

Advancements in medical and surgical treatments of Takayasu arteritis-induced renal arteritis: a systematic review

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Abstract

Background: Takayasu arteritis-induced renal arteritis (TARA), commonly seen in Takayasu arteritis (TA), has become one of the main causes of poor prognosis and early mortality in patients with TA. TARA progressing into Takayasu arteritis-induced renal artery stenosis (TARAS), could lead to severe complications including malignant hypertension, cardiac-cerebral vascular disease, and ischemic nephropathy. Since there existed no guidelines on treatments, this study aimed to review the comprehensive treatments for TARA.

Methods: We searched systematically in databases including PubMed, Ovid-Medline, EMBASE, Web of Science, China National Knowledge Infrastructure, Wanfang, and SinoMed, from inception to May 2018. Literature selection, data extraction, and statistical analysis were performed.

Results: Eighty-two literatures were recruited focusing on medical treatments ($n = 34$) and surgical treatments ($n = 48$). We found that combined medical treatments of glucocorticoids and conventional synthetic disease-modifying anti-rheumatic drugs could reach high rates of remission in patients with TARA, and biological disease-modifying anti-rheumatic drugs were preferred for refractory patients. After remission induction, surgical treatment could help reconstruct renal artery and recover renal function partly. Percutaneous transluminal angioplasty was the first choice for patients with TARAS, while open surgery showed a good long-term survival.

Conclusions: Patients with TARA should benefit both from medical treatments and from surgical treatments comprehensively and sequentially. Multidisciplinary team coordination is recommended especially in patients with severe complications.

Keywords: Renal artery; Takayasu arteritis; Treatment

Introduction

Takayasu arteritis (TA) is a type of unspecific, granulomatous and large-vessel vasculitis^[1] predominantly seen in females (male:female 1:4–9^[2]) under 40 years old among Asian countries and regions with an incidence of 1 to 2 cases/million per year^[3] and an estimated prevalence of 12.9 to 40 cases/million.^[4,5] Renal arteries are commonly involved in type III–V of TA according to the Numano radiological classification in 1996.^[6,7]

Takayasu arteritis-induced renal arteritis (TARA), accounting for 38.0% to 76.2% among patients with TA in China,^[8–10] is considered as an unspecific inflammatory pathophysiological process mediated by immune inflammation disorders, with structural lesions located in renal artery wall as well as hemodynamic dysfunction stimulating renin-angiotensin-aldosterone system (RAAS). Structurally, persistent inflammation of TARA could progress gradually

into obvious luminal stenosis and even occlusion, namely Takayasu arteritis-induced renal artery stenosis (TARAS). Functionally, perfusion pressure of the stenotic side increased and glomerular filtration decreased, which could be aggregated by water and sodium retention from RAAS activation, and hypoxia and ischemia from sympathetic-adrenal system and oxidative stress.^[11] Thus, TARA could lead to a series of severe and multiple-organ involved complications predicting poor prognosis and early death,^[12,13] such as progressive renal dysfunction and ischemic nephropathy, refractory renal vascular hypertension, cardiovascular disorders and heart failure, cerebrovascular disease, and so on.

In early phase, appropriate anti-inflammation treatments may reverse the progression of TARA. When it goes into chronic phase, with stenosis percentage more than 75% and apparent hemodynamic disorders, the lesions of TARA could lead to systematic influence irreversibly. Unfortunately, there has been no published recommendation or guideline

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of treatments for TARA. Therefore, this article systematically reviewed the literatures and had an overview of advancements in medical and surgical treatments of TARA so as to provide solid evidence for clinical practices.

Methods

Search strategy

We underwent a systematic literature search both in home databases including China National Knowledge Infrastructure, Wanfang and SinoMed and in abroad databases including PubMed, Ovid-Medline, EMBASE, and Web of Science. Searching time was set from inception to May 31, 2018, and language was limited to Chinese and English. Taking an example of searching in PubMed, the search strategy was: ((“Takayasu Arteritis”[Mesh]) OR (“Aortic Arch Syndromes”[Mesh])) OR (takayasu* OR “aortitis syndrome” OR “aortic arch syndrome” OR “martorell syndrome” OR “pulseless disease” OR “arteritis brachiocephalica” OR brachiocephalic OR “occlusive thromboasopathy” OR aortoarteritis OR “aorto-arteritis” OR “large-vessel vasculitis” OR “large vessel vasculitis” OR “large-vessel vasculitides” OR “systemic vasculitis” OR “systemic vasculitides” OR “systemic necrotizing vasculitis” OR truncoarteritis).

