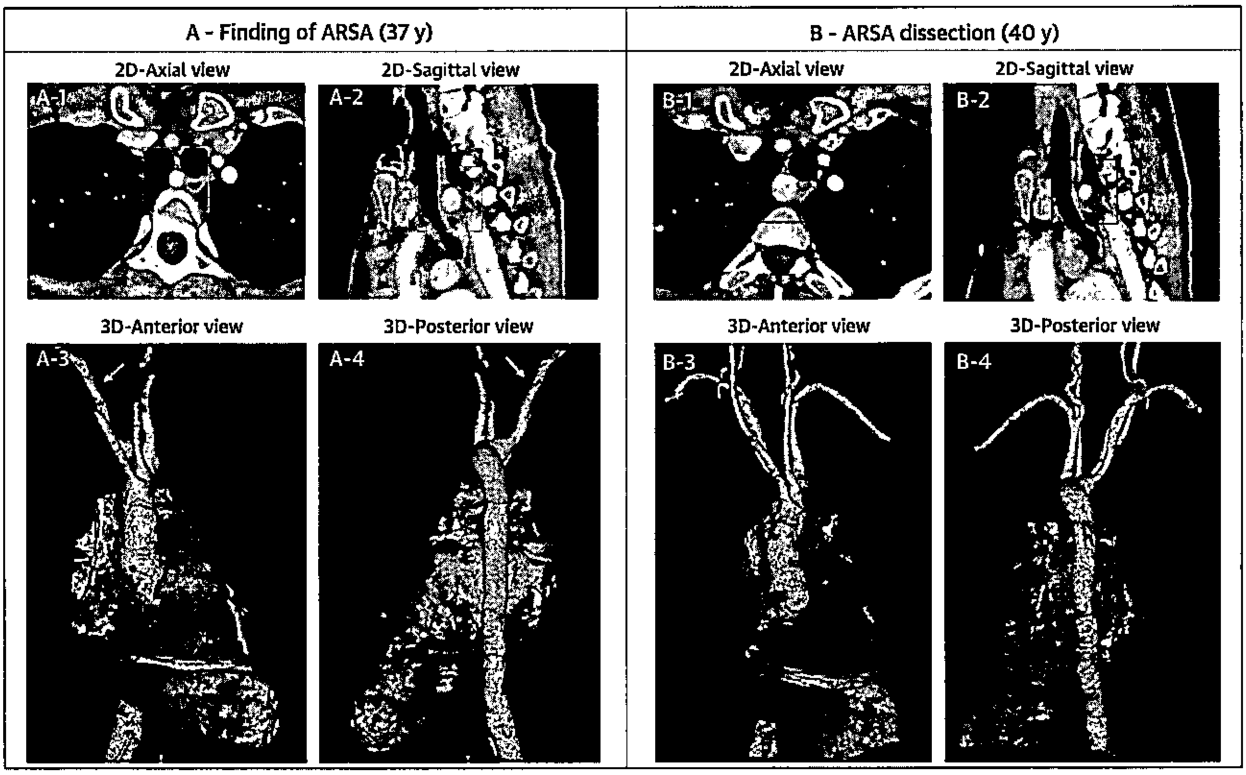
Case II:2 (family B in **Figure 1**). **(A)** First computed tomography angiography (age 14 years). Aortic root dilation. Right aberrant subclavian artery (maximum diameter 23 mm) **(A-1, A-2, red squares)**. **(A-3 and A-4)** 3D anterior and posterior view of dilated ARSA **(red arrows)**. **(B)** Second computed tomography angiography (age 16 years) after acute right lateral cervical-shoulder-chest pain. Severe ARSA dilation (61 mm) with dissection **(red square)** incorporating 18 mm intramural hematoma **(B-1 and B-2, red squares)**. **(B-3 and B-4)** 3D anterior and posterior view of the giant dissected ARSA **(red arrows)**. **Blue arrows** indicate left subclavian artery (Video 1). **(C)** Computed tomography angiography (age 17 years) after heart surgery and ARSA endovascular grafting **(red arrows)**. Unexpected dilation of the left subclavian artery **(C-1, blue squares)**. **(C-2 and C-3)** 3D anterior and posterior view of the dilated left subclavian artery: 21 mm vs 10 mm in 2020 **(blue arrows)**. Abbreviations as in **Figure 2**.

homozygous MFS twins demonstrated similar saccular aneurysms involving the dissected ARSA artery, one with and one without thrombosis. One twin had a spontaneous aortic dissection when her aortic root diameter was 45 mm, and the other twin had an iatrogenic aortic dissection, a well-known potential complication in endovascular procedures.[13,14] In neither of the twins was the dissection of the lusoria in continuity with that of the aorta. In the 3 LDS patients, the observed events were an isolated dissection of lusoria, dissection of lusoria extending to KD, and dissection of lusoria and KD and progression through the thoracic aorta to the mesenteric artery, respectively. Contributors or predisposing factors to lusoria dissection in LDS patients could include the extreme tortuosity of the supra-aortic trunks, but this hypothesis requires confirmation in larger series. A potential hit in an LDS patient (n.17) (**Table 1**) was an arrhythmic storm that triggered 9 appropriate ICD shocks. CTA showed KD dissection and an increase in aortic root dimensions from 41 to 47 mm. It is conceivable that the 9 rapidly occurring ICD discharges may have contributed to the dissection, although there are no data to support this hypothesis. HTx is now strongly considered, and is a decision made challenged by the coexisting need for aortic and lusoria repair in the context of LDS3.

DO GENETIC ARTERIOPATHIES CARRY A HIGHER RISK OF COMPLICATIONS IN PATIENTS WITH ASA?

Decisions about lusoria repair are guided more by contingent observations in individual cases than based on strict criteria. The primary question at present is how to care for the remaining 29 patients with lusoria, especially in the 16 patients with genetic arteriopathies associated with pathogenic variants in *COL3A1, FBN1, FLNA, SMAD3, TGFB2, TGFB3, TGFBR1*, and *TGFBR2*. The risk of dissection remains unpredictable because the observed diameter is stable and below the cutoff for both KD and lusoria repair in this patient cohort, similar to the lusoria diameter in gene-negative patients. We emphasize that gene-negative indicates negative genetic testing of the analyzed genes, and does not exclude defects

FIGURE 4 Dissected Lusoria in LDS3 Patient

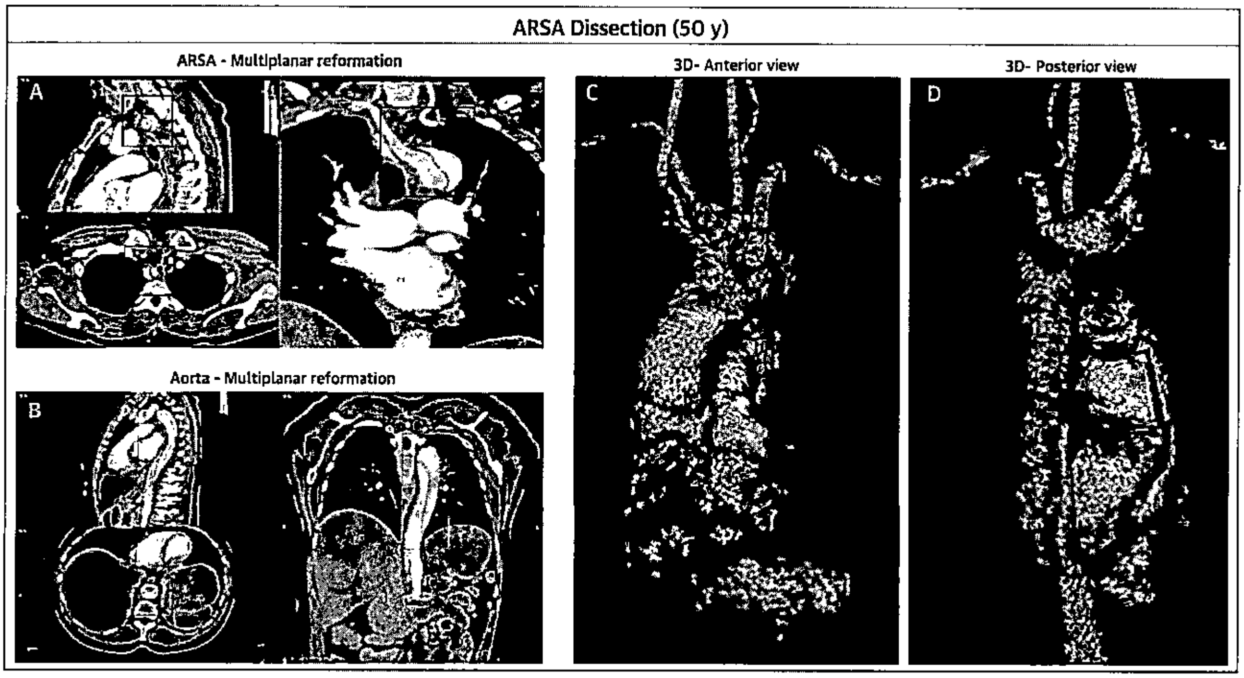


(A) First computed tomography angiography in an LDS3 patient showing ARSA **(A-1 and A-2, blue squares)**. 3D anterior and posterior views of ARSA **(A-3 and A-4, blue arrows)**. **(B)** Follow-up computed tomography angiography showing ARSA dissection **(B-1 and B-2, red squares)**. 3D anterior and posterior view of the dissected ARSA **(B-3 and B-4, red arrows)**. Abbreviations as in **Figure 2**.

in unknown genes or in genes of uncertain significance still unrelated with known genetic arteriopathies. Although our series confirms that there is no causal link between lusoria and genetic arteriopathies, the risk of dilation and dissection in these syndromes is greater than that observed in gene-negative arteriopathies (5 of 21 positive, or 24%, vs 0%), and higher in LDS (3 of 5 or 60%) than in MFS (2 of 14 or 14%) patients (**Central Illustration**). In MFS specifically, the relatively limited size of our cohort does not permit prognostication of systemic score and ASA complications. The detection of lusoria depends on imaging of supra-aortic trunks. Computed tomography or magnetic resonance imaging of the aortic arch is recommended in adults diagnosed with MFS.[23] In an ideal future scenario, fetal and postnatal echocardiography screening could provide information on aortic arch abnormalities in the portfolio of neonatal screening traits, which may require specific monitoring plans.[3,4,24]

LUSORIA AND REPAIR. Risks and complexities differ in elective vs emergency repair. Isolated, uncomplicated lusoria in nongenetic arteriopathies requiring repair for dysphagia can be electively and successfully performed by endovascular interventional procedures with low morbidity and mortality.[25] When the need for repair is dissection, the complexity and procedure-related risk are higher and take into consideration the underlying condition (genetic vs nongenetic) and circumstances (aneurysm, dissection limited to lusoria and/or KD, vs progression of the dissection to the descending thoracic aorta or retrograde extension of the dissection). In genetic arteriopathies, both aortic aneurysms with arch dilation requiring replacement and KD resection, surgery can successfully repair both the aorta and KD.[26] Although the impact of endovascular aortic interventions in connective tissue disorders is debated,[27,28] there are no systematic data comparing interventional strategy in the management of ASA and KD. However, it

FIGURE 5 **Dissected Lusoria in LDS1 Patient**



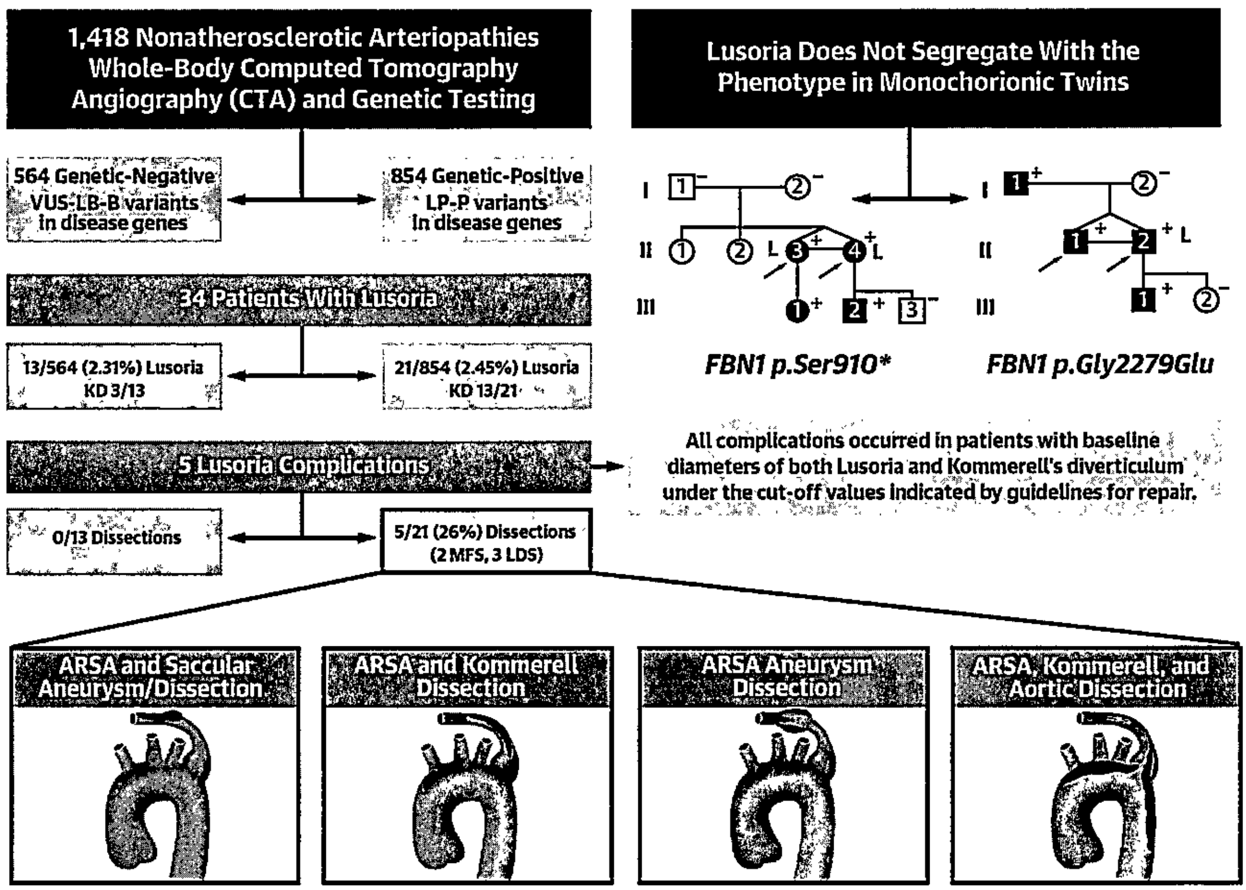
Emergency computed tomography angiography for acute chest and back pain: ARSA and Kommerell's **(A, red squares)** and aortic type B dissection involving descending aorta **(B, blue squares)**. **(C and D)** 3D anterior and posterior view, from the dissected ARSA **(red arrows)** to abdominal aorta **(blue arrow)**. Abbreviations as in **Figure 2**.

should be noted that of the 5 patients in our series with dissection of lusoria, 2 were treated with an endovascular technique and have been doing well without further complication after 2 and 6 years, respectively. In the case of type A aortic dissection, the presence of ALSA or ARSA affects the cannulation strategy for extracorporeal circulation. Cannulation of the right axillary artery is preferable in the case of ALSA and the absence of anatomical anomalies of the anonymous trunk. Selective carotid artery cannulation is mandatory in case of ARSA or in the presence of anomalies of the anonymous trunk.

