

Aortic disease and peripheral artery disease

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ABSTRACT The Annual Report on Cardiovascular Health and Diseases in China (2022) intricate landscape of cardiovascular health in China. In connection with the previous section, this 10th section of the report offers a comprehensive analysis of aortic disease and peripheral artery disease. Aortic dissection is a critical disease, with a higher incidence in men than in women. The main risk factors include hypertension, gene mutations, and so on. Recent studies suggest that young patients with aortic dissection have a higher body mass index, and there is a significant correlation between low ambient temperature and sudden temperature drop and the onset of dissection. The main hazards are aortic rupture or poor branch perfusion, which is life threatening. According to the lesion location, it is divided into Stanford A type (involving the ascending aorta) and Stanford B type (not involving the ascending aorta). The treatment of type A dissection is mainly open surgery, while the treatment of type B dissection is preferably endovascular treatment. In recent years, with the continuous development of endovascular technique, the treatment of aortic arch lesions has transformed gradually from open to hybrid, and then to total endovascular treatment. The prevalence of abdominal aortic aneurysm is relatively low (< 1%), and its risk factors mainly include smoking, hypertension, dyslipidemia, etc. The main hazard is the rupture of the aneurysm leading to death. Currently, treatment methods include endovascular repair and open surgery. According to data from Hospital Quality Monitoring System (HQMS), in the past five years, the number of open and endovascular operations for aortic disease in China has shown an upward trend, which may be due to the popularization of diagnostic and therapeutic techniques and increased attention to aortic disease. The in-hospital mortality rates of thoracic endovascular aortic repair, endovascular aortic repair, and Bentall operations are relatively low (all < 2%). Due to the complexity and difficulty of the operation, the in-hospital mortality of total arch replacement is 5.9%–7.4%. Overall, the in-hospital mortality decreased while the number of surgeries increased. This section also elaborates on the five peripheral artery diseases (PADs): lower extremity artery disease (LEAD), carotid atherosclerotic disease, subclavian artery stenosis, mesenteric artery disease and renal artery stenosis, from the perspectives of epidemiology, risk factors, evaluation methods, diagnosis, and treatment. PAD is common among middle-aged and elderly people, and is significantly related to the risk factors of cardiovascular disease. Diagnosis and treatment methods are constantly being improved and updated. Besides traditional evaluation methods, artificial intelligence, molecular biology and other methods have been continuously developed, improving diagnostic sensitivity and specificity. Treatment methods include risk factor control, medication, revascularization (percutaneous endovascular intervention and surgical treatment), and exercise etc. New treatment methods such as cell engineering and xenogeneic vascular graft have also shown promise in the treatment of LEAD.

AORTIC DISEASE

Aortic Dissection

According to the China Health Insurance Research Data 2015–2016 of over 300 million people living in cities and towns, the annual incidence of acute aortic dissection in China was about 2.78/100,000 person-years, and it was significantly higher in males than in females (3.96/100,000 person-years vs. 1.59/100,000 person-years).^[1] The results of the Registry of Aortic Dissection in China (Sino-RAD) study showed that the average age of Chinese patients with aortic dissection was 51.8 years, which was about 10 years younger than that in Europe and America.^[2,3]

A single-center study reviewed 5352 inpatients from 2002 to 2018 and found that the onset age of aortic dissection ranged from 12 to 92 years, with a mean age of 49.56 ± 11.58 years, with the largest number of patients aged 41–50 years, accounting for 30.7% of all enrolled patients (Figure 1). During this 16 years, the number of patients visited showed a rising trend, and male patients were more than female patients at all ages (Figure 2).^[4] Another study analyzing the data of 2048 patients with aortic dissection from 2011 to 2018 showed that the mean age was 53.4 ± 10.9 years, 1,161 (56.7%) were under 55 years old, 1,657 (80.9%) were male, and 935 (45.7%) had Stanford A dissection.^[5]

Aortic dissection onset has a seasonal pattern, with a

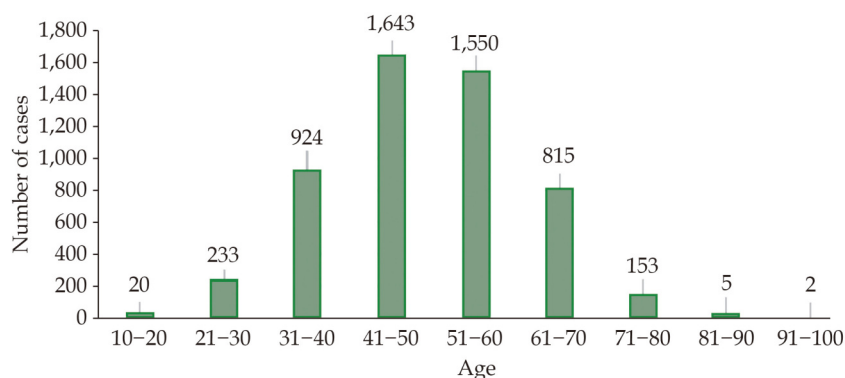


Figure 1 Distribution of aortic dissection cases at different ages.