Inclusion and exclusion criteria

Inclusion criteria were set at the literatures about treatments in patients with TARA, including randomized controlled trial, cohort study, case series, case report, review, pilot study, and so on. Exclusion criteria were as followed: (1) non-TA literature; (2) non-TARA literature; (3) animal researches; (4) literatures about epidemiology, mechanism, diagnosis (variable biomarkers, radiological techniques, etc) and evaluation (disease activity, radiological assessment, etc); (5) case reports fewer than ten cases.

Literature selection

Two authors (Dai XM and Yin MM) performed the literature searches independently based on inclusion and exclusion criteria, with deleting irrelative literatures, abandoning duplications, and screening titles and abstracts. Data extraction was finished by three authors (Dai XM, Yin MM, and Liu Y). Any difference was discussed to reach agreement.

Statistical analysis

Data extraction and data analysis were performed using RevMan software (Version 5.3, the Cochrane Collaboration). Measurement indicators included in the study were weighted mean difference or standardized mean difference and 95% confidence interval (CI) indicate that the efficacy statistics are expressed by the relative risk (risk ratio [RR]) and 95% CI. No clinical heterogeneity measurements ($I^2 < 50\%$) were performed using a fixed-effect model; if $I^2 > 50\%$, indicating a significant heterogeneity, a random-effects model was used and the heterogeneity source was further analyzed. Sensitivity analysis was performed to assess the stability of the results, that is, each study was

deleted each time to reflect the impact of a single data set on the results.

Results

General information on literature recruitment

The initial number of searched items was 15,677. Excluded literatures consisted of non-TA ($n = 15,265$) and non-TARA ($n = 195$) literatures, duplications and case reports (< 10 cases) ($n = 22$), and literatures about epidemiology ($n = 17$), mechanism ($n = 76$), diagnosis ($n = 8$), and evaluation ($n = 12$) on TARA. Finally, there were 82 literatures recruited, focusing on medical treatments ($n = 34$) and surgical treatments ($n = 48$).

Medical treatments in TARA

Medical treatment strategies in patients with TARA referred to those in TA, aiming at reaching disease remission. Anti-inflammation medications as the core therapy included glucocorticoid (GC), conventional synthetic disease-modifying anti-rheumatic drugs (cDMARDs), and biological disease-modifying anti-rheumatic drugs (bDMARDs).

GC

GC has been considered as the cornerstone of remission induction therapy in patients with TA. Only 20% of TA cases could benefit from monotherapy of GC with remission rate of 60%, nearly 80% patients having progressive or recurrent episodes needed treatment of GC combined with immunosuppressive agents.^[14] For prednisone, the initial dosage is 0.5 to 1.0 mg/kg once a day orally for 4 to 8 weeks, and dosage reduction is permitted if obtaining remission. When it decreases to 5 to 10 mg once a day, the therapy still requires 1 to 2 years at least. Short-term large-dose therapy is preferable for those out of control or in severe condition. It is worth noting that GC treatment could not reduce the recurrence of the disease, so that GC combined with other immunosuppressive are superior to the monotherapy. Besides, long-term application of GC could have profiles of adverse reactions.

cDMARDs

Methotrexate (MTX) had clinical remission rate of 75% to 81% and sustained remission rate of 50%, significantly reducing activity scores such as Indian Takayasu Clinical Activity Score as well as maintenance dose and cumulative dose of GC.^[15,16] However, the recurrence rate and radiological progression rate were 54% and 38%, respectively.^[15,16] Gastrointestinal discomfort and abnormal liver function were more common, while secondary infections were less. The prescription oral dose was recommended 7.5 to 15.0 mg/week. Leflunomide (LEF) (10–20 mg/d orally) combined with GC treatment was demonstrated effective in TA with clinical remission rate of 80% and successful reduction in disease activity and GC dosage.^[17,18] Besides, nearly 50% of patients could maintain sustainable remission in 9.1-month follow-up. LEF treatment showed advantages in fewer adverse reactions and better patient tolerance, although 13.3%