LUSORIA IS INDEPENDENT OF THE UNDERLYING GENETIC DISEASE. Our series included 6 pairs of homozygous MFS twins. Lusoria was present in both twins in 1 couple (cases 4 and 5 in **Table 1**) and in a single brother (case 13 in **Table 1** is the twin with lusoria) in another (**Central Illustration**). The remaining 4 pairs of homozygous MFS twins did not show lusoria or other aortic arch abnormalities. The possibility that monochorionic twins are discordant for congenital heart disease has been known for decades,[29] with lusoria being an independent congenital abnormality unrelated to genetic arteriopathies but strongly predicting congenital defects/diseases.[3,4,24] In addition, lusoria may be associated with other congenital anomalies unrelated to genetic arteriopathies. In our series, the 5 patients with ALSA also showed a right-sided aortic arch, of which 4 had MFS and 1 had negative genetic testing. This observation supports the association of ALSA and right-sided aortic arch but does not necessarily support an association between ALSA-right-sided aortic arch and MFS.

The rare PHACES syndrome (malformations of the Posterior fossa, Hemangiomas of the head and neck, Arterial, Cardiovascular, and Eye anomalies) deserves special consideration.[30] We observed a PHACES case in our series of adult patients. This congenital syndrome is usually recognized in childhood with presence of face and neck hemangiomas and is less frequently diagnosed in adults.[31] Anomalies of the aortic arch are common, and among these is the lusoria artery.[32] Clinicians observing patients with aortic abnormalities and hemangioma should consider this diagnosis, which shows a female prevalence, is not heritable, and the search for the hypothesized skewed X chromosome inactivation gives inconclusive results.[33]

CENTRAL ILLUSTRATION The Risk of Lusoria Complications Is Higher in Genetic Arteriopathies



Giuliani L, et al. J Am Coll Cardiol. 2023;81(10):979-991.

The figure shows the prevalence and complications of lusoria and Kommerell's diverticulum (KD) in nonatherosclerotic arteriopathies with positive and negative genetic testing. The 2 couples of monochorionic twins with Marfan syndrome (MFS) exclude a link between lusoria (L) and the genetic arteriopathies. CTA = computed tomography angiography; LDS = Loeys-Dietz syndrome.

STUDY LIMITATIONS. In our series, nearly all patients were adults. Therefore, the prevalence of lusoria in genetic arteriopathies may not necessarily reflect the true prevalence when considering patients of all ages. In addition, our gene-negative series included carriers of VUS that could not otherwise be classified. Although we adopted whole-body CTA as an elective imaging tool since beginning our institutional diagnostic pathway, CTA imaging is not considered a baseline screening tool in all patients with nonatherosclerotic arteriopathies at entry, especially in children. Current guidelines specify that cardiac magnetic resonance imaging or CTA from head to pelvis should be performed in every adult patient diagnosed with MFS and related aortopathies. Children are usually diagnosed and monitored using 2DTTE and peripheral vessels ultrasound and undergo magnetic resonance and CTA only for precise clinical indications. In terms of prevalence of lusoria in genetic arteriopathies, our series reflects typical syndromes associated with arterial aneurysms (eg, MFS, LDS1-5, EDSIV being the most common types) vs other rare genetic diseases or syndromes in which aneurysmal complications are less common (eg, nonvascular EDS).

CONCLUSIONS

Although lusoria is considered a vascular anomaly of limited clinical impact, its complications including aneurysm and dissection can be life-threatening, especially when they occur in context of genetic arteriopathies. In Loeys-Dietz syndromes, in which the fragility of the vascular walls can even exceed that of MFS or be similar to that observed in vascular EDS, lusoria should be an elective monitoring target, even in the absence of dysphagia, as observed in our series. Absence of precise guidelines on indications for elective repair renders the discussion to surgical or multidisciplinary teams,[34] delineated by individual case monitoring and surgical expertise.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: An ASA, a common congenital anomaly of the aortic arch, can become aneurysmal and result in arterial or aortic dissection. Recommendations for repair based on diameter do not distinguish between genetic and nongenetic forms.

TRANSLATIONAL OUTLOOK: Large prospective studies are needed to improve risk assessment in patients with ASA and inform the timing of surgical intervention.

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KEY WORDS aberrant subclavian artery, dissection, genetic arteriopathies, Loeys-Dietz syndrome, Lusoria, Marfan syndrome

APPENDIX For a supplemental figure, tables, and video, please see the online version of this paper.

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Reduced Vascular Practice and Increased Cardiovascular Mortality for COVID-19–Negative Patients

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ABSTRACT

Background: The aim of our study was to compare COVID-19– and not-COVID-19–related mortality rates in two Italian regions during the pandemic period when the same isolation rules and therapeutic approaches were introduced for all hospitals in Italy. Risk factors for not-COVID-19–related deaths during the pandemic were analyzed; we tried to assess a possible correlation between reducing hospital visits and "deferrable" vascular operations and the increased cardiovascular mortality not related to COVID-19 infection.
Methods: We analyzed COVID-19– and not-COVID-19–related mortality rates in two Italian regions in the period January 2020–January 2021. We compared mortality rates during the pandemic period with those of the previous five years. We tried to determine the factors involved in increased mortality rates during the pandemic period.
Results: Despite the same isolation rules for people and the same therapeutic approaches for hospitals, mortality rates did not increase in the region Lazio, where the pandemic was not severe. In the region Lombardy, the mortality rate was doubled in comparison with the previous years, and 50% of the increase was related to not-COVID-19 deaths.
Conclusions: The increase in mortality rates for not-COVID-19–related deaths in the region Lombardy was connected to the generalized turmoil in the acute phase of an overwhelming pandemic, including diffuse stress, inadequate communications, reluctance to ask for medical help unless symptoms were severe, and unexpected inadequate number of health workers, hospital beds, and intensive care unit beds. Reduced hospital visits may have had a fundamental role.

Introduction

In Italy, more than 106,000 deaths from COVID-19 have been reported up to March 30th, 2021; 250 health workers died from COVID-19 infection, and 110,266 health workers were diagnosed positive for COVID-19.[1-4] The pandemic has brought unexpected consequences, including shortage of medical personnel and reluctance from patients to ask for medical help unless their symptoms were severe.[3-5] Isolation rules were introduced for all hospitals in Italy including

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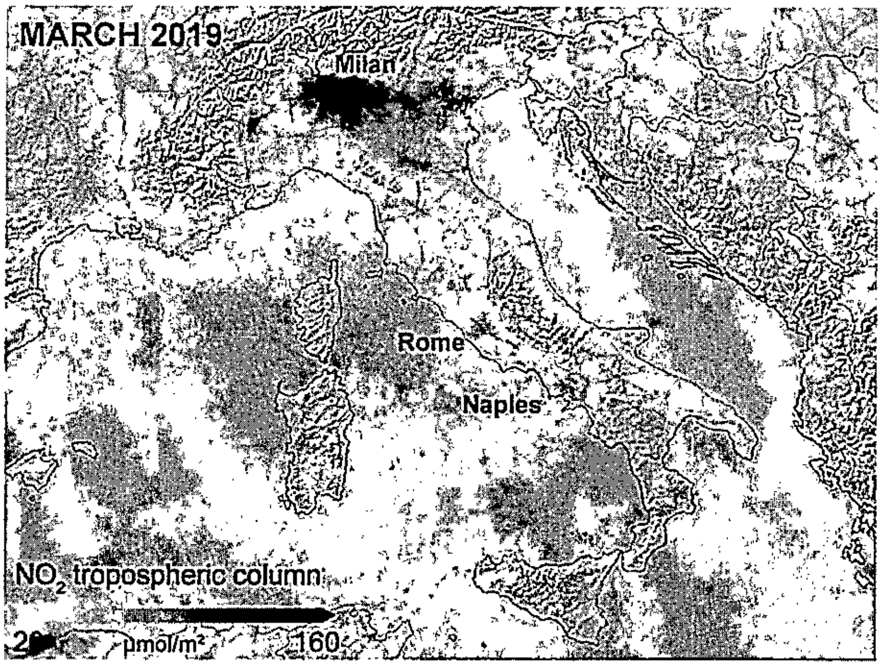

Fig. 1 – Nitrogen dioxide tropospheric columns in Italy. Nitrogen dioxide production is an index of "pollution" related to CO_2 production. COVID-19 pandemic in Italy was more severe in regions with high pollution. In the region Lombardy (Milan-Pavia), with high industrialization, the pandemic was more severe. (Color version of the figure is available online.)[8,9]

separate sections for COVID-19 patients, diffuse testing, and specific measures for health workers and patients. Admissions to hospitals were reduced, avoiding visits for not-urgent conditions and deferrable elective surgeries.[6,7] Often, it is difficult to determine the difference between deferrable and not-deferrable procedures and urgent or not-urgent examinations in patients suffering from vascular diseases.

The objective of our analysis was to identify the potential risk factors for increased cardiovascular mortality not related to COVID-19 infection during the pandemic. We tried to determine the influence of deferring not-urgent visits and operations for patients with vascular disease; we analyzed mortality rates in two Italian regions with different levels of severity of the pandemic (high in Lombardy and low in Lazio) (Fig. 1). In both regions, the same isolation rules for the general population and the same therapeutic attitudes in hospitals were introduced during the acute phases of the pandemic, when the differences were not clear in regional levels of the pandemic.

Material and Methods

Mortality analysis

The mortality data in Italy during the pandemic period March 2020–March 2021 were reviewed. The analysis was based on the data reported by the national health institute (Istituto Superiore Sanità—ISS) and the national statistics institute (ISTAT), which are national not-for-profit institutions supported by public funds. Mortality data are based on a real-time report of deaths in each single town, including more than 95% of the registered resident Italian population (Italian and non-Italian citizens).[1-4] All causes of death are reported to ISS and ISTAT as per the International Classification of Diseases and Related Deaths (ICD 10) as recommended by the World Health Organization. The classification is based on rigid rules. A person is considered dying from COVID-19 infection according to the World Health Organization definition: a patient

Table 1 – Mortality in Italy in the year 2020 (population 60 million) compared with the mean of the previous five years (2015-2019).

Region	Overall mortality	Increase in mortality*	COVID-19–related mortality (% total deaths)	Number of COVID-19 deaths/100,000 inhabitants
Lombardy	136,249	+36.56	25,120 (18.4%)	208.6
Lazio	62,161	+5.5	3717 (5.9%)	56.5
All Italy (20 regions)	746,146	+15.6	75,891† (10.2%)	103.9

*Percentage in comparison with the mean of the previous five years.
†The overall number of COVID-19–related deaths has increased to 106779 including the period January 1–March 30, 2021.

Table 2 – Total deaths and percentage of COVID-19–related deaths in Lombardy and Lazio during the first two acute phases of the pandemic (March-May 2020; October-November-December 2020).

Region	March-May 2020			October-November-December 2020		
	Overall mortality	Increase in mortality (%)	COVID-19–related mortality (% total deaths)	Overall mortality	Increase in mortality (%)	COVID-19–related deaths (% total deaths)
Lombardy	51,902	+111.8	16,223 (31.3)	34,572	+37.1	8243 (23.8%)
Lazio	15,009	+2.5	833 (5.5)	17,996	+22.5	2753 (15.3%)

Comparison with the same periods of the previous five years (2015-2019).

dying with clinical and laboratory evidence of COVID-19 infection, without an alternative cause of death clearly not referable to the COVID-19 infection even if present (e.g., a trauma-related death).[10,11] All laboratory tests to determine a probable COVID-19 infection were performed in specialized regional referral centers with an real time polymerase chain reaction of the oropharyngeal swab.

Comparison of mortality rates during and before the pandemic period

The number of patients who died during the period January 2020–December 2020 was compared with the mean number of patients who died in the previous five years (2015-2019).

Reduced medical and surgical activity during the acute phases of the pandemic

The isolation rules imposed by the Central Government for the general population and the restrictions for hospitals to perform only urgent visits or operations were the same all over Italy, independently from the level of the pandemic. Deferrable, elective operations were not performed. Outpatient visits were performed only for patients with severe symptoms and emergency conditions. There was a spontaneous tendency in the general population to avoid medical facilities. As a result, even the number of not-COVID-19 patients seen and admitted through the emergency rooms of hospitals was significantly reduced. We analyzed the number of vascular outpatient visits and vascular interventions during the acute phases of the pandemic in the University Hospital San Matteo of Pavia. The hospital is a university tertiary center where almost all patients with cardiovascular problems are referred from the city of Pavia (Lombardy) and the surrounding area (population, 545,000 inhabitants; density, 184 inhabitants/km^2). The number of vascular operations and outpatient visits performed during the year 2020 was compared with the numbers of the previous years for the Hospital San Matteo. The same data were collected from four tertiary referral hospitals in Rome (Lazio). The study was approved by the Ethical Committee of the Hospital San Matteo and of the Sapienza University.

Clinical data were tabulated in Microsoft Excel 1 (Microsoft Corp, Redmond, Wash) database: statistical analysis was performed with SPSS, release 25.0 for Windows (IBM SPSS Inc.; Chicago–ILL; USA). Categorical variables were analyzed using a chi-square test or Fisher's exact test where appropriate.

Results

Overall mortality in Italy during the COVID-19 pandemic

During the pandemic, 106,779 COVID-19 infection–related deaths were reported in Italy. The mean age was 81 years (female 44% and male 56%). Of the total number, 30,341 deaths were registered in the region Lombardy (28.4%) and 6,501 in the region Lazio (6.1%) (Table 1).

Increased mortality rates in Lombardy and Pavia (January-December 2020)

Table 1 shows the difference in overall mortality in the regions Lombardy and Lazio during the pandemic. People older than 50 years of age had higher mortality rates in comparison with the previous years (Tables 2-4). This increase was related to

Table 3 – Total deaths and percentage of COVID-19–related deaths in Italy as per age in the year 2020 and in the previous five years (2015-2019).