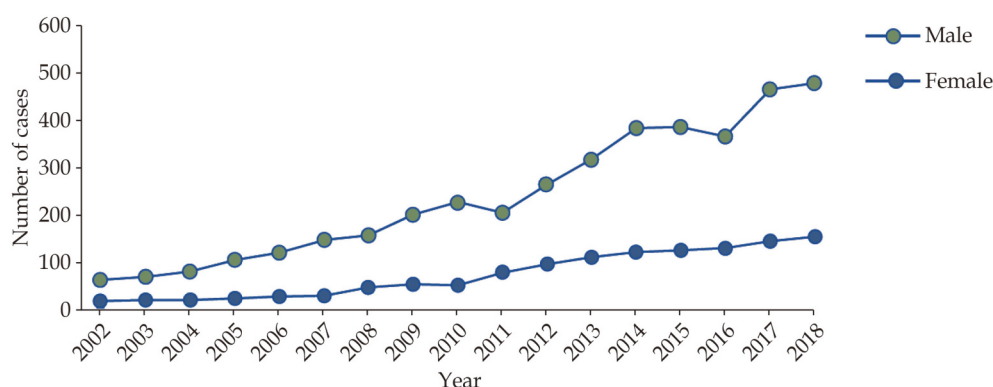


Figure 2 Numbers of male/female aortic dissection patients during 2002-2018.

peak in winter, $RR = 1.519$ ($P < 0.01$), and the incidence was negatively correlated with the monthly average temperature ($r = -0.650$, $P = 0.022$), and exhibits circadian variation with a trough at 2: 00-3: 00 a.m. and a peak at 9: 00-10: 00 a.m. and 4: 00-5: 00 p.m.^[5] In addition, a single-center cross-sectional study in China included 602 patients with aortic dissection. It was found that compared with middle-aged and elderly patients, young patients (< 45 years old) had a greater BMI and a wider range of dissection involvement.^[6]

Risk factors

Hypertension: The prevalence of hypertension in Chinese patients with aortic dissection was 78.6%.^[7] The huge hypertension population base and relatively low hypertension control rate in China are considered to be the most important etiology and risk factors of aortic dissection.

Gene mutation: Congenital defect of aortic wall due to gene mutation is also an important cause of aortic dissection, which is typically represented by Marfan syndrome caused by fibrin (FBN)-1 gene mutation. With the development of domestic molecular diagnosis technology,

it has become a consensus in this field of detecting gene mutations, family screening, early intervention, prevention of dissection and rupture for patients with this kind of disease.^[8]

Low ambient temperature and sudden temperature drop: A time-stratified case-crossover study in the Sino-RAD was conducted among 8,182 patients with antiarrhythmic drugs (AAD) from 14 tertiary hospitals in 11 cities between 2009 and 2019 and found that the risk of aortic dissection increased with temperature drop, and there was a statistical difference when the daily mean temperature was below 24°C. Compared with 28°C, the ORs for aortic dissection onset at -10°C and 1°C were 2.84 (95% CI: 1.69-4.75) and 2.36 (95% CI: 1.61-3.47), respectively. Compared to no change in ambient temperature, the OR of AAD onset at -7°C cumulated over lag 0-6 days was 2.66 (95% CI: 1.76-4.02).^[9]

Clinical manifestation and biomarkers

According to a registry study in China, pain was the most common chief complaint of aortic dissection, 88.1% of aortic dissection patients had pain and 70.3% of them had sudden pain. 89.4% of patients with Stanford type A dis-



section had pain. Among them, anterior chest pain accounted for 76.3%, back pain accounted for 56.5%, migration pain accounted for 12.3%; while in Stanford B dissection, back pain accounted for 73.8% and abdominal pain accounted for 14.2%.^[10]

D-dimer is considered to be a biomarker helpful for the diagnosis of aortic dissection,^[11] while recent studies have shown that soluble ST2 is better than D-dimer in predicting acute aortic dissection, and the areas under the ROC curve of the two are 0.97 and 0.91 respectively. When taking 34.6 ng/mL as the threshold, the positive predictive value of soluble ST2 for acute aortic dissection is 68.7%, and the negative predictive value is 99.7%, suggesting that this biomarker could be used for the early exclusion of acute aortic dissection (within 24 h of symptom occurrence).^[12]

Mortality

The mortality within 24 h from onset of acute Stanford type A aortic dissection, if left untreated, increases by 1% to 2% per hour and the 1-week mortality exceeds 70%. The mortality of acute Stanford type B aortic dissection is relatively low, and its 5-year survival rate is about 60% after the best medication.^[3]

Due to the recent progresses in the diagnosis and treatment of aortic dissection, its in-hospital mortality has decreased. A single-center study showed that the in-hospital mortality of aortic dissection was 18.37% during 2000–2008, with 43.75% for type A and 6.06% for type B; While the in-hospital mortality decreased to 12.23% during 2009–2017, with 27.17% for type A and 5.48% for type B.^[13]

Treatment

The Sino-RAD study showed that for type A aortic dissection, the open surgery treatment rate was 89.6%, drug treatment rate was 7.8%, endovascular treatment rate was 1.6%, hybrid treatment rate was 1.3% and the in hospital mortality was 5.5%;^[14] while for type B aortic dissection, the simple drug treatment rate was 21.3%, and the mortality was 9.8%; the open surgical treatment rate was 4.4%, and the mortality was 8.0%; the endovascular treatment rate was 69.6%, and the mortality was 2.5%.^[3]

Aortic arch replacement plus stented elephant trunk procedure has become the common surgical correction for type A dissection in China,^[15] and the mortality could be reduced to less than 5% in experienced centers.

In addition, due to the progress in endovascular repair

techniques and improved instrumentation, the TEVAR combined with chimney technique, in-situ fenestration technique, on-the-table fenestration technique, and branched stent technique are currently viable options for strictly selected type B dissection involving the arch aorta, with promising near- to medium-term results, however, the long-term outcome needs further observation.^[16,17] At present, the technology related to arch reconstruction is constantly improving (for example, gutter-free design chimney stent-graft to reduce the internal leakage caused by chimney technique),^[18] for single branch reconstruction, the external branch stent-graft independently developed by Chinese scholars has achieved satisfactory long-term results.^[19] For multi-branch reconstruction, the stent-graft system independently developed by Chinese scholars is under clinical trial.^[20] More modular arch stent-graft systems are to come in the future, but presently, total endovascular technique is still not suitable for a comprehensive application in the treatment of aortic arch lesions, with more evidences needed. Therefore, the concept of combination of open surgery with minimally invasive endovascular repair techniques emerged, i.e., the hybrid technique: on the one hand, an exact and safe anchoring zone is obtained by surgical means; on the other hand, surgical trauma is substantially reduced or operation time shortened with the aid of endovascular repair techniques. According to the different surgical procedures of aortic arch hybridization, Chinese scholars classified it into 4 types (Figure 3).^[21]