had imaging progression. Mycophenolate mofetil (MMF) (1.0–1.5 g twice a day orally) combined with GC demonstrated effective for inducing clinical remission in 75% to 90% of patients, which significantly reduced the levels of inflammation indexes, improved the disease activity score, and tapered the GC dose.^[19,20] Cyclophosphamide (CTX) treatment (0.75–1.0 g/m² intravenously guttae per 4 weeks) combined with GC in adult TA patients reached high remission rate of 82.1% to 100%, with significant improvements in inflammatory indexes, disease activity score, systolic blood pressure, renal function, and even positron emission tomography/computed tomography (PET/CT) imaging.^[21,22] However, it showed difficulties in GC tapering and risks at high cumulative dose.^[23-25] The Caucasian population was prone to serious infection, hemorrhagic cystitis, renal insufficiency,^[22] while Asian population might be more common with gastrointestinal reactions, menstrual effects, and other adverse reactions.^[24]

bDMARDs

Refractory TA patients, who failed to obtain remission after using GC and at least two kinds of cDMARDs, are suggested to use bDMARDs for induction treatment if without contraindications such as infection and tumor. (1) Tocilizumab (TCZ): TCZ (8 mg/kg, intravenously guttae per 4 weeks) demonstrated effective for inducing remission

rate of 64% to 100% in case series followed by 6 to 24 months, with GC tapering from 12.5–40.0 to 4.5–5.0 mg per day.^[26-30] However, the randomized double-blinded placebo-controlled phase III clinical trial from Japanese refractory TA patients showed no significant difference in first relapse time between TCZ group and placebo group.^[31] Infection is the most common adverse event, followed by hematocytopenia and hyperlipidemia.^[27-34] (2) Tumor necrosis factor α inhibitor (TNFi): TNFi could reach remission in 74% to 93% of refractory TA patients, but 16% to 28% had lesion progression and 33% to 62% relapsed.^[32,35-37] Compared with other TNFi agents, infliximab yielded the highest remission rate.^[32,33,35-37] Latent tuberculosis and HBV infection must be excluded before treatment, and any infection needed to be on full alert during treatment. (3) Others: rituximab was reported effective in small-sampled clinical cases,^[38-40] while abatacept did not indicate significant reduction of relapse risk at 12 months compared with placebo treatment.^[41]

Surgical treatments in TARA

Surgical treatments in patients with TARA mainly referred to renal vascular reconstruction therapy, consisting of endovascular interventions such as percutaneous transluminal angioplasty (PTA) and stenting, and open surgery such as aortic-renal artery bypass, kidney transplantation, and so on.

