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# Overall survival and mortality risk factors in Takayasu's arteritis: A multicenter study of 318 patients

Adrien Mirouse[a,b,c,d,e], Lucie Biard[f,g], Cloé Comarmond[a,b,c,d,e], Marc Lambert[h], Arsène Mekinian[a,i,j], Yasmina Ferfar[a,b,c,d,e], Jean-Emmanuel Kahn[k], Ygal Benhamou[l], Laurent Chiche[m], Fabien Koskas[m], Philippe Cluzel[n], Eric Hachulla[h], Emmanuel Messas[o], Patrice Cacoub[a,b,c,d,e], Tristan Mirault[o], Matthieu Resche-Rigon[f,g], David Saadoun[a,b,c,d,e,*], for the French Takayasu network

[a] Sorbonne Universités, UPMC Univ Paris 06, UMR 7211, Inflammation-Immunopathology-Biotherapy Department (DHU i2B), F-75005, Paris, France
[b] INSERM, UMR_S 959, F-75013, Paris, France
[c] CNRS, FRE3632, F-75005, Paris, France
[d] AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, F-75013, Paris, France
[e] Centre de Référence des Maladies Auto-Immunes et Systémiques Rares, Centre de Référence des Maladies Auto-Inflammatoires et de l'Amylose, France
[f] AP-HP, SBIM, Hôpital Saint-Louis, Université Paris Diderot, Paris 7, Paris, France
[g] INSERM, ECSTRA Team, CRESS UMR-S 1153, 75010, Paris, France
[h] Hôpital Claude Huriez, Service de Médecine Interne, Centre de Référence des Maladies Auto-Immunes et Systémiques Rares du Nord et Nord-Ouest (CeRAINAO), CHU, Université de Lille, Lille, France
[i] Department of Internal Medicine - Hôpitaux de Paris, Hôpital Saint-Antoine, 184, rue du Faubourg Saint-Antoine, 75012, Paris, France
[j] UPMC University Paris 06, Paris, France
[k] Service de Médecine Interne, Hôpital Foch, Suresnes, France
[l] Service de Médecine Interne, CHU de Rouen, Rouen, France
[m] AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Service de Chirurgie Vasculaire, UPMC-Paris VI, Paris, France
[n] AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Département d'Imagerie CardioVasculaire et de Radiologie Interventionnelle, UPMC Paris VI, INSERM-CNRS-LIB, Paris, France
[o] AP-HP, Hôpital Européen Georges-Pompidou, Service de Médecine vasculaire, INSERM UMR970, PARCC, Centre de référence des maladies vasculaires rares, DHU pathologies artérielles rares et communes, Hôpitaux Universitaires Paris Ouest, Université Paris Descartes, Sorbonne Paris Cité, Paris, France

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ABSTRACT

*Objective:* To report the long term mortality in Takayasu arteritis (TA) and to identify prognosis factors.
*Methods:* We analyzed the causes of death and the factors associated with mortality in a cohort of 318 patients [median age at diagnosis was 36 [25–47] years and 276 (86%) patients were women] fulfilling American College of Rheumatology and/or Ishikawa criteria of TA. A prognostic score for death and vascular complications was elaborated based on a multivariate model.
*Results:* Among 318 TA patients, 16 (5%) died after a median [IQR] follow-up of 6.1 [2.8–13.0] years. The median age at death was 38 [25–47] years with 88% of women. Main causes of death included mesenteric ischemia (n = 4, 25%) and aortic aneurysm rupture (n = 4, 25%). The mortality rate at 5 and 10 years was of 1.9% and 3.9%, respectively. Caucasians (p = 0.049) and smokers (p = 0.002) TA patients were more likely to die. There was an increased mortality in TA (SMR with 95% confidence interval, 2.73 [1.69–4.22]) as compared to age and sex matched healthy controls. We defined high risk patients for death and vascular complications according to the presence of two of the following factors (*i.e* a progressive clinical course, thoracic aorta involvement and/or retinopathy). In the high risk TA group, the 5-year incidence of death and vascular complication was 48.5% compared to 21.6% (p = 0.001) in those with low risk.
*Conclusion:* The overall mortality in our Takayasu cohort was 5% after a median follow-up of 6.1 years. We identified specific characteristics that distinguish TA patients at highest risk for death and vascular complications.

* Corresponding author. Department of Internal Medicine and Clinical Immunology, Hôpital Pitié-Salpêtrière, 83 boulevard de l'hôpital, 75013 Paris, France.
*E-mail address:* david.saadoun@aphp.fr (D. Saadoun).