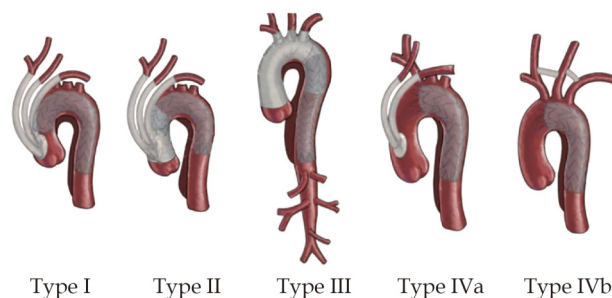


Figure 3 Type of aortic arch hybrid technique.

Hospitalization expenses and time

Hospitalization days and costs varied for different operative approaches in the treatment of patients with thoracic aortic diseases. According to HQMS, in 2021, the median average stay length of TEVAR surgery in China was 15.5 days, and the average hospitalization cost was 170,600 CNY; the median average stay length of simple graft with aortic valve replacement of ascending aortic

(Bentall surgery) was 22.1 days, and the average hospitalization cost was 215,500 CNY; the median average stay length of patients undergoing synthetic interposition graft replacement of aortic arch was 21.5 days, and the average hospitalization cost was 273,100 CNY (Figure 4).

Abdominal Aortic Aneurysm

Prevalence

Screening of 5402 people ≥ 40 years old with relevant risk factors in 3 cities and 2 rural communities in Central China found that the prevalence of abdominal aortic aneurysm was 0.33%, which was higher in men than in women (0.55% vs. 0.14%). The prevalence of abdominal aortic aneurysm was higher in those aged 55–75 years than in those of other ages (0.51% vs. 0.11%, $P = 0.016$).^[22] A cross-sectional survey conducted abdominal aortic ultrasound screening in a total of 3,560 individuals aged ≥ 60 years in 4 cities of Liaoning Province, and the detection rate of abdominal aortic aneurysm was 0.9%, and it was higher in men than in women.^[23]

Risk factors

A domestic study showed that smoking (OR = 5.23, 95% CI: 2.44–11.23), hypertension (OR = 1.88, 95% CI: 1.12–3.18), dyslipidemia (OR = 2.61, 95% CI: 1.45–4.70), serum high-sensitivity C-reactive protein (OR = 2.43, 95% CI: 1.37–4.31) and homocysteine (OR = 2.73, 95% CI: 1.61–4.65) were significantly associated with abdominal aortic aneurysm ($P < 0.05$).^[24] Increased plasma D-dimer ($r = 0.642$, $P < 0.05$) and intraluminal thrombus (growth rate 0.54 mm/year, $P = 0.02$) could predict rapid progression of abdominal aortic aneurysm.^[25,26] miR-145 and miR-30c-2* could down regulate micro RNA so as to inhi-

bit the progression of abdominal aortic aneurysm.^[27]

Complications

A Meta-analysis on the growth rate of Chinese abdominal aortic aneurysms showed that the annual growth rate of abdominal aortic aneurysms in the Chinese population was 0.18 to 0.75 cm. The larger the diameter of the aneurysm, the faster the growth rate was. Individuals with aneurysm diameters of 3.0–3.9 cm, 4.0–5.9 cm and ≥ 6.0 cm had an average annual growth rate of 0.21 cm, 0.38 cm and 0.71 cm, respectively. Further analysis found that the average annual growth rate of small tumors (3.0–4.9 cm in diameter) was 0.28 cm, and that of large tumors (≥ 5.0 cm in diameter) was 0.75 cm.^[28]

Visit time

Most abdominal aortic aneurysms are asymptomatic, and patients find a pulsating mass in the abdomen unintentionally or during physical examination, and thus seek medical consultation. Rupture of abdominal aortic aneurysm usually has symptoms of abdominal pain and patient seeks medical care relatively promptly. Some patients have been sick for several days or longer before seeing a specialist, due to their first visit to general surgery and other departments to probe the cause of abdominal pain, or due to delay during the referral to a higher level hospital.

Prevention and monitoring

The most important measures to prevent abdominal aortic aneurysm include control of risk factors for hypertension and atherosclerosis (AS), smoking cessation, lifestyle intervention, regular physical examination, monitoring, etc.

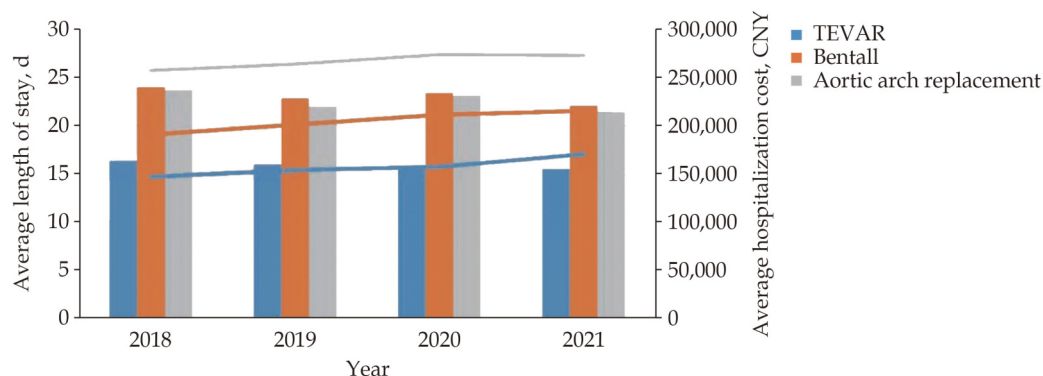


Figure 4 From 2018 to 2021, the average hospital stay (bar) and average hospitalization expenses (line) of patients with different surgical methods for aortic dissection. TEVAR: thoracic endovascular aortic repair.