Age	Mean previous five years (2015-2019)	2020	Difference (%)	% COVID-19–related deaths/total deaths
0-49	19,442	17,788	−1654 (−8.6)	4.6
50-64	52,032	57,395	+5363 (+10,3)	9.2
65-79	164,598	184,708	+20,110 (+12.2)	12.4
80+	409,547	486,255	+76,708 (+18.7)	9.6
Total	645,620	746,146	+100,526 (15.6)	10.2

Table 4 – Increase (%) of deaths in Lombardy and Lazio as per age during the first acute phase of the pandemic (March-April 2020) in comparison with the previous 5 years (2015-2019).

Age	January-February	March	April	May
Italian regions with high diffusion (including Lombardy)				
50-64	−5.2%	+89.0%	+50.1%	+1.9%
65-80	−10.9%	+144.6%	+67.4%	−3.9%
>80	−5.8%	+121.1%	+100.3%	+8.2%
Italian regions with low diffusion (including Lazio)				
50-64	−4.3	−1.3	−4.9	−9.3
65-80	−8.2	+1.2	−0.9	−11.4
>80	−5.4	+4.5	+2.6	−5.2
Italy (all 20 regions)				
50-64	−4.8	+3.5	+15.5	−3.5
65-80	−9.3	+54.7	+27.2	−7.1
>80	−5.3	+51.6	+45.4	+0.9

people dying from COVID-19 infection for its 50%. The remaining 50% of the increase in mortality was related to people not dying from COVID-19 infection (70% of these deaths were defined as a consequence of cardiovascular events). During the overwhelming outbreaks, the collection of data was inevitably inaccurate The cause of deaths was based on the certificate of death written by family practitioners or by hospital staff physicians without an autopsy. Not-COVID-19 cardiovascular mortality was defined in the absence of COVID-19 infection, and it was hypothesized on the past medical history of patients (Fig. 2).

Surgical and medical activity in Pavia

During the pandemic period, surgical and outpatient visits for not-COVID-19 patients in the University Hospital of Pavia were not performed. Admissions to the emergency room of not-COVID19 patients were reduced by 90%, testifying at the fear in the general population of getting infected in medical facilities. In the Hospital San Matteo, 90% of admissions in the first acute phase of the pandemic (March-April 2020) were for patients with COVID-19 infection (942 patients). The number of elective arterial operations during the year 2020 was reduced in comparison with the previous year (483 *versus* 694 $P < 0.001$). We canceled operations for asymptomatic carotid occlusive disease, endovascular operations for claudication, and surgery for small abdominal aortic aneurysms. This decision was based on a frank and open discussion with patients. Sometimes patients preferred to defer operations which we thought indispensable. The number of admissions for emergency operations was slightly reduced (142 *versus* 167). There was an increased number of operations for acute ischemia of the lower limbs secondary to distal embolization (60% of the emboli were in patients with atrial fibrillation) and an increase in patients with frank rupture of an abdominal aortic aneurysm (Table 5). Mortality and complication rates were similar over the two years.

Overall mortality in Lazio and in Rome (January-December 2020)

The mortality rates related or not with COVID-19 infection were lower in the region Lazio than those in the region Lombardy (Table 2).

Surgical and medical activity in Rome (January-December 2020)

In the four major hospitals in Rome, surgical and elective outpatient visits were reduced at a rate similar to Pavia. The number of emergency room visits was almost doubled in the Hospital San Matteo, whereas they were reduced in the four hospitals of Rome ($P < 0.001$). Excluding patients with COVID-19 infection, the number of patients seen in the four hospitals

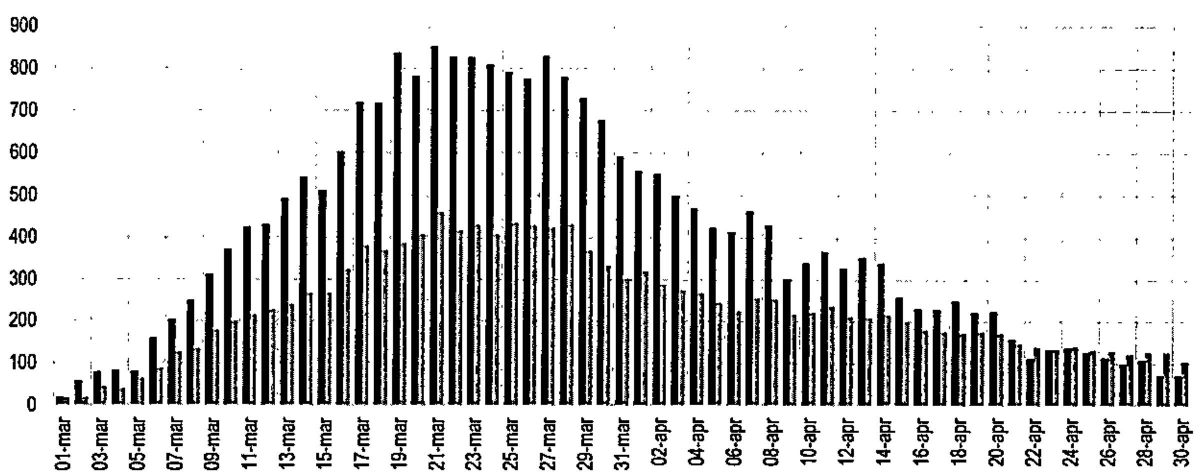

Fig. 2 – Increase in daily mortality for people 50 years of age or more in the acute phase of the pandemic (March-April 2020) in comparison with the average of the mean number of deaths in the same days during the previous five years (2015-2019) in the region Lombardy. Each line indicates the daily increase of deaths in March-April 2020 in comparison with the previous five years. Black represents the overall number of increased deaths. Yellow represents the number of deaths diagnosed as related to COVID-19 infection. (Color version of the figure is available online.)

Table 5 – Arterial surgery 2019 (960 patients—excluding hemodialysis access).

Emergency-not deferrable (N° Patients 166/960; 17.4%)

		N°
1	Abdominal aortic aneurysms	17
	Rupture	5
	Symptoms	12
2	Iliac artery aneurysms	5
	Rupture	2
	Symptoms	3
3	Pararenal abdominal aneurysms	9
	Rupture	5
	Symptoms	4
4	Femoral pseudo-aneurysms	10
5	Carotid occlusive disease (symptoms and stenosis greater than 90%)	13
6	Severe occlusive disease lower-limb arteries with limb at risk	80
	Embolic origin	29
	Acute thrombosis on pre-existing plaque	21
	Chronic limb ischemia (limb at risk)	30
7	Arterial trauma	9
8	Amputation (gangrene)	24
Total		166

Arterial surgery 2020 (624 patients excluding hemodialysis access)

Emergency-not deferrable (N° Patients 141/624; 22.7%)

	Type	N°
1	Abdominal aortic aneurysms	13
	Rupture	11
	Symptoms	2
2	Iliac artery aneurysms	2
	Rupture	2
	Symptoms	0
3	Pararenal abdominal aneurysms	5
	Rupture	5
	Symptoms	0
4	Femoral pseudoaneurysm	4
5	Carotid occlusive disease (symptoms and stenosis greater than 90%)	10
6	Severe occlusive disease lower-limb arteries with limb at risk	78
	Embolic origin	37
	Acute thrombosis on pre-existing plaque	14
	Chronic limb ischemia (limb at risk)	27
7	Arterial trauma	10
8	Amputation gangrene	20
	Total	141

in Rome and in Pavia was reduced in comparison with the previous years in a similar percentage (reduction of 90%). The number of elective vascular operations decreased by 50%. The number of emergency operations for ruptured abdominal aortic aneurysm and for acute ischemia of the lower limbs was similar to the previous years.

Shortage of ICU beds and health workers

In the Hospital San Matteo, there was a significantly high number of admissions for COVID-19 patients with inevitable continuous need and shortage for COVID-19 beds in the wards and in the semi-intensive and intensive care unit (ICU). In the region Lombardy, the number of available ICU beds at the time of the acute phase of the pandemic was 861 (8.5/100,000 residents). The admissions for COVID-19 patients were less common in the four hospitals in Rome, without an overwhelming shortage of ward and ICU beds for COVID-19–positive and –negative patients. In the region Lazio, the number of available ICU beds was 571 at the time of the first acute phase of the pandemic (9.5/100,000 residents).

Discussion

The COVID-19 pandemic has changed perspectives and attitudes in medicine.[12-14] During the pandemic, there has been a general tendency to cancel and to defer elective surgeries, reserving hospital admission only for patients with problems that could pose a threat to survival. This situation is the consequence of a general attitude to prevent contamination, involving all levels of the society, from legislators to the general population. In the acute phases of the pandemic, only patients with severe symptoms asked for medical advice. The general attitude of surgeons, not rarely forced by the patient's desire to avoid operations in this period, has been to eliminate low-value treatments and to modify therapeutic schema.[15-17] It is not easy to decide which operation is deferrable or not in a significant proportion of patients with cardiovascular pathology. Therapies considered to have a marginal effect are often delayed or even canceled, but this decision is difficult for patients with vascular disease. In the four major hospitals in Rome, surgical and elective outpatient visits were reduced at a rate similar to Pavia. The number of emergency room visits was almost doubled in the Hospital San Matteo, whereas it was reduced in the four hospitals of Rome ($P < 0.001$). In the Hospital San Matteo, the overall number of arterial procedures was reduced in the year 2020 in comparison with the previous years (625 *versus* 961). We canceled operations for asymptomatic carotid occlusive disease, endovascular operations for claudication, and surgery for small abdominal aortic aneurysms. This decision was based on a frank and open discussion with patients. Sometimes patients preferred to defer operations that we thought indispensable. Despite the reduced number of elective operations, the number of emergency operations was not increased, as one might expect analyzing the high number of people dying during the pandemic period. There was an increase in operations for acute ischemia of the lower limbs secondary to emboli and an increase in surgeries for ruptured abdominal aortic aneurysm.

Despite the high number of COVID-19–negative patients dying from cardiovascular events in the pandemic period, the number of emergency admissions for acute cardiovascular events did not increase in Pavia. Several factors may explain this discrepancy: high stress level in general population,[18] reluctance of patients to ask for medical help unless symptoms are unbearable, and difficult communication between patients and the medical system. The possibility that the reduced number of clinic visits imposed in the pandemic periods may have contributed to the increased number of cardiovascular mortality in patients negative for COVID-19 infection should be considered.[19-21]

Despite the inevitable problems related to the overwhelming number of COVID-19–positive patients, the overall results of arterial vascular procedures in the Hospital San Matteo were similar to those of the previous year, either for COVID-19–positive or COVID-19–negative patients. This accomplishment has been the consequence of adapting surgical therapy to the specific levels of the pandemic, often giving preference to endovascular treatments in patients in whom usually an open surgery was preferred.

Patients with cardiovascular pathology, who are older than 65 years, and with pulmonary problems are at a higher risk for COVID-19 infection and mortality.[22,23] General anesthesia with endotracheal intubation, postoperative pain, and ICU permanence are some of the most common risk factors for postoperative pulmonary infection and pulmonary major complications. Minimally invasive operative procedures like endovascular surgery generally require shorter operative time, no general anesthesia and tracheal intubation, and less organizational effort. Hospital stay is shorter.

There were no significant differences in therapeutic attitude and hospital isolation rules between the two examined Italian regions (Lombardy and Lazio). The only major difference was the level of the pandemic severity. In Rome, the pandemic had a low intensity, and the medical system was adequate without major deficits of hospital beds and equipment. In Pavia, the pandemic was severe, and in the acute phase, the workforce had limited capacity, and the health care system was overwhelmed with COVID-19 cases with problems concerning hospital and intensive care beds and equipment. The tendency to limit outpatient visits and to defer elective surgery may have played a major role for the increased mortality of not-COVID-19–related deaths, even if this matter is difficult to analyze and to quantify.[24] In Pavia, the number of admissions for ruptured abdominal aortic aneurysm and for acute ischemia of the lower limbs was higher in the year 2020 than that in the previous year. This problem was not evident in the region Lazio where the pandemic was less severe.[25,26]

Despite optimistic reports from local governments and the media, the communication between patients, hospitals, and organizational centers was less than appropriate in the acute phases of the pandemic. This observation does not want to be a negative criticism, but rather a constructive thought. The pandemic and its consequences were unpredictable.[14,27]

COVID-19 has forced widespread adoption of remote encounters by video applications, patient portals, or phone calls. Patients, hospitals, and physicians are rapidly adapting to this new way of communicating, but there are many problems to solve. Inevitably, this new form of communication resulted inadequate in the acute phases of the pandemic. Efforts should be made to improve it, and this enterprise may be more difficult than expected considering that most patients requiring help and information are old and often without a continuous-efficient help.

Our study presents inevitable limits: the retrospective nature of the analysis and possibility of inaccurate data, which were collected in the difficult acute phase of the pandemic.

The increased contamination and mortality rates in Northern Italian regions may be related to several factors, including higher air pollution and lower temperatures and higher number of elderly people, international exchanges, and contacts.

Surgeons should adapt indications and therapeutic approaches considering the level of the pandemic.[28-30] Analysis of the factors influencing increased not-COVID19–related mortality rates during the acute phases of the pandemic is of paramount importance for the present and for the future organization of the medical system.[31,32] In the Hospital San Matteo, we have a close and valid collaboration with the administration staff, and as soon as the pandemic level reduced, a regular surgical activity was resumed.

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Disclosure

The authors have no conflicts of interest to declare.

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Case Report

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Sudden Rupture of Abdominal Aortic Aneurysm in COVID19 Patients

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Abstract

Purpose: The purpose of the paper is to report the clinical outcomes of 4 patients with ruptured abdominal aortic aneurysm (AAA) during (3 patients) or immediately after (1 patient) moderate-severe SARS-CoV-2 infection. We discuss COVID-19-related mechanisms which could impact AAA rupture.

Patients and Methods: During the period of the pandemic (March 2020—May 2021), we performed surgery in 18 patients with ruptured AAA. Four patients were affected by moderate or severe SARS-CoV-2 infection (in 3 patients the rupture occurred during the infection and in 1 patient 3. months after discharge from the hospital). Two patients underwent open repair and 2 endovascular surgery.

Results: No postoperative mortality and no major complication occurred. Rapid growth of the AAA in comparison with a previous Duplex scan was evident in all 4 patients.

Conclusions: Family doctors and vascular surgeons should be aware about the possibility of AAA degeneration in patients with moderate-severe COVID19 infection. The risk is increased by steroid therapy which is essential in more advanced stages of the infection. In this clinical setting, endovascular repair is a valid choice.