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**Table 1**
Main characteristics of 318 Takayasu patients and according to gender and geographic origin.

| | Overall population n = 318 | Gender | | | Ethnic origins | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Women (n = 259) | Men (n = 42) | p-value | White (n = 87) | North Africa (n = 73) | Black (n = 56) | Other (n = 17) | p-value |
| **Age > 35 at TA diagnosis** | | 127 (52%) | 18 (47%) | ***0.61*** | 49 (58%) | 35 (51%) | 16 (30%) | 11 (65%) | ***0.006*** |
| **Cardiovascular risk factors (n = 267)** | | | | | | | | | |
| Smoker | 75 (28%) | 57 (26%) | 15 (42%) | ***0.07*** | 33 (40%) | 8 (12%) | 7 (15%) | 5 (31%) | ***0.0002*** |
| Hypertension | 70 (26%) | 57 (26%) | 8 (22%) | ***0.69*** | 10 (12%) | 22 (32%) | 14 (29%) | 7 (44%) | ***0.005*** |
| Dyslipidemia | 35 (13%) | 32 (14%) | 2 (5%) | ***0.19*** | 13 (16%) | 9 (13%) | 3 (6%) | 2 (12%) | ***0.44*** |
| Diabetes mellitus | 16 (6%) | 15 (7%) | 1 (3%) | ***0.71*** | 8 (10%) | 3 (4%) | 1 (2%) | 2 (12%) | ***0.16*** |
| **Topography of arterial lesions (n = 260)** | | | | | | | | | |
| Supra-aortic branches | 219 (84%) | 189 (73%) | 30 (71%) | ***0.85*** | 78 (90%) | 59 (81%) | 38 (68%) | 13 (76%) | ***0.012*** |
| Thoracic aorta | 176 (67%) | 149 (58%) | 27 (64%) | ***0.50*** | 66 (76%) | 45 (62%) | 35 (62%) | 11 (65%) | ***0.19*** |
| Abdominal aorta | 142 (55%) | 124 (48%) | 18 (43%) | ***0.62*** | 51 (59%) | 39 (53%) | 29 (52%) | 12 (71%) | ***0.52*** |
| **Signs/Symptoms at TA diagnosis (n = 318)** | | | | | | | | | |
| Constitutional symptoms | 106 (33%) | 87 (55%) | 19 (73%) | ***0.90*** | 37 (70%) | 21 (60%) | 24 (62%) | 4 (57%) | ***0.74*** |
| Heart failure | 14 (4%) | 9 (4%) | 5 (14%) | ***0.034*** | 5 (6%) | 4 (7%) | 2 (4%) | 0 (0%) | ***0.96*** |
| Myocardial infarction | 7 (2%) | 5 (4%) | 2 (12%) | ***0.19*** | 1 (3%) | 1 (4%) | 2 (7%) | 0 (0%) | ***0.86*** |
| Retinopathy | 14 (4%) | 12 (9%) | 1 (5%) | ***1*** | 4 (10%) | 4 (13%) | 2 (6%) | 3 (38%) | ***0.11*** |
| Stroke | 32 (10%) | 27 (12%) | 5 (14%) | ***0.79*** | 12 (15%) | 5 (58%) | 4 (8%) | 3 (21%) | ***0.32*** |
| Aneurysmal lesion | 194 (61%) | 175 (76%) | 19 (51%) | ***0.005*** | 57 (67%) | 50 (78%) | 39 (72%) | 14 (88%) | ***0.27*** |
| Elevated CRP | 130 (41%) | 110 (75%) | 18 (72%) | ***0.81*** | 42 (76%) | 32 (73%) | 27 (68%) | 4 (67%) | ***0.74*** |
| **Clinical course of TA (n = 273)** | | | | 0.86 | | | | | 0.87 |
| Acute clinical course | 149 (55%) | 123 (56%) | 20 (54%) | | 42 (52%) | 35 (54%) | 29 (59%) | 7 (50%) | |
| Progressive clinical course | 124 (45%) | 97 (44%) | 17 (46%) | | 39 (48%) | 30 (46%) | 20 (41%) | 7 (50%) | |
| **Treatments (n = 293)**[a] | | | | 0.074 | | | | | 0.58 |
| Corticosteroids | 283 (89%) | 64 (33%) | 12 (32%) | | 20 (28%) | 16 (29%) | 17 (36%) | 3 (25%) | |
| Immunosuppressants[b] | 196 (66%) | 76 (39%) | 18 (47%) | | 35 (49%) | 23 (42%) | 20 (43%) | 4 (33%) | |
| Biotherapy | 11 (5%) | 9 (5%) | 2 (5%) | | 0 (0%) | 2 (4%) | 2 (4%) | 0 (0%) | |

Data are expressed as n (%) or median [interquartile].
[a] Fisher's test comparing Corticosteroid only, Immunosuppressants, Biotherapies and absence of treatment.
[b] Immunosuppressants: methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide.