Asymptomatic abdominal aortic aneurysms are usually found in physical examination. If the diameter of the aneurysm is less than 4 cm, it is recommended to perform Color Doppler ultrasound examination every 2 to 3 years; if the diameter of the tumor is 4 to 5 cm, it is recommended to perform ultrasound or CTA examination at least once a year; once the aneurysm is found to be > 5 cm (male) or > 4.5 cm (female), or the aneurysm is growing too fast (1 cm/year), surgical treatment is required as soon as possible. Once diagnosed, smoking should be strictly prohibited during the observation period, and blood pressure and heart rate should be controlled.

Treatment

At present, the treatment of abdominal aortic aneurysm mainly includes drug therapy, open surgery and endovascular treatment.

Open surgery: The mortality of elective open surgery for abdominal aortic aneurysm is 2%–8%, and that of ruptured abdominal aortic aneurysm is 40%–70%. The 5-year survival rate of the infrarenal abdominal aortic aneurysm surgery is 60% to 75%, and the 10-year survival rate is 40% to 50%.

Endovascular treatment: A 10-year single-center study in China showed that the technical success rate of endovascular therapy was 91.1%. The perioperative mortality was 1.3%. The 1-, 3-, 5- and 10-year cumulative overall survival rates were 95.1%, 84.0%, 69.5% and 38.6%, respectively. Among them, old age, preoperative aneurysm rupture and short aneurysm neck are independent prognostic factors for long-term survival after abdominal aortic EVAR.^[29] A Meta study showed that Chinese people were more prone to endovascular treatment than Western people (44.5% vs. 41.5%, $P = 0.012$). The mortal-

ity of EVAR patients 30 days after EVAR was significantly lower than that of open surgery patients.^[30]

Hospitalization expenses and length of stay

Data from HQMS in China indicated that in 2021, the median length of hospital stay was 23.1 days and the average hospitalization cost was 151,500 CNY for the treatment of abdominal aortic aneurysm by synthetic interposition graft replacement of abdominal aorta. The estimates were 13.1 days and 188,300 CNY for abdominal EVAR treatment (Figure 5).

Aortic Operation Volume and Outcomes

According to HQMS data, the volume of endovascular and open aortic operation for treatment of aortic diseases has been on the rise in recent years. In HQMS included hospitals, the number of endovascular procedures rose from 21,320 in 2017 to 46,651 in 2021 (an increase of 118.8%), that of Bentall procedures rose from 3,105 to 5,901 (an increase of 90.0%), and that of synthetic interposition graft replacement of aortic arch rose from 3,707 to 9,400 (an increase of 153.6%) (Figure 6).

In HQMS included hospitals, from 2017 to 2021, the in-hospital mortality of TEVAR decreased from 2% to 1.3%, and the rate of in-hospital death plus discharge against medical advice (DAMA) decreased from 4.9% to 4%. The in-hospital mortality of EVAR decreased from 1.7% to 1.3%, and the rate of in-hospital death plus DAMA ranged from 3.7% to 3.9%. The in-hospital mortality of Bentall surgery was between 1.5% to 1.9%, while the rate of in-hospital death plus DAMA ranged from decreased from 4.4% to 2.5%. For synthetic interposition graft replacement of aortic arch, the in-hospital mortality ranged from 5.9% to 7.4%, and the rate of in-hospital death plus DA-

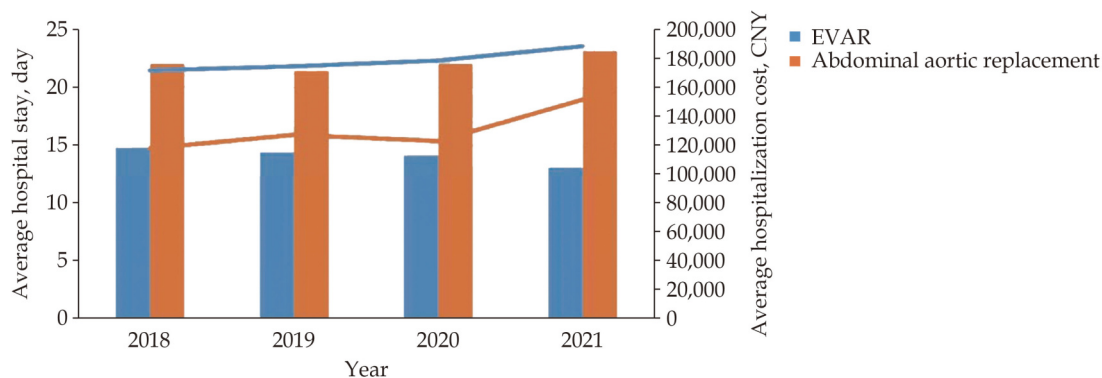


Figure 5 Hospitalization days (bar) and average hospitalization cost (line) of patients with abdominal aortic aneurysm treated by different surgical methods from 2018 to 2021. EVAR: endovascular aortic repair.