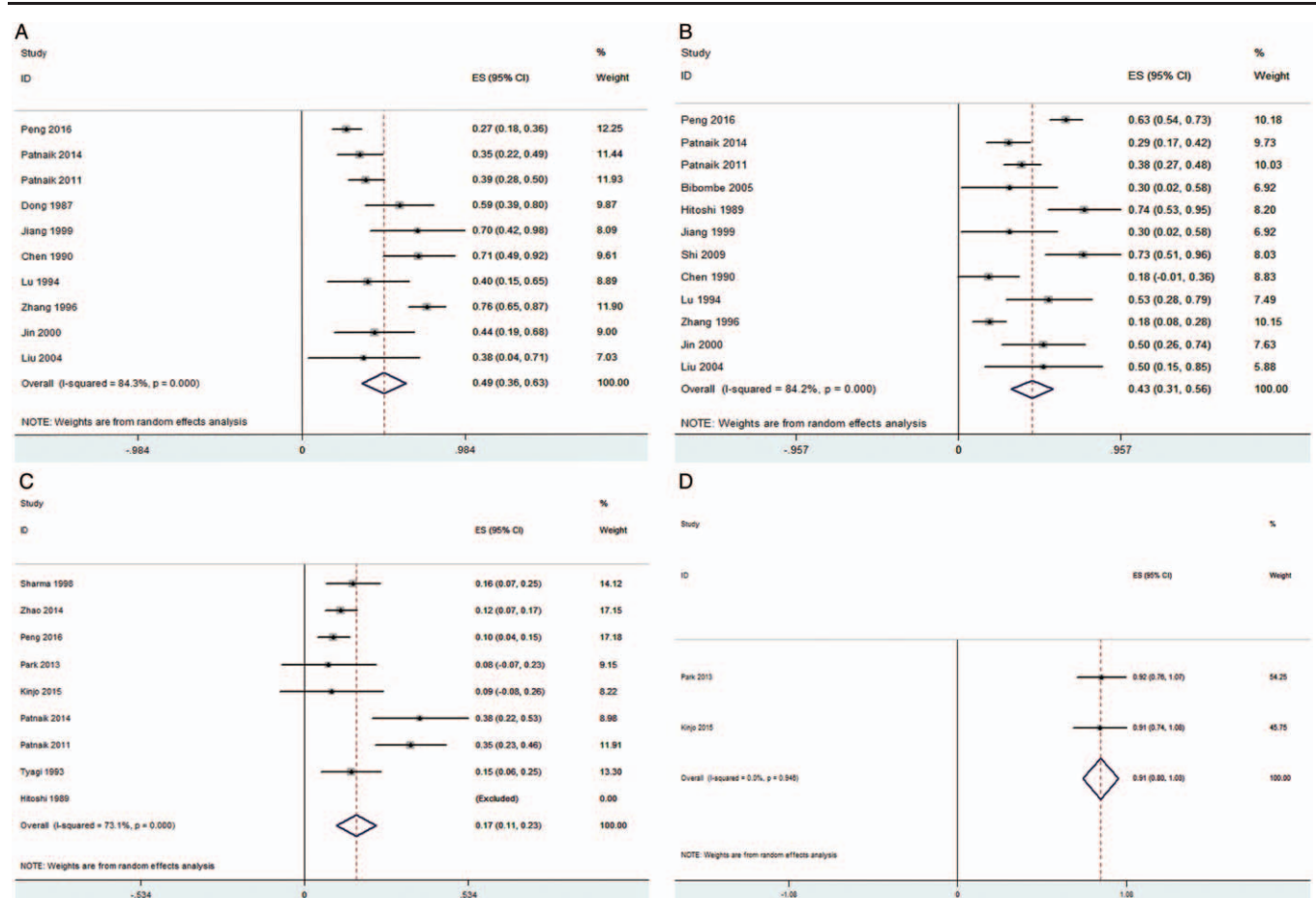


Figure 1: Systematic analysis of HBP cure rates (A), HBP improvements rates (B), restenosis rates (C), and 5-year patency rates (D) in patients with TARAS after PTA. HBP: Hypertension; PTA: Percutaneous transluminal angioplasty; TARAS: Takayasu arteritis-induced renal artery stenosis.

Surgical treatments could help further improve severe complications such as refractory hypertension and renal insufficiency, quality of life, and long-term survivals. So far, there has been no systematic review and evidences of efficacy and safety all came from single-center case reports. Data from China showed satisfactory long-term survival rates after surgeries (5-year survival rate: 93.1%, 10-year survival rate: 90.1%), peri-operative mortality (2.12%), long-term mortality (8.23%), and reoperation rate (8.23%).^[42] Other countries also revealed the 20-year cumulative survival rate of 73.5%.^[13] Restenosis and aneurysm in anastomotic stoma were the major long-term complications, while heart failure was one of the common causes of death.

Endovascular intervention

PTA was considered as the first-choice surgical procedure in patients with TARAS, which was technically simple and easily successful with success rate of 91.6% (95% CI, 89.3%–94.0%, $P < 0.001$). What's more important, no graft was left and repetition was allowed. PTA treatment showed hypertension cure rate of 49% (95% CI, 36%–63%, $P < 0.001$) [Figure 1A], hypertension improvement rate of 43% (95% CI, 31%–56%, $P < 0.001$) [Figure 1B], restenosis rate of 17% (95% CI, 11–23%, $P < 0.001$) [Figure 1C], and 5-year patency rate of 91% (95% CI, 80–100%, $P < 0.001$) [Figure 1D]. Nevertheless, sometimes

there were technical difficulties in crossing unnatural stenosis and inability to repeat and prolong balloon expansion, especially in patients with abdominal aortic disease, proximal renal artery, and stenosis. Few cases of adverse events were seen in congestive heart failure, renal failure, renal artery rupture, renal pseudo-aneurysm, renal artery fistula, thrombosis or occlusion, and so on.