Keywords

abdominal aortic aneurysm, endovascular aneurysm repair, COVID19, inflammation, mortality

Introduction

The recent COVID-19 pandemic has deeply changed medical practice. COVID-19 pandemic has brought to reduced visits and surgical procedures for patients with cardiovascular disease.[1,2] The general attitude of surgeons, not rarely forced by the patient desire to avoid operations in this period, was to modify therapeutic approaches.[3,4] Screening for abdominal aortic aneurysms (AAA) and follow-up of patients with AAA have been postponed. During the first lockdown, the U.K. National Joint Vascular Implementation Board suggested that in individuals with AAA measuring 5.5 to 6.0 cm elective surgery could be delayed for up to 12 months, and up to 6 months for those with AAA measuring 6.0 to 7.0 cm. The capacity to offer elective AAA repair has been severely reduced and the number of elective AAA repairs during the lockdown period fell dramatically.[5] Steroid therapy has been a cornerstone in the treatment of patients with moderate-severe COVID19 infection; steroid therapy may lead to deregulation of the immune system and of collagen metabolism which are well known risk factors for AAA degeneration.[6] COVID19 infection may influence AAA degeneration. The cytokine storm which accompanies viral and bacterial infections activates several metallic proteinases involved in elastin and collagen digestion with consequent weakening of the aneurismal wall. The cytokine storm is more evident in advanced COVID19 infection[7].

During the overwhelming pandemic period, epidemiological studies were inevitably inaccurate. It was not possible to determine the real prevalence of AAA rupture, directly or indirectly related with COVID19 infection.

We report the clinical outcomes of 4 patients with ruptured AAA which occurred during or soon after moderate-severe COVID19 infection, speculating about the possible

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Table 1. Clinical Characteristics of Patients With Abdominal Aortic Aneurysm Rupture During COVID-19 Pandemia.

	COVID-19 free (14 patients)	COVID-19 (4 patients)	
Age (range)	74.1 (54-87)	76.7 (67-81)	
Sex (M/F)	12/2	3/1	
Arterial hypertension	13/14 (92.8%)	4/4 (100%)	
CAD	4/14 (28.5%)	2/4 (50%)	
Diabetes	3/14 (21.4%)	1/4 (25%)	
COPD	6/14 (42.8%)	2/4 (50%)	
Renal failure	1/14 (7.1%)	1/4 (25%)	
Pulmonary embolism	1/14 (7.1%)		
Previous EVAR	0	2/4 (50%	
Type of surgery			
OPEN	9/14 (64.3%)	2/4 (50%)	
EVAR	5/14 (35.7%)	2/4 (50%)	
Mean serum CRP values at rupture (mg/dl)	2.1 (0.04-7.81)	5.7 (0.55-14.32)	P<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CRP, C Reactive Protein; EVAR, endovascular aortic repair.

correlations between AAA degeneration and SARS-CoV-2 infection.

Patients and Methods

This study was approved by our Institutional Review Board and informed consent was obtained from the patients or from their families. We analyzed the prospective data of patients treated for ruptured AAA from March 2020 to May 2021 at our Tertiary Care Hospital. Patients were divided into 2 groups: COVID-19-free group (14 patients) and COVID-19 group (4 patients). Analyzed data included age, sex, COVID-19 disease, other underlying chronic diseases like arterial hypertension (HTN), diabetes mellitus (DM), chronic renal disease (CRD), history of symptomatic coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), pulmonary embolism (PE), and previous vascular surgery. Serum C-reactive protein (CRP) values at the time of aneurysm rupture were recorded. We describe separately the 4 patients with AAA rupture potentially correlated with COVID19 infection.

Statistical Analysis

To prepare the database and perform descriptive analysis, the Statistical Package for Social Sciences software (SPSS Inc., Chicago, IL, USA) version 14.0 for Windows was used. The results are presented in tables. Categorical variables are expressed as frequencies and percentages. Continuous variables with normal distribution were expressed as mean and standard deviation. Student's *t* test and Chi square were used when appropriate.

Results

We observed 18 patients with ruptured AAA during the pandemic period March 2020 to May 2021. Four patients (Table 1) suffered from moderate-severe COVID-19 infection with fever and dyspnea. In all 4 COVID19 patients, the aneurysm showed a sudden increase in diameter (Table 2). In 3 of these 4 patients the maximum transverse diameter was less than 55 mm 6 months before rupture: Two patients had postponed duplex scan control due to organizational directives imposed during the pandemic. The remaining 2 patients were scheduled for endovascular treatment of an endo-leak, and they decided to postpone surgery during the pandemic, fearing the risk for contamination.

At the diagnosis of AAA rupture, these 4 patients had a statistically significant higher mean value of C Reactive Protein ($p<0.001$) in comparison with COVID-19 free patients (Table 1). Patients with COVID19 infection had more co-morbidities, even if these differences were not statically significant ($p>0.9$).

There was no mortality or major postoperative morbidity in the 4 COVID19 patients (2 open and 2 endovascular surgeries).

Four out of the 14 COVID19 free patients died in the postoperative period (1 out of 5 Endovascular Aneurysm Repair-[EVAR], 3 out of 9 open surgeries). The overall mean postoperative intensive care unit (ICU) hospital stay was 6.3 days (range: 0-38 days). We describe separately the 2 patients with primary rupture of the AAA (Patient 1,2) from the 2 patients who have had a previous endovascular repair (Patient 3,4).

Table 2. Characteristics of Four COVID19-Positive Patients With Sudden Increase in Diameter and Rupture of Abdominal Aortic Aneurysm.

	Age/sex	Characteristics AAA	Postponed US or surgery	Previous AAA maximum diameter (date)	Maximum diameter at rupture (date)	Growth rate (mm) and time	Type of surgery	Follow up
1	67/M	Fusiform, infrarenal (contained rupture)	Postponed US	47 mm (December 2019)	58 mm (November 2020)	11 mm/11 months	EVAR	Alive and well at 9 months
2	77/F	Fusiform, iuxtarenal (contrast extravasion at CT scan)	Postponed US	42 mm (November 2019 and October 2020)	53 mm (May 2021)	11 mm/17 months	OPEN	Alive and well at 4 months
3	82/M	Previous EVAR (rupture)	Waiting list/ patient postponed	68 mm (November 2020)	85 mm (December 2020)	17 mm/1 month	OPEN	Alive and well at 8 months
4	81/M	Previous EVAR (rupture pararenal AAA above EVAR)	Postponed US and severe COVID19	57 mm (October 2019)	80 mm (April 2020)	26 mm/7 months	EVAR	Alive and well at 12 months

Abbreviations: AAA, abdominal aortic aneurysm; EVAR, endovascular aortic repair; F, female; M, male; US, ultrasonography.

Case 1

A 67-year-old man was admitted with moderate COVID19 infection (confirmed by RT-PCR assay on rhino-pharyngeal swab-RPS) with fever, cough, and dyspnea in November 2020. His medical history was consistent with HTN, moderate CRD, CAD and infrarenal AAA with a 47-mm diameter at the last ultrasound (US) (December 2019). Due to respiratory distress, corticosteroid therapy (dexamethasone 4 mg/ 2 times per day) and oxygen (Venti mask, FiO2 = 30%) were administered. Five days after admission the patient complained abdominal pain. The patient was hemodynamically unstable with hypotension and tachycardia. Computed tomography (CT) angiography showed rupture of the AAA, contained in the retroperitoneum, with a maximum diameter of 58 mm. The patient underwent EVAR under local anesthesia. The postoperative course was uneventful, with normalization of clinical and serum inflammatory parameters within 7 days from surgery.

Case 2

A 77-year-old female was admitted for abdominal and back pain and hypotension in May 2021. Her medical history was consistent with HTN, CAD, and COPD. The patient was previously hospitalized in October 2020 for moderate COVID19 infection; treatment consisted in corticosteroid therapy (dexamethasone 4 mg/ 2 times per day) and oxygen (c-PAP). During this admission, the diameter of the aneurysm was unchanged in comparison with a Duplex scan performed 10 months before (4.2 cm). She was discharged in January 2021 in good general conditions. At the last admission in May 2021, a CT scan was immediately performed showing a 5.2 cm maximum transverse diameter of the AAA with extra-luminal contrast. The AAA showed a short, hostile neck and open surgery under general anesthesia was preferred. The postoperative course was uneventful (ICU stay 3 days).

Case 3

An 82-year-old man was admitted for moderate COVID19 infection (confirmed by RT-PCR assay on rhino-pharyngeal swab [RPS]) with fever and bilateral interstitial pneumonia in December 2020. His medical history was consistent with HTN and DM. Three years before the patient had EVAR for aorto-iliac aneurysm and he was followed up for type 2 endo-leak from the right hypogastric artery (sac diameter 68 mm in November 2020). The previous endovascular repair extended to the external iliac artery in both sides. He was scheduled for endo-leak embolization, but the procedure was postponed during the pandemic. Corticosteroid therapy (dexamethasone 4 mg/ 2 times per day) and oxygen (c-PAP) were administered. Ten days after admission the patient suddenly complained of abdominal pain. He was hemodynamically unstable with hypotension and tachycardia. Angio CT showed retroperitoneal contained rupture of the right common and internal iliac aneurysm with a maximum diameter of 85 mm. The AAA had a short neck. The patient underwent immediately open surgery under general anesthesia. Surgery consisted of removal of the endoprosthesis and aortic reconstruction with a bifurcated Dacron graft. The postoperative course was uneventful with a 3-days ICU stay. CT scan performed 4 months after surgery showed no complications of the aortic reconstruction.

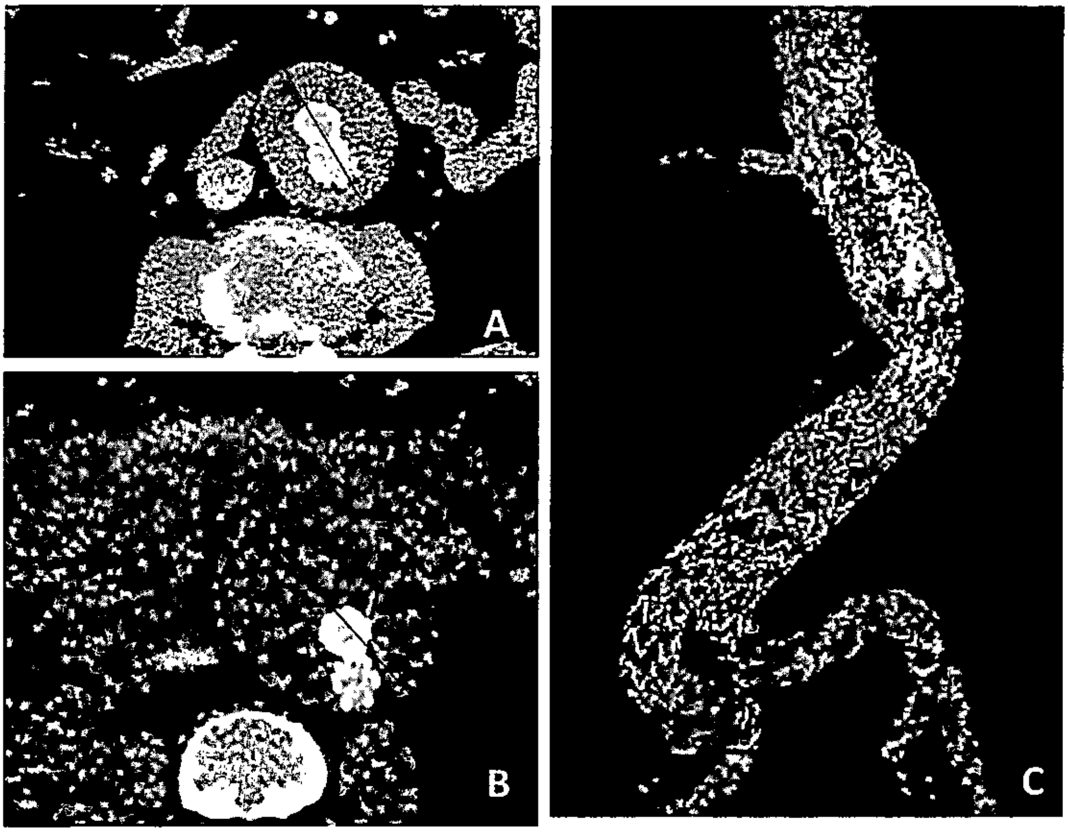

Figure 1. Patients N 4: CT scan shows abdominal aortic aneurysm sac with a diameter of 57 mm in October 2019 (A) and sudden increase of diameter (80 mm) in April 2020, (B) during admission for severe COVID-19 infection. The patient underwent immediate endovascular proximal aortic cuff placement with a double chimney (right renal and superior mesenteric arteries; the left renal artery was chronically occluded), (C): control CT scan control 12 months from surgery. CT, computerized tomography.

Case 4

An 81-year-old man underwent EVAR in 2018 for an AAA and he was followed up for type 2 endo-leak from lumbar arteries with serial U.S. scans (sac diameter 54 mm in October 2019). The patient was scheduled for endovascular treatment of the endo-leak, but he preferred to avoid admission during the pandemic. In April 2020, the patient was admitted for severe COVID-19 infection (confirmed by RT-PCR assay on rhino-pharyngeal swab [RPS]) with dyspnea and bilateral interstitial pneumonia. During hospitalization, the patient complained of sudden onset of abdominal and back pain; CT scan showed rupture of the AAA in the pararenal segment. The maximum transverse diameter of the aneurysm was 80 mm. The patient underwent endovascular proximal aortic cuff placement with a double chimney (right renal and superior mesenteric arteries; the left renal artery was chronically occluded). The postoperative course was uneventful with a 11-days ICU stay. No endo-leak and/or gutter were found at the 12-month CT scan follow-up (Figure 1).

Discussion

COVID-19 infection may increase directly or indirectly the risk for AAA rupture. "Indirect" potential influence of COVID19 infection on increased AAA rupture rate is related with the situation determined by the overwhelming severity of the pandemic. The pandemic has brought to several, unexpected consequences, including shortage of medical personnel and reluctance from patients to ask for medical help unless symptoms are severe. Admissions to hospitals have been reduced, avoiding visits for not-urgent conditions and deferrable elective surgeries. Often it is difficult to determine the difference between deferrable and not-deferrable procedures and urgent or not-urgent examinations in patients suffering from vascular diseases. During the COVID19 pandemic, it was not possible to perform an accurate and timely follow-up of patients with AAA and vascular procedures were reserved only for emergency conditions.[1–3]

To these "indirect" risk factors for AAA rupture we should add the conceptual possibility of direct effects of COVID19 infection on AAA degeneration.