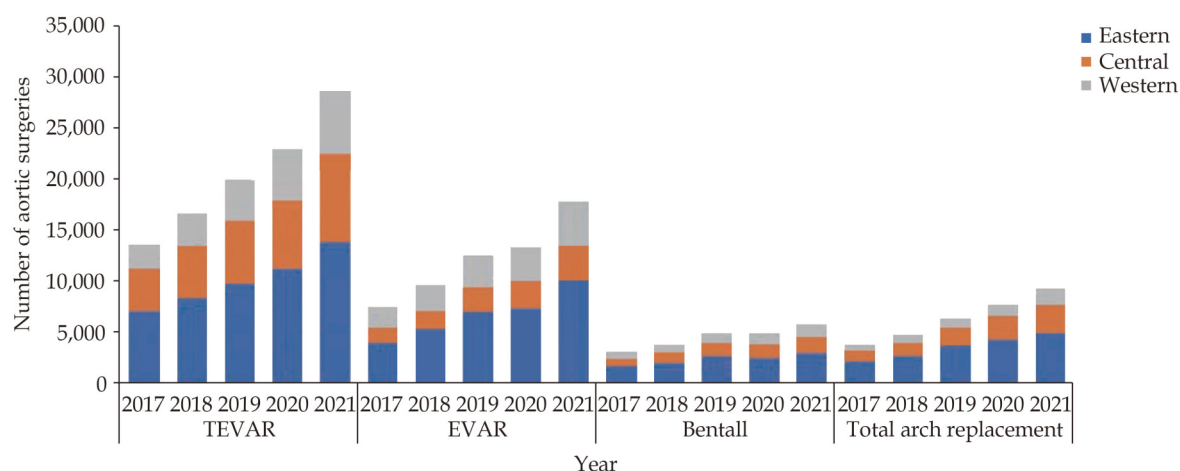


Figure 6 Changes in the number of aortic surgeries in different regions of China from 2017 to 2021. EVAR: endovascular aortic repair; TEVAR: thoracic endovascular aortic repair.

MA ranged from 11.2% to 14.6% (Bentall surgery alone, that is, no other aortic surgery was performed during this hospitalization except for Bentall surgery) (Figure 7).

PERIPHERAL ARTERY DISEASE

The main cause of PAD is AS; others include thrombus, Takayasu arteritis, fibromuscular dysplasia, dissection, trauma, etc. This section reports the below five types of PAD: LEAD, CASD, SCAS, MAD and RAS.

LEAD

Prevalence

LEAD is a common disease in the middle-aged and the elderly. A stratified, multi-stage random sampling survey in China showed that the prevalence of LEAD in the natural population ≥ 35 years old was 6.6%. Based on this, it was inferred that the number of LEAD patients in

China was about 45.3 million.^[31] Age, region, and disease status affect the prevalence rate. The prevalence of LEAD was up to 21.2% among patients with T2DM.^[32] Some studies have found that 70 years of age seemed to be a dividing line among T2DM patients ≥ 50 years old. The prevalence of LEAD in people ≥ 70 years old was significantly higher than that in people < 70 years old (34.44% vs. 14.22%).^[33]

Complications and risk factors

LEAD is an important component of systemic AS. Early detection of LEAD is of great value for the diagnosis and treatment of systemic atherosclerotic cardiovascular disease (ASCVD). However, asymptomatic LEAD accounts for about 95% in Chinese population.^[31] A retrospective study found that lower limb arteriosclerosis obliterans was an independent predictor of MACCE (HR = 2.448, 95% CI: 1.730–3.464, $P < 0.001$).^[34] The mortality of LEAD patients was significantly higher than that of non-

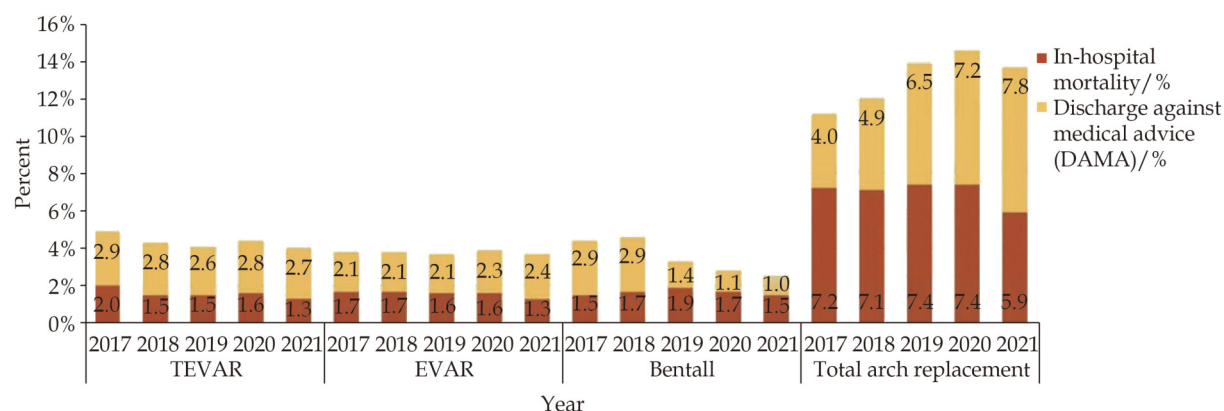


Figure 7 Hospitalization outcome of aortic surgery during 2017–2021.



LEAD patients of the same age, and the lower the ankle brachial index (ABI), the higher the risk. The all-cause mortality and cardiovascular mortality of patients with $ABI \leq 0.4$ multiplied (Figure 8).^[35] Another study found that subclinical LEAD might be an independent risk factor for decreased total hip bone mineral density in T2DM men aged ≥ 55 years (adjusted RR = 8.933, 95% CI: 1.075–74.222, $P = 0.043$).^[36]

The main risk factors of LEAD in Chinese population are smoking, hypertension, hypercholesterolemia and T2DM. Among them, the pathogenicity of smoking was particularly strong, the OR of LEAD caused by current smoking was 2.62,^[37] and secondhand smoke had a dose effect, the OR of exposure to secondhand smoke for more than 25 hours per week was 7.86.^[38]