Stent procedures were usually considered in ostial and long lesions of TARAS and in cases concomitant with aneurysm or dissection. Stent treatment indicated hypertension improvement rate of 41% (95% CI, 22%–59%, $P = 0.001$) [Figure 2A], restenosis rate of 48% (95% CI, 16%–80%, $P = 0.006$) [Figure 2B], 1-year patency rate of 73% (95% CI, 54%–92%, $P = 0.140$) [Figure 2C], and 5-year patency rate of 35% (95% CI, 13%–58%, $P = 0.857$) [Figure 2D]. Progressive renal insufficiency was seen in 3.4% of patients, and further Cox regression analysis showed that stenting was a risk factor for restenosis in TARAS (RR 3.41, 95% CI: 1.575–7.370, $P = 0.002$).^[43]

Open surgery

Open surgical treatments were suggested having hypertension improvement rate of 57% (95% CI, 42%–72%, $P = 0.015$) [Figure 3A], restenosis rate of 27.6% (95% CI,

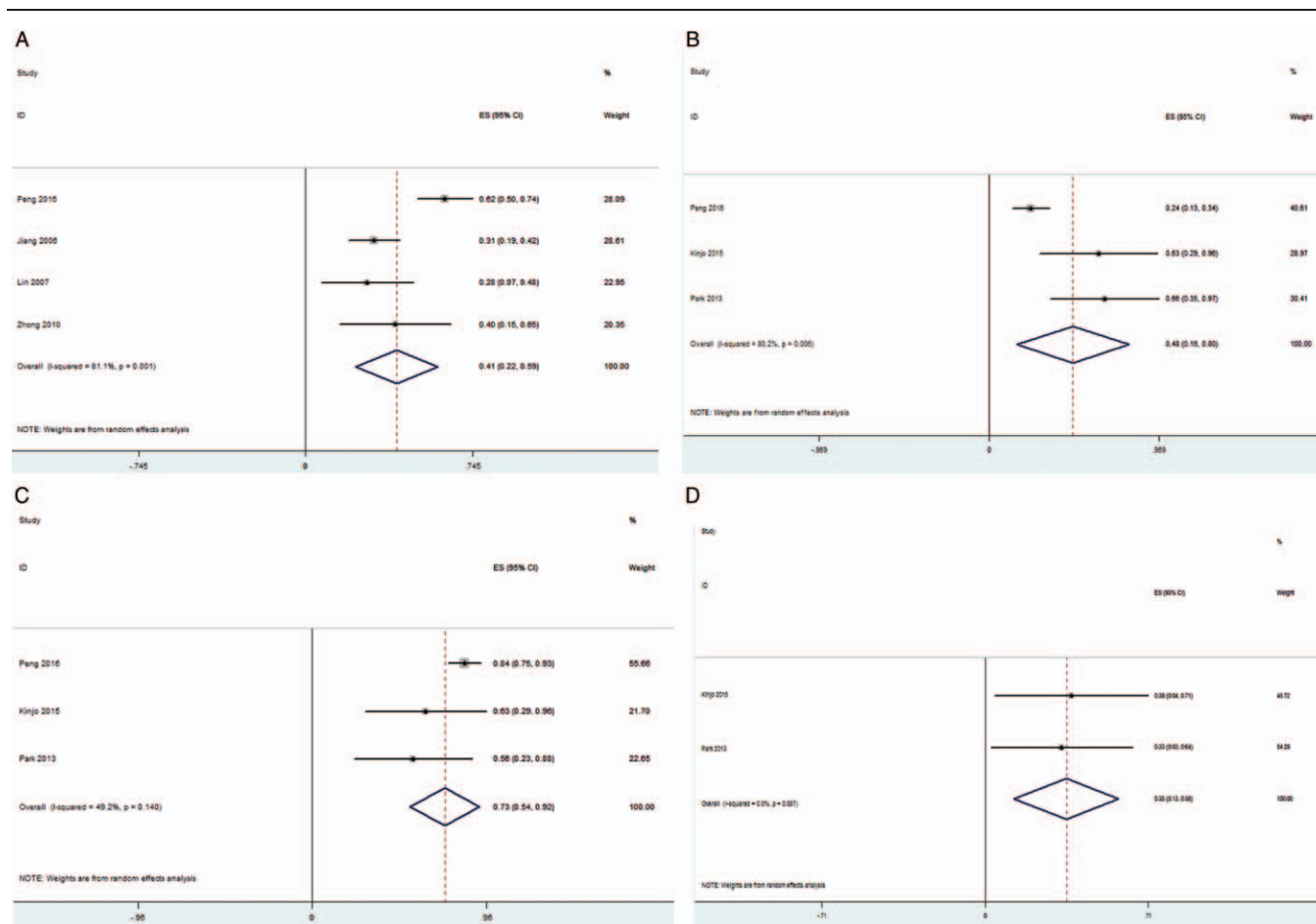


Figure 2: Systematic analysis of HBP improvements rates (A), restenosis rates (B), 1-year patency rates (C), and 5-year patency rates (D) in patients with TARAS after stents. HBP: Hypertension; TARAS: Takayasu arteritis-induced renal artery stenosis.