The inflammatory storm associated with SARS-CoV-2 infection and the deregulation of the immune system secondary to steroid therapy have the potentials to trigger different mechanisms, traditionally considered risk factors for altered collagen metabolism and consequent aneurysm degeneration. Although intracranial and coronary arterial aneurysms have been described with a higher prevalence than usual in adults and children with COVID-19 infection,[7] the relationship between COVID19 infection and AAA degeneration has been rarely described.[8–13] Several COVID19-related mechanisms may impact AAA degeneration, including augmented angiotensin converting enzyme (ACE)-II-AT1 receptor activity, increased elastin and collagen digestion by enzymes triggered by viral spike proteins in ACE2-negative myeloid cells, hypoxemia related with thrombosis of micro vessels of the aneurismal wall[13–16] In general, viral and bacterial systemic infections are associated with high levels of inflammatory cytokines. High systemic levels of inflammatory cytokines are characteristic of the so-called cytokine storm, a condition in which inflammation, a physiological defense response to infection, become overwhelming, representing a damaging factor for the host. It has been shown that the so-called "cytokine storm" may be severe in advanced COVID19 infection. Systemic high levels of inflammatory cytokines in COVID19 severe infection have been found in many studies. High levels of interleukin-1β, interleukin-6, IP-10, tumor necrosis factor, interferon-γ, macrophage inflammatory protein 1α and 1β have been documented in patients with COVID19 infection and correlated with the severity and clinical outcome of the disease[13]. These cytokines may activate enzymes (metallic proteinases) able to digest collagen and elastin favoring degeneration of the aneurismal wall. Inflammasome NLRP3 levels are correlated with aneurysm degeneration and are correlated also with disease severity in COVID19 infection.[13–18]

Another important "indirect" risk factor is represented by steroids therapy, which represents a cornerstone in hospitalized COVID19 patients. Inhibition of excessive inflammation through timely administration of steroids in the early stage of the inflammatory cytokine storm effectively prevents the occurrence of ARDS and protects the functions of the organs. For patients with progressive deterioration of oxygenation indicators, rapid imaging progression, and excessive inflammatory response, steroids improve clinical outcome.[13,17,18] Corticosteroid therapy have a potential double, contrasting effect: steroids may attenuate the inflammatory reaction reducing the activation of metallic proteinases and AAA degeneration; at the same time, steroids may determine reduced host immunological response and may lead to altered collagen metabolism, which could facilitate AAA rupture.

In all 4 patients, preoperative CT scan showed a significant peri-aneurismal inflammatory reaction. The inflammatory reaction may be just a consequence of the sudden increase in diameter of the aneurysm with compression of the peri-aneurismal lymphatic and venous system and/or a reaction of blood in the retroperitoneal space.

Finally, we should underline the importance of endovascular surgery in this clinical setting. Endovascular surgery can be performed often under loco-regional anesthesia, avoiding tracheal intubation, with reduced postoperative pain and intensive care unit permanence. The possibility of pulmonary complications, which may predispose and aggravate COVID-19 contamination and clinical course, is therefore potentially reduced. Hospital stay is shorter. Endovascular procedures which have the same results of standard surgery, or even a marginal less effective result, represent a valid option. During the acute phase of the pandemic outbreaks, we have preferred to perform endovascular procedures whenever possible.

Conclusion

AAA rupture is one of the possible collateral problems resulting from patient reluctance to seek timely medical attention and from the difficulties to perform an adequate screening and follow-up in patients with AAA in the acute phases of the pandemic.[5,19,20] Furthermore, patients with AAA suffering or recovered from COVID19 infection should be monitored more carefully because the inflammatory storm secondary to SARS-CoV-2 infection may favor AAA rupture.[21,22]

Declaration of Conflicting Interests

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ELSEVIER

General Review

Intraoperative Cerebral Monitoring During Carotid Surgery: A Narrative Review

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Background: Intra-operative neurological monitoring (IONM) during carotid endarterectomy (CEA) aims to reduce neurological morbidity of surgery.
Objective: This narrative review analyses the role and results of different methods of IONM.
Methods: review articles on PUBMED and Cochrane Library, by searching key words related to IONM and CEA, from 2000 up to date.
Results: regional anesthesia in some centers represents the "gold standard". The most often used alternative techniques are: stump pressure, electroencephalogram, somatosensory evoked potentials, transcranical doppler ultrasound, near infrared spectroscopy and routine shunting. Every technique shows limitations. Regional anesthesia can make difficult prompt intubation when needed. Stump pressure shows a wide operative range. Electroencephalogram is unable to detect ischemia in sub-cortical regions of the brain. Somatosensory evoked potentials certainly demonstrate the presence of cerebral ischemia, but are no more specific or sensitive than the electroencephalogram. Transcranical doppler monitoring is undoubtedly operator-dependent and suffers from the limitations that the probe has to be placed relatively near to the surgical site and may impede the operator, especially if it needs constant adjustments; moreover, an acoustic window may not be found in 10% –20% of the subjects. Near infrared spectroscopy appears to have a high negative predictive value for cerebral ischemia, but has a poor positive predictive value and low specificity, because predominantly estimates venous oxygenation as this makes up about 80% of cerebral blood volume. The data on the use of Routine Shunting (RS) from RCTs are limited.
Conclusions: currently, with no clear consensus on monitoring technique, choice should be guided by local expertise and complication rates. With reflection, best practice may dictate that a standard technique is selected as suggested above and this remains the default position for individual practice. Nevertheless, current techniques for monitoring cerebral perfusion during CEA are associated with false negative and false positive resulting in inappropriate shunt insertion.

INTRODUCTION

Introduced in the early 1950s and improved during the following years, Carotid Endarterectomy (CEA) is a preventive treatment for patients who are at risk of embolic stroke from severe stenosis due to atherosclerotic plaques at the carotid bifurcation or internal carotid artery. The number of CEAs has increased since early 1990s until becoming the most frequently performed non cardiac vascular procedure in the United States. The indication for CEA has been proved by several large Randomized Controlled Trials (RCTs) both in asymptomatic

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and, even more clearly, in symptomatic patients.[1] CEA risk assessment includes several factors: high volume series and surgical skill appear to be strongly associated with the outcome, with a postoperative stroke-rate threshold conventionally fixed within 3%. Other factors such as age, sex, plaque complication, operative risk and the long-term benefit for CEA need to be taken into account, especially in the asymptomatic patients, so as serious co-morbidities, particularly cardiac and pulmonary diseases. The two major perioperative complications of CEA are myocardial infarction and cerebrovascular accident. Pooled data from the three major trials of CEA for symptomatic carotid stenosis show a global perioperative mortality rate of 1.1% due to operative stroke, with a global perioperative stroke rate of 7%. % [2] The Cochrane meta-analysis concerning regional versus general anesthesia pointed out a perioperative stroke rate of 3.4%. % [3] The Cochrane meta-analysis regarding both symptomatic and asymptomatic carotid stenosis show a cumulative disabling stroke – death rate of 2.9%. % [4] The threshold rate of perioperative stroke of 3% is mandatory to maintain the effectiveness of CEA to prevent stroke.

Many devices and methods have been used in the 50 years of CEA history in order to monitor the state of cerebral perfusion during and after the cross clamping, that is the crucial moment in which lays the highest probability of brain damage, because of cerebral haemodynamics destabilization. The aim of this manuscript is to analyze the role of different methods for Intra-Operative Neurological Monitoring (IONM). We reviewed articles on PUBMED and Cochrane Library, by searching and crossing key words related to IONM and CEA (carotid endarterectomy, cerebral monitoring, intraoperative cerebral ischemia, regional anesthesia, general anesthesia, stump pressure, somatosensory evoked potentials, transcranial Doppler, near infrared spectroscopy, shunt). We took into account only reviews, systematic reviews, meta-analysis and randomized controlled trials in the interval between 2000 and 2020.

INTRAOPERATIVE NEUROLOGICAL MONITORING DURING CEA: THE STATE OF THE ART

Anesthetic Management

CEA may be carried out under regional or general anesthesia. The impact of different anesthetic techniques on the outcome of CEA has been extensively studied. One of the main goals of anesthetic management of CEA is to prevent ischemic brain injury by correcting preoperative risk factors and by maintaining adequate cerebral perfusion and haemodynamic stability. Appropriate monitoring allows prompt intervention to prevent potentially catastrophic neurological events. Many years has passed since debate started between regional (RA) and general anesthesia (GA) supporters.

The prime advantage of RA over GA is the viability of a continuous neurologic check up of the patient during the intervention. Surgeons and anesthesiologists remain in constant verbal contact with the patient, especially after cross-clamping. This should consist of more than simply asking the patients if they feel alright. It is appropriate to check frequently that the patient is oriented in time and place and can perform simple mental tasks such as counting backwards. The patient should be asked to demonstrate that they can move the side of their body contralateral to surgery. If the patient's hand is under the drapes, a squeaky toy or a fluid filled bag connected to a pressure transducer may be placed in their hand before surgery and they can be asked to squeeze this regularly. If the patient becomes confused and restless, or stops responding to commands, or simply ceases to communicate, these are all signs of cerebral ischemia and shunt insertion is indicated. The decision to shunt is more difficult when the patient is under GA: in this case physicians have to rely on monitor techniques.[5]

While the use of RA has the merit of allowing direct neurological monitoring of the conscious patient, GA also has laudable qualities. Patients can find CEA under RA stressful: they must lie still with their head turned to one side for 90 min or more and the positioning of the drapes may be profoundly unpleasant for a claustrophobic patient. The access to the patient airway during surgery can be difficult with the head turned to one side. Watts et al.[6] analyzed a total of 263 CEAs under RA and 285 CEA under GA performed during a 30-months period. The RA group was associated with a lower incidence of shunt placement, operative time, and perioperative hemodynamic instability compared to the GA group, but no differences in neurologic complications or mortality were found between the 2 groups. Hyperlipidemia was a risk factor for postoperative morbidity in both the RA and GA groups, while age greater than 75 years was associated with increased overall morbidity in the GA group but not the RA group. Jacques et al.[7] have found retrospectively in their

72 CEAs series a significative association of RA with less systolic blood pressure variation and less frequent requirement of vasopressors. Conversely there was no significant difference between groups in hypotension or hypertension episodes seen in the postoperative recovery room. Weber et al.[8] detected a significant increase in serum levels of the neurobiochemical marker S100 beta protein after CEA performed under GA compared to RA, with a corresponding, significative, postoperative neurocognitive performance decrease. Evidence of efficacy of mild hypothermia is absent for CEA.[9]

Eventually no solid evidence has emerged from literature in favor of one or the other techniques. In his review Guay concluded that the number of patients included in RCTs or even in prospective studies is too low to allow any conclusions on the differences in outcome between the 2 anesthetic techniques and better outcomes for RA are suggested when results from retrospective studies are added.[10] The 2008 Cochrane review[3] shows the same conclusion: there is insufficient evidence from RCTs comparing carotid endarterectomy performed under regional and general anesthetic. Non-randomized studies suggest potential benefits with the use of regional anesthetic, but these studies may be biased. AbuRahma argues that prior to the GALA trial, there was insufficient evidence from RCTs comparing CEA under RA versus GA to support the superiority of either technique in reducing major perioperative events, i.e. stroke, myocardial infarction or death.[11] The GALA trial is the first and only multicentre RCT that compares RA versus GA during CEA and its conclusions are clear: "We have not shown a definite difference in outcomes between general and local anesthesia for carotid surgery. The anesthesiologist and surgeon, in consultation with the patient, should decide which anaesthetic technique to use on an individual basis."[12]

Schechter et al. in their recent cohort study of patients undergoing CEA have found that the choice of GA versus RA does not appear to impact postoperative patient outcome. In particular, there was no significant difference between the 2 groups in either composite 30-day postoperative stroke/myocardial infarction/death rate or in the incidence of other complications. However, they only showed that RA may have potential cost advantages compared to GA. Specifically, they observed that (1) combined anesthesia and operative times were approximately 30 minutes shorter for RA than for GA, and that (2) RA patients were more likely to be discharged on the first postoperative day after CEA than GA patients.[13] Actually, none of the IONM can detect cerebral ischemia to the same extent as regional anesthesia (Table I).[14–18]

Stump Pressure

Once the common and external carotid arteries are clamped, the pressure measured in the internal carotid artery reflects the perfusion pressure transmitted around the circle of Willis and the pressure generated by collateral vessels: this pressure is known as "stump pressure" (SP). A certain critical SP value has never been determined for ischemia threshold and a range of values between 25 and 70 mmHg has been suggested and used.[19–20] Nevertheless, we have to consider the effects of anesthetic agents upon the cerebral vasculature so it cannot be assumed that pressure thresholds determined in awake patients also apply to patients undergoing CEA under GA. Hans et al. in a prospective clinical trial performed in awake patients, demonstrated that SP has a low false positive rate (1.0%), but a high false negative rate (40.6%) for detecting significant ischemia.[19] On the contrary, Jacob et al identified a value of $\geq$ 45 mmHg of SP as a reliable predictor of adequate cerebral perfusion during 1135 consecutive CEAs performed under GA. They concluded that the percentage of indwelling shunts utilized in this series was not significantly different from ones using more expensive and sophisticated techniques of monitoring.[20] In the same way Calligaro et al. in a series of 474 CEAs performed in awake patients, conclude that a carotid artery SP >40 mmHg systolic may be considered as an equally reliable but more cost-effective method to predict the need for carotid shunting during CEA under GA compared with EEG monitoring, with an equivalent false-negative rate (1.0%).[21] Belardi et al. in a series of 147 CEAs performed under RA, found that none of the hemodynamic SP criteria resulted absolutely reliable in predicting the need for carotid shunt.[22] SP measuring has also been used as a predictor of post CEA hyperperfusion syndrome: patients with SP lower than 40 mmHg are significantly more likely to experience postoperative hyperperfusion.[23] Recently AbuRahma et al.[24] have reported the results of a prospective RCTs of routine versus selective shunting in CEA based on SP (threshold for systolic SP 40 mmHg) involving 200 patients under GA: the perioperative stroke rate was 0% for the group of routine shunting and 2% for the group of selective shunting.

Table I. Results for all cerebral intraoperative monitoring system

Type	Sensitivity (95% CI)	Specificity (95% CI)
TCD	0.81 (0.69 – 0.91)	0.92 (0.89 – 0.94)
Stump Pressure	0.75 (0.69 – 0.81)	0.88 (0.86 – 0.89)
Stump 25 mmHg	0.67 (0.57 – 0.76)	0.85 (0.83 – 0.88)
Stump 40mmHg	0.82 (0.73 – 0.89)	0.90 (0.88 – 0.92)
EEG	0.70 (0.58 – 0.80)	0.96 (0.94 – 0.97)
Evoked Potentials	0.84 (0.66 – 0.95)	0.78 (0.69 – 0.86)
NIRS	0.74 (0.54 – 0.89)	0.82 (0.76 – 0.88)

95% CI, 95% confidence interval; TCD, trans-cranial Doppler; EEG, electroencephalography; NIRS, near infrared spectroscopy.