Diagnosis and treatment

The methods for diagnosing LEAD are constantly updating, and functional evaluation methods and artificial intelligence diagnosis are gradually applied to clinical practice. The indicators obtained by synchronous measurement of limb blood pressure and brachial ankle pulse wave velocity would change before the occurrence of anatomical stenosis in arteries, which is of certain value for the early diagnosis of arteriosclerosis and is increasingly being recognized. With the development of artificial intelligence, the accuracy and specificity of a deep learning modality of computed tomography angiography (CTA) of the lower limb arteries have improved, though its sensitivity is lower than that of human film reading. The sensitivity and specificity of the artificial intelligence algorithm in the diagnosis of LEAD in the elderly were 100.0% and 90.3%, which was superior to ABI.^[39]

As technology advances, LEAD treatment strategies are also changing. A study from 2012 to 2015 showed th-

at 1.9% or estimated 860,000 patients with LEAD underwent revascularization.^[31] A single-center study retrospectively analyzed the changes of revascularization methods and prognosis of 1,613 patients with LEAD from 2002 to 2011, suggesting that the proportion of interventional therapy has gradually increased, and the limb salvage rate has also increased. From 2002 to 2006, the proportion of patients who received interventional therapy was 20.1%, and the proportion of patients who received traditional surgical treatment was 47.5%. While from 2007 to 2011, the proportion of interventional therapy increased to 68.7%, and the proportion of traditional surgical treatment decreased to 18.5%.^[40] Besides conventional interventional techniques, excimer laser atherectomy (ELA), directional atherectomy (DA), percutaneous mechanical thrombectomy (PMT), etc. could bring certain clinical effects for lower limb artery calcification, stent restenosis, and acute ischemia.^[41,42]

Relevant research on new therapy for critical limb ischemia (CLI) is also promising. A phase II, double-blind, randomized placebo-controlled trial investigated the efficacy and safety of intramuscular injection of plasmid pUDK-HGF which encodes the human hepatocyte growth factor gene in CLI patients. Patients with rest pain ($n = 119$) and patients with leg ulcers ($n = 121$) were enrolled as two cohorts. The results showed that the pUDK-HGF group was better than the placebo group in pain relief and ulcer healing, while there was no significant difference in adverse effects.^[43]

CASD

Prevalence

cIMT thickening, carotid artery plaque and carotid artery stenosis are common in people all over the world. A cross-sectional study conducted by the health manage-

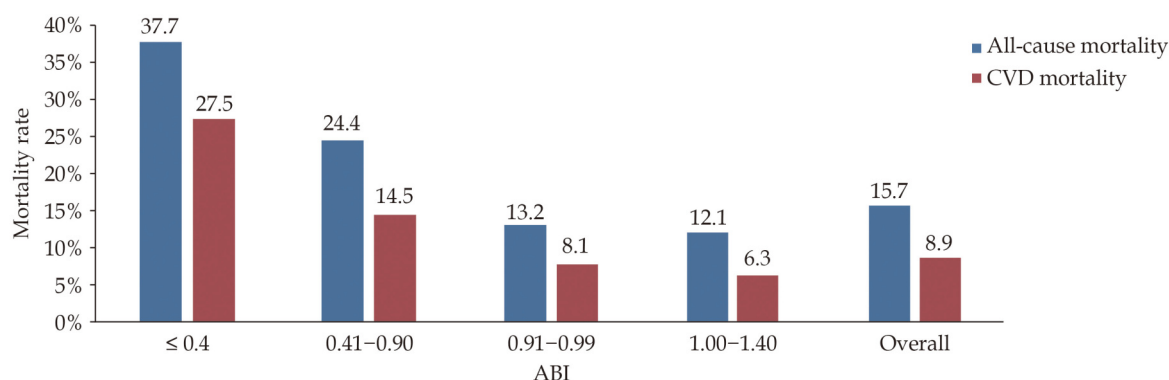


Figure 8 Three year follow-up mortality of atherosclerotic high-risk population with different ABI grades. ABI: ankle brachial index

ment centers of two tertiary hospitals in Northern and Southern China from 2017 to 2019 included 38,642 subjects with a median age of 46 years. The prevalence of CASD was 30.0%.^[44] Among 9,215 stroke high-risk people (average age 60 ± 9 years) screened in 8 community hospitals in Beijing, the prevalence of CASD was as high as 74.7%.^[45] See Table 1 for the prevalence of moderate and above carotid atherosclerotic stenosis in different populations.

Risk factors

The risk factors of carotid atherosclerotic stenosis include traditional risk factors (sex, age, hypertension, DM, dyslipidemia, obesity, smoking, homocysteinemia, etc.) and genetic factors.

A cross-sectional study of 84,880 people aged ≥ 40 years in the Chinese Stroke Prevention Program (CSPP) showed that the risk factors of carotid atherosclerotic stenosis included age (50–59 years old, 60–69 years old, ≥ 70 years old vs. 40–49 years old, OR = 2.01, 4.29, 5.75, respectively), male gender (OR = 1.10), rural residents (OR = 1.77), smoking (smoking cessation, current smoking vs. never smoking, OR = 1.58 and 1.52, respectively), drinking (frequent drinking, occasional drinking vs. no drinking, OR = 1.44 and 1.21, respectively), lack of exercise (OR = 1.30), obesity (OR = 1.27), hypertension (OR = 1.43), diabetes (OR = 1.39) and dyslipidemia (OR = 1.65).^[50]

Other studies have shown that menopause, visceral obesity index, thyroid hormone level, glucose triglyceride (TyG) index, serum uric acid, etc. are also related to the risk of carotid AS.