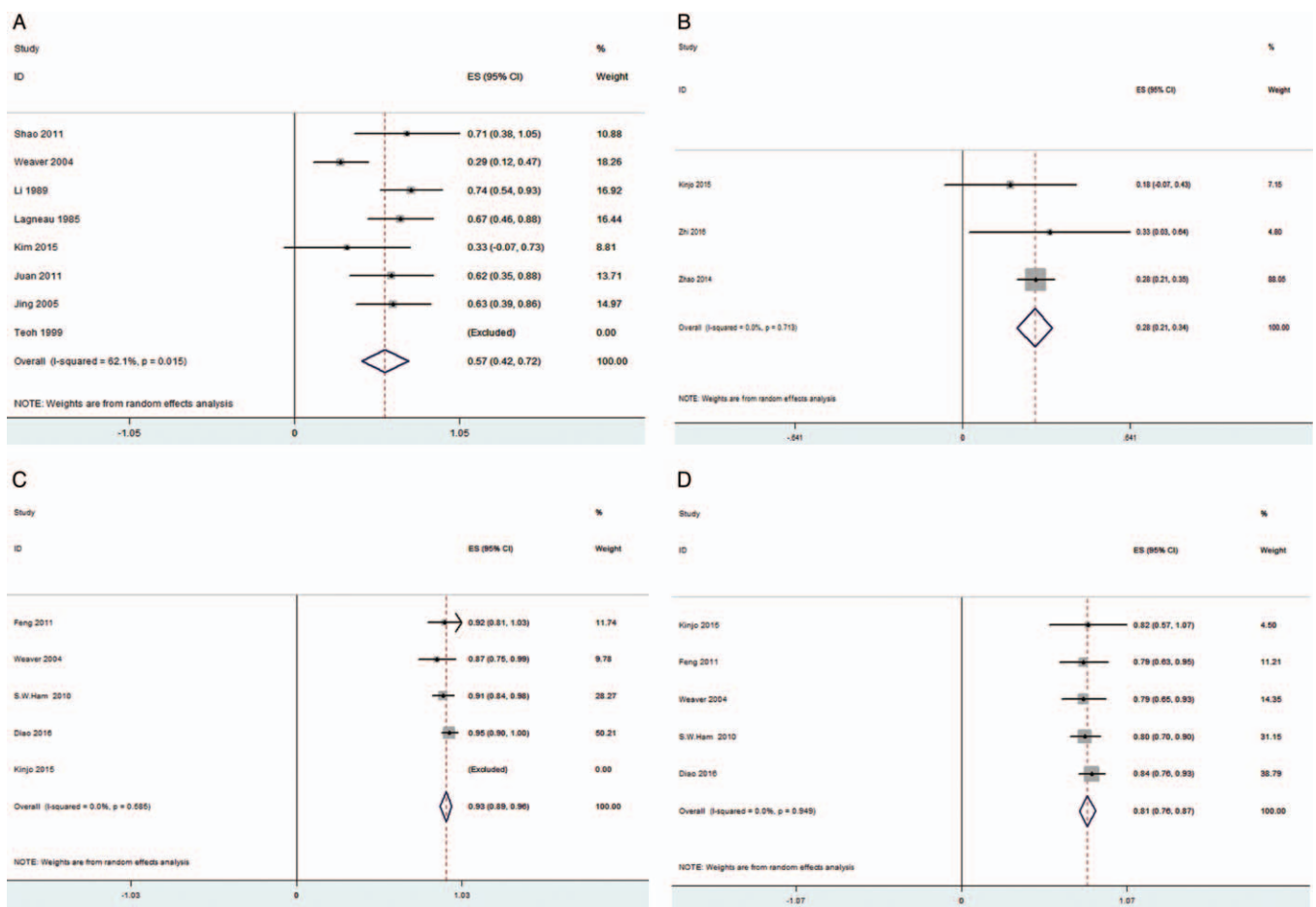


Figure 3: Systematic analysis of HBP improvements rates (A), restenosis rates (B), 1-year patency rates (C), and 5-year patency rates (D) in patients with TARAS after open surgery. HBP: Hypertension; TARAS: Takayasu arteritis-induced renal artery stenosis.