Electroencephalography

Both the raw and the processed electroencephalography (EEG) have been used for IONM during CEA. EEG detects spontaneous electrical activity of neurons in the brain cortex. Normal cerebral blood flow is between 45 and 55 mL/100 g of brain tissue/min, and alteration of the EEG signal occurs when the flow rate falls below 12 –15 mL/100g/min. There is no doubt that EEG is affected by cerebral ischemia: ischemia affecting the cortex shows up as ipsilateral waves slowing, attenuation or both. Unfortunately EEG has several limitations when applied during CEA because, though effective to detect ischemia in the cerebral cortex, it is unable to do so in sub-cortical regions of the brain. For this reason it has low specificity and its sensitivity is reduced in patients with active neurological deficit, as in recent stroke. Even the recent analysis algorithms seems to be ineffective to detect deep layer ischemia during CEA.[25] Tan et al.[26] in a series of 242 CEA performed with routine EEG monitoring and selective shunt placement, sustain a low risk of perioperative stroke (0.8%). Predictors of significant intraoperative EEG changes were anatomic factors including degree of contralateral carotid artery disease and moderate ipsilateral carotid artery stenosis (50% – 79%). This study suggests that high-grade contralateral disease and moderate ipsilateral carotid stenosis are associated with cerebral ischemia resulting in EEG changes and should prompt consideration for nonselective shunting. Hans et al. match SP and EEG monitoring in 314 consecutive CEAs under RA: 10% of patients required a shunt placement during CEA. Shunt placement was necessary in 56.8% of patients with SP less than 40 mm Hg. EEG identified cerebral ischemia in only 59.4% of patients needing shunt placement, with a false-positive rate of 1.0% and a false-negative rate of 40.6%. They concluded that both SP and EEG as a guide to shunt placement have poor sensitivity and IONM of the awake patients under RA is the most sensitive and specific method to identify patients requiring shunt placement.[19] Laman el al.[27] sustain that 4-channel EEG monitoring during CEA has to be adjusted to the anesthetic regimen used: spectral edge frequencies parameters are superior to band power parameters when isoflurane anesthesia is used, but are as effective as the delta band power parameter when propofol anesthesia is used. Reuter et al.[28] compared SP with a threshold of 40 mmHg and EEG in a series of 196 patients: using EEG monitoring they observed an unusual high rate of neurologic complication of 9%, whereas of 1% using SP. Even if an overall neurologic complication rate of 6% is exceedingly high, this study stresses the limits of EEG in CEA monitoring. On the other hand, some authors support the routine use of EEG monitoring during CEA: Melgar et al in a series of 102 CEAs reported a 1% perioperative stroke rate and recommend a "selective" induced arterial hypertension and etomidate cerebral protection as a good alternative for shunting.[29]

Somatosensory Evoked Potentials

Somatosensory evoked potentials (SSEPs) offer theoretical advantages over the EEG for cerebral ischemia monitoring. This type of monitoring examines not only the cortex but the deeper structures of the brain. Stimulation from a peripheral nerve passes through first- and second-order neurones and brainstem synapses before evoking a response in the somatosensory cortex. SSEPs certainly demonstrate the presence of cerebral ischemia, but are no more specific or sensitive than the EEG. However, they may be superior in patients whose baseline EEG is not easily interpretable because of a previous stroke. It should be kept in mind that the volatile anesthetic agents can reduce the amplitude of SSEPs. An evoked potential amplitude reduction >50% or a decrease in latency time >10% is considered pathologic. Measurements are made every minute. The SSEPs changes can be qualitatively classified as mild, moderate, or severe and three types of decisions can be taken as function of SSEPs monitoring: head repositioning, systemic blood pressure restoration if the modification occurred when the patient had a low blood pressure, or installation of a shunt in case of persistent moderate or severe alterations despite a good systemic blood pressure. Astarci et al. found that the severity of ipsilateral carotid stenosis influence significantly the evolution of the SSEPs response: the greater the stenosis, the lower is the SSEPs modifications. The severity of contralateral carotid stenosis has also a significant influence: the greater the contralateral stenosis, the greater were the SSEPs modifications.[30] In their experience on 100 CEAs in GA comparing SSEPs and SP, Baton et al concluded that SSEPs appeared to provide good results in terms of patient and surgeon comfort during the procedure and freedom from neurologic deficit. They recommend selective shunting on the basis of intraoperative electrophysiologic findings.[31] In an experience of 500 cases of neurophysiological monitoring in CEA, Stejskal et al.[32] found that a reduction of more than 50% in the amplitude of the thalamo-cortical SSEPs complex N20/P25 proved to be the most reliable warning danger of ischemia.

Transcranial Doppler

Transcranial Doppler (TCD) relies on the fact that the thin petrous temporal bone provides an acoustic window that allows ultrasound visualization of the Middle Cerebral Artery (MCA). A probe is placed on the petrous temple bone and a skilled operator is able to detect the Doppler signal generated by blood flow in the MCA. It may be also helpful in discriminating between hemodynamic and embolic neurological events, as it is also efficient in detecting the occurrence of emboli. Unfortunately, TCD monitoring is undoubtedly operator-dependent. It suffers from the limitations that the probe has to be placed relatively near to the surgical site and may impede the operator, especially if it needs constant adjustments, and an acoustic window may not be found in 10-20% of the subjects. In a large 2 centres experience involving 1058 patients, Ackerstaff et al. report that intraoperative monitoring with TCD can identify patients at an increased risk for perioperative stroke, considering four TCD independent variables. They consisted of a) embolism during the dissection and b) wound closure phases of surgery, c) a drop of ≥90% in the MCA flow velocity at cross-clamping, and d) an increase of ≥100% in the pulsatility index at clamp release.[33] This study provides specific criteria for surgeons to detect brain ischemia during CEAs, but it is retrospective and a neurologist was consulted only in patients with possible cerebral deficit, raising the possibility that some strokes were missed.

In the last years, TCD allowed to outline the role of microembolization in cerebral damage during CEA. In a series of 163 CEAs, Ogasawara et al.[34] demonstrated that the combination of low MCA mean blood flow velocity (≤ 28 cm/sec) and more than 10 microembolic signals during carotid dissection resulted in improved specificity and positive predictive value for the development of new postoperative neurological deficits when compared with either criterion used alone. Comparing EEG and TCD, Dunne et al[35] found the average MCA velocity drop on cross clamping was 46 ± 12.1%, expressed as a percentage of the individual's 24-hr pre-operative value. Clamping ischemia developed in 6 cases of 32 CEAs (18.8%) of which 3 (9.4%) demonstrated TCD changes only, and 3 demonstrated both TCD and EEG changes (9.4%). The average increase in MCA velocity at 60–120 min postarteriotomy, was 18 ± 17.5% and 6 cases developed hyperperfusion. Postoperative emboli were seen in 88% of cases with 31% of patients demonstrating more than 50 embolic loads per hour.

In their review about the use of TCD in detecting intraoperative signals for postoperative cognitive function, Martin et al.[36] concluded that the literature remains to this day largely undecided on the link between high-intensity transient signals and cognitive impairment after surgery, with most studies being underpowered to show a relationship. Althought the cognitive effects of high-intensity transient signals may be difficult to detect, subclinical microemboli present potential harm, which may be modifiable. Belardi et al., in a series of 87 CEAs using TCD associated with acetazolamide test to calculate cerebrovascular reactivity, did not prove this is a valid preoperative test for predicting cerebral ischemia caused by carotid clamping.[37]

Near Infrared Spectroscopy

Near Infrared Spectroscopy (NIrS) assesses changes in cerebral blood flow by measuring Regional Cerebral Oxygenation (RCO_2), which is a composite measurement of arterial, venous and capillary haemoglobin oxygenation. NIrS predominantly estimates venous oxygenation as this makes up about 80% of cerebral blood volume. NIrS has several advantages when compared with EEG and TCD as it is easy to use, the displayed values are simple to interpret, it is low cost, and is non-invasive and portable. In patients undergoing CEA, carotid cross-clamping produces a significant decrease in ipsilateral RCO_2 values compared with preclamp and postclamp values. Unfortunately, this change is not consistently related to other measures of cerebral blood flow. NIrS appears to have a high negative predictive value for cerebral ischemia, but has a poor positive predictive value and low specificity. NIrS is of limited value in CEA as the sensors are placed over the frontal lobes and are therefore not suitable placed for picking up reductions in the parietal lobes that are most at risk of ischemia during CEA. The signal may also be contaminated by ambient light and by blood flow in skin and muscle. There is also considerable variation in the values obtained with different NIrS monitors and even in dead subjects an average RCO_2 value of 51% is obtained, compared with 68% in normal controlled subjects indicating that there is no well-defined biological zero.[5] The study of Mille et al of 2004 on 594 CEAs,[38] points out that a relative decrease in RCO_2 of <20% from preclamp to early cross clamp value has a high negative predictive value, hence if RCO_2 does not decrease more than 20%, ischemia by hypoperfusion is unlikely and a shunt should not be necessary. Moreover, a relative decrease >20% may not always indicate intraoperative neurological complications. In their recent review, Pennekamp et al.[39] found that NIrS values correlated well with TCD and EEG values indicating ischemia. However, a threshold neither for postoperative cerebral ischemia nor for selective shunting can be determined since shunting criteria varied considerably across studies. The evidence suggesting that NIrS is useful in predicting cerebral hyperperfusion syndrome is modest. NIrS has been compared with other methods of cerebral monitoring during CEA, but results are discordant. Moritz el al.[40] reported that TCD, NIrS and SP measurement provide similar accuracy for the detection of cerebral ischemia during CEA in a small series of 48 patients operated in RA. Others small studies express a favorable opinion for NIrS: Rigamonti el al.[41] showed a good clinical and EEG correlation in 50 CEAs in RA, Pugliese et al.[42] observed a greater reliability with the NIrS than with TCD in 40 patients enrolled for a prospective study and operated in RA, and eventually Lee et al.[43] reported a significant correlation between RCO_2 changes on the operated side and carotid SP such that a larger change in RCO_2 due to cross-clamping was strongly and significantly correlated with lower carotid SP. Conversely, a larger study on 323 CEAs performed in GA comparing NIrS,[44] EEG and SSEPs concluded that relying on RCO_2 alone for selective shunting is potentially dangerous and might led to intraoperative ischemic strokes in seven patients and the unnecessary use of shunts in at least 16 patients in the series. Compared with EEG/SSEPs, they found for NIrS a sensibility of 68%, a specificity of 94%, a positive predictive value of 47% and a negative predictive value of 98%. Therefore, in these authors opinion, the use of RCO_2 adds nothing to the information already provided by EEG and SSEPs in determining when to place a shunt during CEA. NIrS has been used also to determine the amplitude of early post-ischemic hyperemia, which is related with the duration and intensity of prior ischemic insult.[45]

Routine Shunting

The data on the use of Routine Shunting (RS) from RCTs are limited. There are promising but non-significant trends favoring a reduction in both deaths and strokes within 30 days of surgery with RS, but these are based on very small numbers of outcome events. There is still insufficient evidence from RCTs to support the use of RS in CEA, although a clinically important benefit from RS cannot be excluded. Conversely there is no reliable evidence at present to support the use of Selective Shunting (SS), even considering the possible complications, as dissection, embolism, thrombosis and inefficacy due to carotid tortuosity. In those who wish to use SS in patients under GA, there is again little evidence to support the use of one form of monitoring over another. The use of EEG monitoring combined with SP may reduce the number of shunts required without increasing the stroke rate but much more data are required to prove this.[46]

Goodney et al. in their recent series of 353 primary CEAs performed in patients with controlateral carotid occlusion (CCO) found that the risk of 30-day stroke or death was higher in patients with CCO than in patients without CCO. Further, their data indicate that surgeons who placed shunts routinely had low rates of 30-day stroke or death when they placed a shunt, and surgeons who did not routinely use a shunt and performed CEA in the setting of CCO without a shunt also had low rates of 30-day stroke or death, but only when they did not place a shunt. The highest risk-adjusted chance of stroke or death occurred when surgeons who did not typically utilize a shunt placed a shunt during CEA in the setting of a CCO. Therefore, surgeons should consider their own practice pattern in shunt utilization pre-operatively when faced with a patient who may require shunt placement.[47]

Other Techniques

Jugular venous bulb oxygen saturation has been tried as a surrogate measure of cerebral perfusion, but as with NIRS it has low sensitivity and positive predictive value for cerebral ischaemia detection.[48]

Xenon-133 washout has also been investigated. It relies on the injection of radioactive Xenon-133 into the ipsilateral carotid artery and calculation of flow through scintillography of the head. This technique is very expensive, requires bulky equipment to be placed over the operative side of the head, needs considerable expertise to interpret the results and has a low specificity.

During ICA clamping for shunt placement, ipsilateral and contralateral *conjunctival capillary perfusion* is significantly decreased, but it was completely restored after reperfusion with carotid shunting. Reclamping of the ICA for shunt removal caused microvascular dysfunction, which is significantly less pronounced than that observed during the first clamping. The individual degree of ICA stenosis is inversely correlated with the ipsilateral and contralateral decrease in conjunctival functional capillary density during the first ICA clamping. These results suggest adaptive mechanisms of capillary perfusion with increasing stenosis and development of collateral compensatory circulation in the vascular region of the human ICA. Conjunctival orthogonal polarized spectral imaging during unilateral ICA reconstruction enables continuous noninvasive analysis of bilateral conjunctival microcirculation in the terminal region of the ICA and enables monitoring for efficient carotid shunt perfusion during and after endarterectomy.[49]

Implementation of an artificial neuronal network to predict shunt necessity in CEA in a series of 850 patients basing on preoperative and intraoperative parameters has shown an accuracy of 96% and 91% respectively, where the regression analysis showed an accuracy of 98% and 96%, respectively.[50]

CONCLUSIONS

After a literature analysis, it is difficult to draw a definitive conclusion regarding the IONM method to be used in everyday practice during CEA. The aforementioned techniques for monitoring IONM during CEA are all associated with false negative and false positive results that may lead to unnecessary shunt insertion with its associated complications, or to a false sense of security in face of ischemia. Shunt insertion carries a 1%–3% risk of embolism or dissection and is therefore not routine surgical practice.[42] There are surgeons who insert shunts for every CEA they perform and they would argue that complications related to shunt insertion arise when they are inserted in a rush in response to monitoring suggestive of ischemia. Should shunting be routine? This is largely an individual surgeon's decision and results in the surgical literature do not favour either selective or routine shunt placement techniques. The ideal monitor to detect cerebral ischemia should be highly specific and sensitive, clinically easy to use and unobtrusive when attached to a patient, and it has yet to be found. The ongoing debate between those anaesthetists and surgeons who favour regional anaesthetic techniques versus those who favour general anaesthesia shows no signs of being settled soon, and a major part of this argument is the ability to detect and deal with cerebral ischemia in a prompt manner. There are practitioners who argue that continuous clinical assessment of the neurological status of an awake patient is the only way to reliably detect significant cerebral ischemia during CEA, but there is no objective evidence to support this view. The best cerebral function monitoring technique remains unclear due to the lack of RCTs with sufficient statistical power. At present there is no evidence suggesting that any anesthetic or monitoring technique for CEA is superior either in global or specific population of patients. Until robust evidence will arise from literature, practice will vary according to single practitioners' competence and preference. Choosing a specific monitoring technique depends on the internal organization of every single surgical facility and on a concerted choice by the surgeon and anesthesiologist.