Evaluation means and risk prediction

A retrospective study collected the data of 162 pati-

ents with carotid stenosis. Multivariate logistic regression analysis showed that intra-plaque hemorrhage (IPH) (OR = 7.568, 95% CI: 1.933–26.627) and lipid-rich necrotic core (LRNC) (OR = 3.835, 95% CI: 1.409–10.441) were independent predictors of symptomatic plaque. In the training cohort ($n = 121$), the areas under the curve of IPH and LRNC were 0.697 and 0.715 respectively.^[51]

Carotid atherosclerotic stenosis is closely related to TIA and ischemic stroke. The Chinese Atherosclerosis Risk Evaluation II (CARE-II) study found that in patients with recent cerebrovascular events, the detection rate of high-risk carotid atherosclerotic plaques (MRI scan of carotid artery showed plaque surface rupture, LRNC $> 40\%$ or IPH) was 28%, which was 1.5 times higher than that of severe internal carotid artery stenosis (degree of stenosis $\geq 50\%$). In the identification of high-risk plaques, the predictive ability of maximum wall thickness was better than that of lumen stenosis [area under curve (AUC): 0.93 vs. 0.81].^[46]

In patients with CASD, many laboratory tests and measurements that are not specific to the plaque itself have also become indicators for risk prediction. Regression analysis showed that neutrophil/lymphocyte ratio (OR = 1.23, 95% CI: 1.05–1.43) and visceral fat index (OR = 1.39, 95% CI: 1.21–1.61) were independent risk factors for carotid AS.^[52] Another study showed that circulating exosomal circRNA could be used as a novel biomarker to predict large artery atherosclerotic stroke and plaque rupture, and its diagnostic value might be better than that of plasma circRNA.^[53]

Correlation with cardiovascular disease

The Kailuan study in China found that carotid plaque

Table 1 Prevalence of moderate or severe carotid atherosclerotic stenosis in different populations.

Project	Time of investigation	Population characteristics	Sample volume/ <i>n</i>	Examination method	Prevalence of carotid stenosis $\geq 50\%$
Chinese Atherosclerotic Risk Evaluation II study (CARE-II) ^[46]	2012–2015	18–80 years old, symptoms of anterior circulation ischemia occurred within 2 weeks	1,047	MRI of carotid artery	18.9
Screening and intervention project for high-risk groups of stroke ^[47]	2014–2015	Urban and rural residents aged ≥ 40 years	106,918	Carotid ultrasound	0.5
Study on the current situation of carotid atherosclerosis among urban and rural residents in Dongying area ^[48]	2014–2015	Permanent urban and rural residents aged ≥ 45 yrs	10,182	Carotid ultrasound	1.2
Investigation of carotid artery stenosis in rural area of Tianjin ^[49]	2017–2018	Rural residents aged ≥ 45 yrs, asymptomatic, no history of CVD	3,126	Carotid ultrasound	6.7



and hypertension combined with carotid plaque were associated with increased risks of first-episode cardiovascular events (HR = 1.85, 95% CI: 1.01–3.44; HR = 2.97, 95% CI: 1.66–5.29), cerebral infarction (HR = 2.66, 95% CI: 1.16–6.15; HR = 4.15, 95% CI: 1.87–9.19) and all-cause mortality (HR = 1.96, 95% CI: 1.16–3.31; HR = 1.85, 95% CI: 1.09–3.13).^[54]

Treatment

Improving lifestyle and controlling risk factors are the basis for the prevention and treatment of carotid atherosclerotic stenosis and its complications. Patients of carotid stenosis with poor effect of drug treatment and high risk of stroke could be revascularized according to their situation, including carotid endarterectomy (CEA), carotid artery stenting (CAS) and so on. In recent years, a novel technique for the treatment of carotid stenosis transcatheter artery revascularization (TCAR) with flow reversal has emerged, but its safety, effectiveness and gold standard of treatment are still uncertain.

According to the data from “China Stroke Prevention and Treatment Report 2019”, in 2018, the number of reported CEA operations was 4,910, and the incidence of serious complications was 2.79%. A total of 15,801 CAS operations were carried out, and the incidence of serious complications was only 1.92%.^[55] “China Stroke Prevention and Treatment Report 2020” showed that, in 2019, the number of CEA and CAS by advanced stroke centers were 6,600 and 18,649 respectively.^[56] However, there are still some problems, such as uneven level of CEA, too wide application of CAS, lax patient selection and so on.

SCAS

Epidemiology

Inter-arm systolic blood pressure difference (sIAD) $\geq$ 15 mmHg has been recognized as a potent indicator for predicting SCAS $>$ 50%, which could be used for epidemiological screening and diagnosis of SCAS. A prospective study of 3,133 residents aged $\geq$ 60 years in a community in Shanghai showed that 1.75% of them had inter-arm SBP difference $\geq$ 15 mmHg.^[57] A single-center study on the etiology of SCAS inpatients showed that AS accounted for 95.9% in patients aged $>$ 40 years, while Takayasu arteritis accounted for 90.5% in patients aged $\leq$ 40 years.^[58] SCAS increases the risk of cardiovascular death, all-cause death and stroke.

Diagnosis and treatment

For patients with symptomatic SCAS, color Doppler ultrasonography indexes, peak systolic velocity (PSV) of the stenosis segment, and the ratio of the stenosis segment PSV to the distal PSV (PSVr) are strongly correlated with SCAS. The optimal values for predicting $\geq$ 50% and $\geq$ 70% stenosis are PSV $\geq$ 230 cm/s, PSVr $\geq$ 2.2, and PSV $\geq$ 340 cm/s, PSVr $\geq$ 3.0 respectively.^[59]

Generally, interventional therapy is the first choice for symptomatic SCAS patients. A single-center study found that its success rate was 82.6%–91.3% for subclavian artery occlusive disease.^[60,61] Arterial bypass remains the primary treatment for subclavian artery occlusion, for which, endoluminal intervention is not possible. A study of 51.4-month follow-up found that the bypass vessel patency rate was 83.3%.^[62] For patients undergoing coronary artery bypass grafting (CABG), cardiologists should evaluate SCAS before operation. Once moderate to severe stenosis of the proximal left subclavian artery is confirmed, preoperative stent implantation is an effective treatment.