21%–34%, $P = 0.713$) [Figure 3B], 1-year patency rate of 92.7% (95% CI, 89%–96%, $P = 0.585$) [Figure 3C], and 5-year patency rate of 81.5% (95% CI, 76%–87%, $P = 0.949$) [Figure 3D]. The total technical success rate of open surgeries was 50% (95% CI, 18%–83%, $P = 0.052$). Early complications included infection, hemorrhage, acute thrombosis, and so on, while 10-year late complications included renal artery restenosis, chronic thrombosis or occlusion, stroke, and so on.

Discussion

The principles of treating patients with TARA are to actively control inflammation, to induce disease remission, to protect organ function, and to prevent complications. Rheumatologists should be dominated for disease diagnosis, activity evaluation, and initial treatment strategy-making. Collaborations of multidisciplinary team (MDT) consisting of vascular surgery, nephrology, cardiology, cardiac surgery, urology, and neurology are encouraged and preferred especially in patients of TARA with multiple organs involvement or with severe complications. Thus, it is wise and beneficial to combine medical treatment and surgical treatment as a whole system.

For active patients with TARA, medications are the first-step treatment to suppress the immune-mediated

inflammatory responses. The alternatives and applications of medications in TARA referred to those in TA. In induction treatment phase, the regimen of GC combined with cDMARDs is a classic initial therapy strategy. MTX, LEF, or MMF is preferred for patients without severe complications, while CTX is the priority for patients with severe complications. In maintenance treatment phase after remission, GC and cDMARDs could decrease gradually to maintenance dose to ensure disease stability. For refractory patients who failed to reach remission with first-line therapy or occurred relapse, bDMARDs are preferred for alternatives.

For the patients with severe vascular lesions caused by arterial stenosis or occlusion and without reversible benefits from anti-inflammation treatments, surgical interventions provide the further possibility of directly reconstructing renal artery, alleviating hypertension, and improving organ functions of kidney, brain, and heart. It is fundamentally important to make sure that disease activity has been controlled, because active disease of TARA increases the risks of operation-related death and post-operation complications.^[44] It has been supported that early and comprehensive medical treatments contribute to better long-term prognosis.^[45] Patients who accepted open operation or PTA might enjoy significantly higher 10-year patency rate of target vessels compared to those who

implanted stenting. However, there was no significant difference in 10-year cumulative survival rate between open surgeries and endovascular interventions, although more severe complications such as cerebral hemorrhage and tamponade occurred in patients receiving open surgeries.^[46]

Actually, TARA is not separated from the patients and usually accompanying with other vascular involvements such as carotid artery, intracranial artery, coronary artery, and so on. The comprehensive discussion and balance of treatment strategy by MDT is strongly recommended to consider pros and cons of surgical treatments, and to figure out timing and procedure in details. Only in rare emergencies such as aortic aneurysm and aortic dissection, immediate surgical interventions could be undergone before medical treatment. After surgeries, continuous medical treatments are necessary in follow-ups.^[47]

There are still some limitations in current evidence. First of all, as a rare disease, it is difficult to conduct randomized controlled clinical trials in medical and surgical treatments in patients with TA to obtain high-quality evidences. Second, existed evidences derived from retrospective, small-sample, and single-center cases with discrepancies in treatment alternatives are weak, for lacking the standardized guidelines in TARA. Third, there is no consensus on evaluation and follow-up indicators to assess the therapeutic efficacy and safety, so that it is quite difficult to perform a valuable meta-analysis. Fourth, dead patients are neglected and missed so that there might exist bias and confounders in assessing long-term efficacy and survivals. Last but not least, the majority literatures provide little information on pre-operative and post-operative medical treatment, which might obviously influence the judgement on therapeutic efficacy.

Conclusions

Management of TARA is one of the greatest challenges in patients with TA. A model of multidisciplinary consultation and collaboration should be recommended for the management process. Based on these evidences, it is necessary to establish further consensus or guideline of diagnosis, assessment, and treatment in TARA to help clinical physicians standardize management and improve outcomes.

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Conflicts of interest

None.

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