Ethics Approval is not required by our local Committee.

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Acute Thrombosis of Lower Limbs Arteries in the Acute Phase and After Recovery From COVID19

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In advanced stages of COVID19 infection dysfunctional alveolar-capillary oxygen transmission and impaired oxygen diffusion capacity are characteristic features. In severe COVID-19 infection, activation of coagulation and consumption of clotting factors occur.[1,2] Patients who develop acute arterial thrombosis during COVID19 infection are considered in a critical condition, in which thrombosis represents the iceberg of a general hemostatic derangement.[1–3] The aim of our study was to analyze the clinical outcome of 9 patients who developed lower limb arteries thrombosis, during the COVID19 pandemic. The 9 patients included in the study were admitted to our hospital (a tertiary referral regional center) during the COVID19 pandemic in the city Pavia (Lombardia). During the months of March and April 2020, we admitted 942 patients with major symptoms from COVID19 in our hospital. The overall mortality in the city of Pavia during these 2 months of acute SARS-Cov-2 infection increased by 140% in comparison to the mortality rates in the same periods of the previous 5 years.[2] Out of 4586 deaths, 1225 (27%) were related to COVID19 infection according to the precise definition of the World Health Organization[1,2]), for COVID19 related mortality of 181/100,000. Out of the 942 patients with severe symptoms admitted during the acute phase of the pandemic, 32 patients developed deep vein thrombosis (3.4%) and 6 patients (0.6%) were admitted with acute arterial thrombosis of the lower limb arteries. Since the end of May, there has been a steady and significant decrease in contamination and mortality rates in Italy and Pavia. All the 9 patients with acute arterial thrombosis presented severe ischemia, with absent distal pulses, no pedal Doppler signals, and impending limb loss.

Six patients developed acute lower limbs ischemia during the acute SARS-CoV-2 infection and 3 other after recovering from COVID19 with complete normalization of clinical and hemostatic parameters and with multiple negative swab tests (the acute thrombosis occurred after a mean of 99 days from the initial diagnosis of SARS-CoV-2 infection and after a mean of 40 days from 2 consecutive negative oral-pharyngeal swab tests for COVID 19). The 3 patients who developed acute thrombosis after recovering from COVID19 infection were treated at home for the initial infection with generic anti-inflammatory drugs and antibiotics because symptoms were not severe.

Supplement Table 1, http://links.lww.com/SLA/C824 shows the clinical characteristics of the patients who developed acute arterial thrombosis in the acute phase of the infection (patient 1–6). All patients showed altered hemostatic and inflammatory parameters before thrombectomy. Thrombectomy was successful in all 6 patients with return of pedal pulses and good distal perfusion. Successful thrombectomy was confirmed by intraoperative angiography (3 patients had also endovascular stenting) and by Doppler analysis. Two patients suffered from early rethrombosis 24 hours after the initial successful thrombectomy. A new thrombectomy was performed with initial clinical success, followed again by rethrombosis. In these 2 patients, the initial, apparently successful thrombectomy was not followed by normalization of hemostatic and inflammatory parameters. One of these 2 patients (patient 6) had clinical and hematologic parameters suggesting disseminated intravascular coagulation. In the other 4 patients, thrombectomy was successful (mean follow up 6 months), with postoperative normalization of hemostatic and inflammatory parameters. In 3 patients, percutaneous transluminal angioplasty was added to dilate minor stenoses of the popliteal and iliac arteries. In the other 3 patients, there was no evidence of atherosclerosis clinically, at angiography and surgery (soft arteries). No potential embolic source could be identified and none of the patients suffered from atrial fibrillation.

Moreover, Supplement Table 1, http://links.lww.com/SLA/C824 shows the clinical characteristics of the 3 patients (patients 7, 8, 9) who developed acute arterial thrombosis after clinical resolution of COVID19. There were no significant alterations of hemostatic and inflammatory parameters before surgery. Thrombectomy was successful without recurrence at a mean follow-up of 4 months. One patient had history of cardiovascular events (endovascular abdominal aortic aneurysm repair). In the other 2 patients, there was no evidence of atherosclerosis clinically, at angiography and surgery (soft arteries).

All 9 patients received full anticoagulation before and after surgery. The 7 patients who had successful thrombectomy had long-term oral anticoagulation and all are in good general conditions, with distal pedal pulses, good Doppler pedal signals, and no symptoms referable to poor distal perfusion at a mean follow-up of 5 months.

It is probable that patients with acute arterial thrombosis are at risk for rethrombosis if significant hemostatic derangement (D-Dimers levels above 15,000) is present and there is no early normalization of hemostatic parameters after successful thrombectomy. Preoperative high D-Dimers levels (above 15,000) are associated with a generalized hemostatic derangement with severe functional endothelial damage with high probability of re thrombosis despite initial successful thrombectomy.[5–10] For patients who had successful

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thrombectomy during the acute phase of COVID19 pandemic a close follow-up and long-term anticoagulation seem appropriate. The 3 patients who developed acute thrombosis after apparently clinical resolution of COVID19 infection did not show any significant hematologic abnormality, except for a minor, specific, persistent increase in serum LDH levels. Despite successful treatment of initial COVID19, there is the possibility of acute thrombosis during follow-up, despite normalization of hemostatic and inflammatory parameters. The real prevalence of this event is difficult to determine because the three patients were initially treated at home for the COVID19. The clinical picture of the last 3 patients supports the hypothesis that the integrity and functional characteristics of the endothelial cells, initially deranged during the viral infection may persist for a longer period, despite apparent normalization of hemostatic parameters. This possibility may also explain other long-term complications of patients who recovered from COVID19.[4,5] These observations may lead to the conclusion that antiplatelet and anti-inflammatory therapy is a wise choice in patients recovering from COVID19, even if we do not have enough data neither to support this assumption nor to determine the duration of therapy, which should inevitably be personalized according to the clinical characteristics of each patient.

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Acute arterial and deep venous thromboembolism in COVID-19 patients: Risk factors and personalized therapy

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ABSTRACT

Background: The Lombardy region suffered severely during the acute phase of the coronavirus disease 2019 outbreak in Italy (Mar–Apr 2020) with 16,000 diagnosed coronavirus disease 2019–related deaths (49% of the total coronavirus disease 2019–related deaths in Italy). In the area surrounding Pavia during the critical stage of the outbreak (Mar–Apr 2020), 1,225 of the documented 4,200 deaths were related to coronavirus disease 2019 infection, with a mortality rate of 181/100,000 inhabitants and an increase in deaths of 138% compared with the same period during previous years. Our aim was to report the experience of the Department of Vascular Surgery of Pavia (Lombardy, Italy), including the lessons learned and future perspectives regarding the management of coronavirus disease 2019 patients who developed severe acute ischemia with impending lower limb loss or deep vein thrombosis.
Materials and Methods: We carried out a retrospective data collection of coronavirus disease 2019 patients with severe acute ischemia of the lower limbs or deep vein thrombosis, which we observed in our department during the period March 1, 2020, to April 30, 2020. Primary outcomes of the analysis were postoperative mortality for all patients and amputation rates only in those coronavirus disease 2019 patients suffering from acute lower limb ischemia. Secondary outcomes were the prevalence of the disease among admitted coronavirus disease 2019 patients, and any possible correlation among inflammatory parameters, thrombolytic status, and the presence of acute ischemia or deep vein thrombosis.
Results: We observed 38 patients (28 male) with severe coronavirus disease 2019 infection (6 with lower limb arterial thrombosis and 32 with deep vein thrombosis). The median patient age was 64 years (range 30–94 y). In the arterial group, 3 had thrombosis on plaque and 3 on healthy arteries ("simple" arterial thrombosis). All underwent operative or hybrid (open/endo) revascularization; 1 patient died from major organ failure and 1 patient underwent major amputation. In the deep vein thrombosis group, 9 (28%) patients died from major organ failure, despite aggressive medical therapy. In patients with simple arterial thrombosis and those with deep vein thrombosis, we observed a decrease in inflammatory parameters (C-reactive protein) and in D-dimer and fibrinogen after aggressive therapy ($P < .001$).
Conclusion: Our study confirms that critically ill, coronavirus disease 2019 patients who develop arterial and deep vein thrombosis have a high risk of mortality, but, if treated properly, there is an improvement in overall survival, especially in patients of 60 years of age or younger.

Introduction

As of July 9, 2020, more than 34,000 deaths from coronavirus disease 2019 (COVID-19) were identified in Italy. The critical phase

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of the outbreak seemed to be in Italy, as well as in other European countries (eg, Spain and England). The Lombardy region suffered severely during the acute phase of the outbreak (Mar–Apr 2020), with 16,000 diagnosed COVID-19–related deaths (49% of all COVID-19–related deaths in Italy). During the acute phase of the outbreak (Mar–Apr), in the area surrounding Pavia, 1,225 of the documented 4,200 deaths were related to COVID-19 infection, with a mortality rate of 181/100,000 inhabitants and an increase in deaths of 138% in comparison with the same period during previous years[1] The mean age of patients dying from the disease was 81 y, and 70% were older than 75 y. The median age of the patients who died was 20 years older than the median age of infected patients (61 y). Mortality was greater in patients with associated cardiac morbidities (arterial hypertension in 66% of patients who died, coronary artery disease in 28%, atrial fibrillation in 23%, and congestive heart failure in 16%), renal failure (20% of patients), and cancer (16% of patients). The mortality rate increased from 14% in patients with only 1 comorbidity to 61% in patients with 3 or more comorbidities.[1] In the elderly population, the simultaneous occurrence of the COVID-19 infection and the presence of diffuse atherosclerotic disease were of course a common clinical scenario, specifically in the Lombardy region, where the outbreak was severe and overwhelming and a high proportion of the population is elderly.[2,3] Since the end of May 2020, there has been a steady and marked decrease in rates of infection and mortality in Pavia and in Italy as a whole.

The high mortality rate in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can also be attributed to the non-respiratory complications of COVID-19, although the mechanism by which the virus migrates to these other locations remains poorly understood. Furthermore, COVID-19 predisposes patients to both venous and arterial thromboembolic disease because of high-grade inflammation, hypoxia, immobilization, and diffuse intravascular coagulation, but direct damage to the endothelium by the virus has not yet been demonstrated.[4]

The aim of our analysis was to report our experience in the Department of Vascular Surgery of Pavia (Lombardy, Italy), focusing on the lessons learned and future perspectives regarding the management of COVID-19 patients who developed severe acute ischemia with impending lower limb loss or deep vein thrombosis (DVT).

Material and Methods

A general lockdown with strict social isolation rules for the general population and health care workers was established in Italy in March 2020, when the high spread/contagiousness and virulence of the virus became apparent. Unfortunately, the dangerous characteristics of the virus were immediately evident attributable to not only the high number of admissions of infected patients in poor general condition but also to an unexpectedly inadequate health care system overwhelmed with COVID-19 cases. This pandemic exposed the poor capacity with respect to hospital and intensive care unit beds and to workforces worldwide, not only in Italy. After initial organizational problems, hospitals were divided into sections devoted to COVID-19 patients only. Admissions to hospitals were decreased, thereby precluding non-urgent conditions and deferrable elective operations.[5-7] Our activity as vascular surgeons had been reduced dramatically, and we were required to perform other duties in the pneumology departments and emergency departments for COVID-19–positive patients, in addition to our consultancy activities. Table I presents the number of vascular procedures performed in our department during the lockdown period in comparison with the year 2019. Only those emergency procedures which could not be deferred and could not be transported to another COVID-free hospital were performed.

Table I
Operative vascular procedures at the Vascular Surgery Department of Fondazione IRCCS Policlinico San Matteo of Pavia, Italy, during phase 1 of the COVID versus the same period of 2019

	March 1–April 30, 2020		March 1–April 30, 2019	
	Emergency	Elective	Emergency	Elective
AAA				
EVAR	2	0	4	12
Open	0	0	5	18
Carotid				
CAS	0	0	0	3
CEA	0	0	5	27
PAD				
PTA/Stent	9	0	8	18
Open	6	0	6	12
Acute thrombosis	6	0	8	0
Amputation	4	0	3	9

AAA, abdominal aortic aneurysm; *EVAR*, endovascular aortic repair; *CAS*, carotid artery stenting; *CEA*, carotid endarterectomy; *PAD*, peripheral arterial disease; *PTA*, percutaneous transluminal angioplasty.

We carried out a retrospective data collection of COVID-19 patients with severe acute ischemia of the lower limbs or DVT observed at the Vascular Surgery Unit of the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, during the period of March 1, 2020, to April 30, 2020. All patients gave written consent. The study was approved by the local ethical committee. Primary outcomes of the analysis were postoperative mortality and amputation rate only in those COVID-19 patients suffering from acute lower limb ischemia. Secondary outcomes were the prevalence of the disease among admitted COVID-19 patients, and any possible correlation between inflammatory parameters, thrombolytic status, and the presence of acute ischemia or DVT.

Statistical analysis

We used the Statistical Package for Social Sciences software version 14.0 (SPSS Inc, Chicago, IL, USA) for Windows to prepare the database and to perform descriptive analysis. The results are presented in Tables. Categorical variables are expressed as frequencies and percentages. Continuous variables with normal distribution are expressed as mean and standard deviation, and those with non-normal distribution as median and interquartile range. The Student's *t*-test and the χ^2 test were used when appropriate.

Results

Arterial occlusion related to COVID-19 infection

Admitted to our department were 6 patients (4 male, 2 female) with acute ischemia of the lower limbs. The median age was 71 years (range 49–83 y). In all 6 patients, the limb was at risk, and the only alternative was a major amputation. Cases 1, 2, and 5 (3 patients) reported previous symptoms of claudication and computed tomography-angiography posed the diagnosis of acute "superimposed" thrombosis over atherosclerotic occlusive disease. The remaining 3 patients (cases 3, 4, and 6) had no clinical evidence of chronic, obstructive, lower limb disease. The occlusion was related to acute "simple" thrombosis of the aortoiliac system with distal embolization and confirmed by computed tomography-angiography.