MAD

Epidemiology and risk factors

MAD includes the stenosis, occlusion, or embolism of celiac artery, superior/inferior mesenteric artery. The incidence of ischemic bowel diseases caused by MAD is rising, with clinical manifestations such as acute or chronic mesenteric ischemia, ischemic colitis, and so on. Epidemiological data are very scarce, but acute or chronic MAD is found to be poorly diagnosed, with a high misdiagnosis rate and mortality.

A meta-analysis of cases of mesenteric artery embolism and thrombosis reported during 1994 to 2006 found that the misdiagnosis rate was 61.3% and the mortality was 60.6% in 111 confirmed cases.^[63] Another meta-analysis found that 312 out of 492 patients (63.4%) suffering from ischemic bowel disease were misdiagnosed during 1998–2008, and abdominal pain was the most common clinical manifestation (97.2%, 478 cases/492 cases), suggesting that in clinical practice the possibility of ischemic bowel disease should be considered when elderly patients visiting with abdominal pain as the first symptom, so as to reduce misdiagnosis.^[64]

For MAD patients, when the blood PH value was less than 7.35, B-ultrasound or CT indicated abnormal ch-



ange in the blood flow of the intestinal wall, or there was a systemic inflammatory response syndrome, intestinal necrosis should be considered. Elevated levels of white blood cells or D-dimer could be used as an auxiliary predictive factor.^[65] For patients with acute superior mesenteric artery embolism, weight loss associated with chronic ischemia might be a protective factor for survival (OR = 0.75, $P = 0.038$), while peritoneal irritation sign (OR = 8.51, $P = 0.014$), peritoneal effusion (OR = 3.07, $P = 0.028$), and main superior mesenteric artery embolism (OR = 5.05, $P = 0.039$) were independent risk factors for death.^[66]

Diagnosis and treatment

Imaging examination should be done as soon as possible for suspected mesenteric ischemia, and CTA is preferred. Endovascular therapy has gradually become a promising alternative therapy for acute superior mesenteric artery thrombosis/embolism. Compared to open surgery, the proportion of endovascular therapy requiring laparotomy was lower (33.3% vs. 58.3%, $P = 0.18$), significantly reducing the length of intestinal segment resection (88 ± 44 vs. 253 ± 103 cm, $P = 0.01$).^[67] For patients with no clinical evidence of bowel necrosis, endovascular therapy had advantages in duration of surgery time, blood loss, bowel rest time, ICU time, and ventilator use. There was no difference in bowel necrosis, length of necrotic bowel resected, or in-hospital mortality between the two groups. Endovascular treatment has altered the management of superior mesenteric artery embolism, and it may be adopted in selected patients who are not at risk for bowel necrosis.^[68]

Renal Artery Stenosis(RAS)

Epidemiology and risk factors

RAS prevalence is often underestimated. RAS can cause renovascular hypertension, which accounted for 1.9% of hospitalized patients with hypertension in a study from Xinjiang.^[69] A study from Taiwan Health Insurance Database (23 million people) found that 14,025 patients with renal vascular diseases were diagnosed from 2000 to 2008, with an incidence of 6.69/(100,000 person-years). The incidence increased with age, 10.56/(100,000 person-years) in people aged 45–64 and 27.03/(100,000 person-years) in people aged > 65 years.

The detection rate of RAS was 16.3% when renal angiography was performed simultaneously with coronary

angiography. Age > 65 years, female gender, hypertension, LEAD, renal insufficiency and left main with triple coronary artery disease are independent risk factors for RAS.^[71] Based on these indicators, researchers have developed a predictive model to guide clinicians to decide whether to perform renal angiography simultaneously with coronary angiography.

40.5% of RAS patients were complicated with left ventricular hypertrophy, and it's even higher (65.4%) in bilateral RAS patients.^[72] RAS was a predictor of all-cause death (HR = 4.155, 95% CI: 1.546–11.164; $P = 0.005$) and cardiovascular death (HR = 3.483, 95% CI: 1.200–10.104; $P = 0.022$).^[73]

A single-center study involving 2,905 patients with RAS for 18 years found that the main causes of RAS in Chinese population were AS (82.4%), Takayasu arteritis (11.9%), fibromuscular dysplasia (4.3%).^[74] The etiologic composition was related to age and sex. Non-AS causes were more common in patients ≤ 40 years old, and the etiological composition changed greatly over years, i.e., AS increased from 50% in 1999–2000 to 85% in 2015–2016.

Diagnosis and treatment

Besides traditional imaging modalities, contrast-enhanced ultrasound (CEUS) had a sensitivity of 88.9% to 94.7%, a specificity of 84.0% to 87.8%, and an accuracy of 88.5% to 92.5% for the diagnosis of RAS, and its positive predictive value and negative predictive value were 93.5% and 80.0% respectively.^[75,76] The grading of RAS was close to that of renal arteriography.^[76] Therefore, CEUS is of high diagnostic value for RAS in patients with chronic kidney disease.

At present, contradictions exist in evidences on the effect of interventional therapy for atherosclerotic RAS. Some single-center case studies in China have shown that interventional therapy is effective for blood pressure control in elderly patients, patients with severe RAS and patients with transplant renal artery stenosis.

The unilateral glomerular filtration rate (GFR) measurement or blood oxygen level-dependent magnetic resonance imaging for evaluating atherosclerotic RAS could be used to guide percutaneous renal artery stenting and to evaluate prognosis.^[77,78] A retrospective study of 230 patients with unilateral or bilateral RAS found that the incidence of adverse cardiac and renal events at 3-year follow-up after intervention was 24.3% (56/230). These events might be associated with age (≥ 65 years old), Ch-



arlson complication index score ≥ 2 , diabetes, stroke and congestive heart failure.^[79,80]

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