Table II
COVID19 patients who had emergency surgery for acute thrombosis of lower limb arteries

Surgery	Age/sex	Comorbidities	Oxygen therapy	CRP (mg/dL)	Discharge conditions
			Survival with arterial patency		
1–Embolectomy iliac-femoral-popliteal + iliac stenting	81/F	3	Y/high flow	1.3 (A) 0.3 (B) 0.3 (C)	Arterial patency improved general conditions
2–Embolectomy iliac-femoral-popliteal + popliteal PTA	82/M	4	Y/high flow	2.6 (A) 0.6 (B) 0.5 (C)	Arterial patency improved general conditions
3–Embolectomy iliac-femoral-popliteal	83/F	3	Y/high flow	1.5 (A) 5.4 (B) 1.0 (C)	Arterial patency improved general conditions
4–Embolectomy iliac-femoral-popliteal	49/M	3	Invasive mechanical ventilation	20 (A) 11 (B) 9 (C)	Arterial patency improved general conditions
			Survival with arterial re-thrombosis		
5–Embolectomy iliac-femoral-popliteal + popliteal PTA	67/M	3	Noninvasive mechanical ventilation	12 (A) 5.6 (B) 10 (C)	Re-thrombosis 5 days after initial successful surgery. New embolectomy. Amputation. Improved general conditions
			No survival		
6–Embolectomy iliac-femoral-popliteal	62/M	3	Invasive mechanical ventilation	8 (A) 24 (B) 28 (C)	Re-thrombosis 1 day after initial successful surgery. Died 30 days later (MOF).

(A) Denotes the day after surgery. (B) Denotes the day before surgery. (C) Denotes 2–3 days after surgery.
CRP, C-reactive protein; *MOF*, multiple organ failure; *PTA*, percutaneous transluminal angioplasty.

All patients tested positive for COVID-19 and all had general clinical symptoms, including fever and dyspnea at rest.

All 6 patients underwent urgent revascularization (embolectomy in 3 cases and hybrid open/endo procedures in the others). Postoperatively, all patients started heparin therapy with enoxaparin 0.5 mg/kg twice daily with the first dose given 6 h postoperatively and combined with acetylsalicylic acid 75 mg in the case of embolectomy or acetylsalicylic acid plus clopidogrel 75 mg in the case of simultaneous angioplasty.

In the group of 3 patients with occlusion from "superimposed" arterial thrombosis, 1 patient suffered from early thrombosis postoperatively, noted on day 2, and eventually required above-the-knee amputation. The mean hospital stay was 9 days, and all patients left the hospital in generally good clinical conditions. In the 3 patients with occlusion from "simple" arterial thrombosis, the superficial femoral artery was involved to the common iliac artery; clinical and diagnostic studies supported the hypothesis of an acute "simple" parietal aortoiliac thrombosis with distal embolization. In this group, proximal and distal embolectomy was performed through the femoral artery with initial success. One patient entered the hospital with critical hemodynamic conditions and disseminated intravascular coagulation and required immediate mechanical ventilation (pH = 7.437, lactate = 5.5 mmol/L, sO_2 = 76.4%, PO_2 = 44.8 mmHg, pCO_2 = 24.7 mmHg, calculate pO_2/FiO_2 ratio = 44.8 mmHg). A new femoral embolectomy was required from re-occlusion one day postoperatively. Unfortunately, this patient died a month later from multiple organ failure (MOF). The remaining 2 patients left the hospital in generally good condition. Laboratory parameters varied considerably among patients. Patients with "simple" arterial thrombosis tended to have more increased levels of serum D-Dimer, C-reactive protein (CRP), and a decreased platelet count as compared with patients with "superimposed arterial thrombosis." In the 2 patients with early re-occlusion (1 with simple thrombosis and the other with superimposed thrombosis), these parameters were more altered in comparison with the other 2 patients in each group who had eventual successful arterial revascularization (Table II).

DVT related to COVID-19 infection

The number of requests for in-hospital consultation for patients with DVT increased by more than 100% in comparison with previous years. During this period, 32 hospitalized patients, all of whom were in critical condition (24 male, 8 female) with severe COVID-19 infection (fever, pulmonary complications requiring assisted ventilation), were diagnosed with DVT at a mean of 393 hours after admission on the basis of clinical evidence (edema) confirmed by non-invasive tests and had been evaluated prospectively. The median age was 63 years (range 30–94 y). Of the 32 patients, 9 (28%) died from MOF despite aggressive medical therapy with high doses of selective and non-selective anti-inflammatory agents, full anticoagulation, and antibiotic therapy; 23 patients survived and left the hospital in generally good condition, and, at 1-month follow-up, none of these patients complained of major symptoms..

Treatment of these patients on admission included aggressive supportive management of acute hypoxic respiratory failure and of hemodynamic instability, use of antibiotic therapy, and the correction of the fluid-electrolyte and metabolic unbalances. All patients received prophylaxis with low molecular weight heparin (LMWH) and anti-inflammatory therapy. At the time of diagnosis of DVT, patients began full anticoagulation, and the dosage of anti-inflammatory therapy was increased. Table III presents the laboratory parameters at admission and at diagnosis. In all patients, there were alterations in hemostatic and inflammatory parameters at hospitalization, and, on univariate analysis, advanced age (70 years or older) and associated specific comorbidities (coronary artery disease, diabetes, renal failure) as well as high levels of D-dimers (15,000 or more), fibrinogen, lactate dehydrogenase, and creatine kinase were statistically significant risk factors for mortality ($P < .0001$). Such an aggressive approach to therapy allowed for a 72% survival, involving these patients in critical clinical condition and with high risk parameters. Moreover, we observed that a lack of increase in several laboratory parameters, including CRP values subsequent to initial treatment, levels of D-dimers, and fibrinogen, after full anticoagulation and aggressive anti-inflammatory therapy, represented a good prognostic factor ($P < .001$). The persistence of high systemic

Table III
Mortality in hospitalized COVID19 patients with deep vein thrombosis

	Mortality (9 patients)	No mortality (23 patients)	
Sex (M/F)	8/1	16/7	
Age, y (mean; range)	71.2 (62–83)	58.8 (30–94)	$P < .05$
Comorbidities (mean)	4 (3–5)	3 (2–4)	
Oxygen therapy			
High flow	-	4	
Noninvasive mechanical ventilation	4	7	
Invasive mechanical ventilation	5	12	
Localization thrombosis			
Lower limb proximal	5	7	
Lower limb distal	2	10	
Upper limb	2	6	
Evidence pulmonary embolism	4	4	
Padua score (mean; range)	3.6 (3–4)	3.2 (3–4)	
Platelet (mean; range)			
At admission	222 (154–289)	255 (63–526)	
At diagnosis	272 (112–669)	242 (139–324)	
Fibrinogen			
At admission	599 (367–700)	450 (219–775)	$P < .05$
At diagnosis	418 (122–657)	397 (172–717)	
PT			
At admission	72.2 (51–83)	74.8 (49–93)	
At diagnosis	57.6 (37–74)	75.7 (36–118)	$P < .05$
aPTT	25 (20–34)	25 (20–43)	
D-dimers			
At admission	13,875 (1712–35,000)	6,682 (488–35,000)	$P < .001$
At diagnosis	25,270 (10,800–35,000)	14,430 (985–35,000)	$P < .001$
LDH	482 (276–778)	437 (250–876)	
Creatine kinase	362 (15–2264) (100)	124 (15–842) (78)	
CRP			
At admission	15.9 (7.3–27.0)	20.2 (5.4–37.4)	
At diagnosis	26.3 (1.4–100)	16.7 (0.1–33.6)	$P < .05$
WBC			
At admission	8.9 (6.0–14.7)	10.9 (2.1–29.0)	
At diagnosis	10.4 (1.4–21.3)	10.6 (3.7–18)	

Laboratory values refer to the time of diagnosis unless otherwise specified.
CRP, C-reactive protein (mg/dL) platelet ($\times 10^3$/ mcL); *PT*, prothrombin time (%); *aPTT*, activate thromboplastin time (%); *D-Dimers* (mcg/L); *LDH*, lactate dehydrogenase (mU/mL); *creatine kinase* (mU/mL); *WBC*, white blood count.

levels of CRP and of altered laboratory parameters—despite full anticoagulation and increased dosage anti-inflammatory therapy—was associated with increased mortality rates and was more evident in patients aged 70 years or older with associated diabetes and/or renal failure, who might have had impaired immunologic defenses. Conversely, decreased systemic levels of CRP after therapy for the DVT increased the possibilities for survival and preceded normalization of hemostatic parameters.

Discussion

COVID-19 can lead to acute respiratory disease syndrome, multiorgan involvement, and shock.[8-10] The review of clinical, laboratory, and imaging findings demonstrated an increased risk of thrombotic events in COVID-19 patients.[11] The precise incidence of thrombosis in these patients has not been determined. In a retrospective study of 138 patients, of whom 16.7% of were in a critical condition, 17.3% of these patients were diagnosed with DVT at 3 to 18 days after admission despite the use of guideline-recommended thromboprophylaxis.[12] The prevalence of DVT has been demonstrated to vary 16%–49% in patients with COVID-19 admitted to intensive care, and 40% in autopsy studies.[10,13,14]

Arterial thrombosis has also been reported, and, since the beginning of the pandemic, there have been reports of cases of ischemia (ischemic stroke, myocardial infarction, or systemic arterial embolism). Arterial thrombosis accounts for about 4% of thromboembolic complications during COVID-19.[15]

COVID-19 patients with severe clinical conditions present characteristics of a systemic inflammatory condition associated with hemostatic abnormalities. There is now evidence that some patients respond to COVID-19 with a "cytokine storm" responsible for a hypercoagulability state.[8,9] COVID-19 hospitalized patients displayed hypercoagulability via 3 possible mechanisms: (1) the formation of pro-inflammatory cytokines, which are mediators of atherosclerosis, contributing directly to the rupture of the atherosclerotic plaque by local inflammation, (2) the induction of procoagulant factors, and (3) hemodynamic changes that predispose to ischemia and thrombosis[4]; these thrombotic events contribute to the severity of infections, creating a vicious circle. There is no readily available evidence on any potential therapy or prophylaxis that may provide clinical benefits in patients with severe COVID-19 infections as defined by marked tachypnea with respiratory rate ≥30 breaths per minute, hypoxemia with oxygen saturation ≤93%, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen <300, and lung infiltrates >50% of the lung field involved within 24 to 48 h).[16] Moreover, clinical trials have not confirmed a clear efficacy of antimalarial (hydroxychloroquine or chloroquine) with or without azithromycin and anti-retroviral drugs (lopinavir/ritonavir/remdesivir). Currently, several immunomodulating therapies, including glucocorticoids, convalescent plasma, and anti-cytokine therapy, are being investigated.[17,18] LMWH is recommended for all hospitalized patients, unless there are contraindications.[19–22]

In our experience with COVID-19 critically ill patients with acute arterial and DVT, we observed systemic abnormalities in hemostatic and inflammatory parameters. An aggressive medical and surgical therapeutic approach with anticoagulation, anti-inflammatory agents (selective and non-selective), and antibiotic therapy resulted in a survival of 74% (28/38) in these very critical conditions.[14,19,23,24] In this specific clinical setting, our analysis of the initial abnormalities in hemostatic and inflammatory parameters, demonstrated that these abnormities appeared to be similar in both patients who survived and in those who did not. Even patients with markedly altered parameters recovered after aggressive medical or surgical treatment. Despite the small number of patients in the arterial group of our study, it appears that surgical revascularization in this clinical setting is beneficial for several reasons: 4 of the 6 patients had their legs saved and survived the severe COVID-19 infection. Moreover, in these 4 patients we found a decrease in CRP levels, improved platelet counts, and decreased levels of D-dimers. These data support the possibility that early distal revascularization might reduce the inflammatory storm. The improvement of these parameters was not observed in the 2 patients who suffered from early re-thrombosis postoperatively. We believe that early interventions aimed at decreasing the systemic inflammation may help to prevent thrombosis and its complications. Moreover, although specific or broad-spectrum anti-inflammatory drugs, such as aspirin, decrease the inflammatory condition, their use has been the source of a number of debates. In severe COVID-19 infection a low platelet count is often evident. In the 3 patients with acute "simple" thrombosis, despite 2 patients having a normal platelet count, distal embolization suggests an abnormality in platelet function and adhesion. Conceptually, selective inflammatory inhibitors may prevent the complications related to the simultaneous platelet inhibition; however, in the unregulated and overwhelming inflammatory storm associated with severe COVID-19 infection, alternative activation of other pro-inflammatory cytokines is highly probable.[25,26] These possibilities support the use of anti-inflammatory inhibitors, either selective or non-selective, according to the specific stage and level of the infection.

We observed the same phenomenon in patients affected by DVT in whom early thromboprophylaxis and anti-inflammatory therapy had been established. In particular, in relation to the known high incidence of DVT (25–31%) despite adequate prophylaxis,[27] we preferred to use an escalated dose of LMWH with enoxaparin 0.5 mg/kg twice daily, especially in patients with high levels of D-dimers or fibrinogen being treated in the intensive care unit. We reserved unfractionated heparin for patients who developed severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73 m^2). Patients with atrial fibrillation or mechanical cardiac valves continued their full-dose anticoagulation. Furthermore, we extended prophylactic anticoagulation for a duration of 30 days after discharge. Alternatively, those who were low risk could receive only low-dose aspirin prophylaxis (aspirin 81 mg twice daily) for no less than 4 weeks duration after discharge.[28]

Finally, there are little data available on the use of recombinant tissue plasminogen activator in severely hypoxemic patients who do not respond to therapeutic dose anticoagulation or in the case of arterial thrombosis.[29]

In conclusion, we observed that the most important prognostic factor in this specific group of patients was the response to therapy. Improvements in inflammatory and hemostatic parameters soon after the initiation of therapy were correlated to a greater probability for survival. Acute arterial and DVT may worsen the inflammatory condition with endothelial damage. Resolution of the acute thrombosis may overcome the vicious circle of inflammation and -coagulopathy. The results of our study support the use of high doses of anti-inflammatory agents from the initial phase of severe COVID-19 infection and underline the importance of aggressive, anti-thrombosis prevention and treatment. The findings of our study confirm that critically ill COVID-19 patients who develop arterial and DVT are at high risk of mortality. Nevertheless, if properly treated with surgical treatment (in the case of arterial thrombosis), high doses of anti-inflammatory agents, and full anticoagulation and large-spectrum antibiotics, there is an overall survival of 74% (28/38) and of 100% in patients 60 y of age or younger in this large group of patients.

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