## 1. Introduction

Takayasu arteritis (TA) is a chronic large vessel vasculitis of unknown origin, mainly occurring in young women. It affects predominantly aorta and its branches, leading to wall thickening, fibrosis, stenosis, and vessel occlusion [1]. Prevalence of TA varies from 0.004% in Japan to 4.7 cases per million in the UK [2,3]. Clinical manifestations are varied and related to stenotic or occlusive vessels' lesions, such as the aortic arch (pulseless disease), descending thoracic or abdominal aorta (atypical coarctation), renal arteries, coronary arteries, and pulmonary arteries and reflect end-organ ischemia.

Although TA has a worldwide distribution, the disease is known to be more common in young women mostly in the second or the third decade of life, originating more commonly from Asia or North Africa than from Europe and North America. Most epidemiologic data come from Asia since TA is more frequent in these countries. Some studies have suggested there might be some differences according to gender but also ethnic origin [4–6]. Moreover, the clinical features of TA may differ depending on age onset [7]. These differences point out the need to dispose of data on TA epidemiology in Caucasian countries as well.

TA significantly increases morbidity and mortality [8]. TA has been reported to be associated with a higher mortality rate compared to general population of the same age [9,10]. Due to the wide variation in the course of TA, predicting outcome is challenging. An early identification of patients with higher mortality could help to prevent deaths and vascular complications. Prognosis factors have been reported in the past [11,12]. Ishikawa et al. first suggested that either the presence of a major complication or a progressive course were factors predicting poor prognosis [11]. The presence of both a major complication and progressive course were the worst prognostic indicators, with an estimated survival rate of 43% at 15 years. However, in these studies, patients with poorer outcome were those who already had vascular complications. There is still an unmet need to identify prognosis factors prior to complications to target patients needing more aggressive therapies.

The present study was undertaken to report the long term mortality in TA. We analyzed the main causes of death and the standardized mortality ratio (SMR) in a cohort of 318 patients with TA from the French Takayasu network. We defined high risk patients for death and vascular complications according to a multivariate model.

## 2. Patients and methods

### 2.1. Patients

We conducted a retrospective multicenter study in referral centers from the French Takayasu network between 1970 and 2014. We identified 318 patients with TA fulfilling the TA ACR and/or Ishikawa criteria modified by Sharma [13,14]. This study was approved by the local ethics committee. The patients' clinical baseline characteristics, age at diagnosis of TA, geographic origin, gender, years of diagnosis of TA, pattern of clinical course (as previously described [11]), cardiovascular risk factors, associated diseases, constitutional symptoms, symptoms of TA, blood tests [hemogram, creatininemia, C-reactive protein (CRP) levels], and imaging features were recorded.

### 2.2. Definitions of study endpoints

Vascular complications were defined as the occurrence of at least one of the following events: new arterial occlusion, myocardial infarction and/or heart failure, aortic regurgitation, new-onset or worsening arterial aneurysm, occurrence of stroke/transitory ischemic attack, end-stage renal failure. Mortality and cause of death were assessed for all patients during the follow-up. At each visit, criteria for disease activity were applied based on symptoms assessment, physical examination, and laboratory studies. Complete aortic and supra aortic trunks imaging was performed every 6 months or sooner if there was suspicion of disease flare or disease progression.

**Table 2**
Comparison between died and alive TA patients.

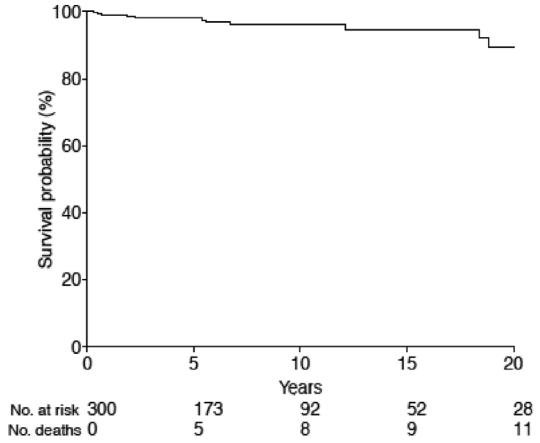
| | Dead n = 16 | Alive n = 284 | p-value[a] |
|---|---|---|---|
| Gender, male | 2 (12%) | 38 (14%) | 0.97 |
| Age at TA diagnosis, years | 38 [25–47] | 36 [25–47] | |
| > 35 at TA diagnosis | 9 (56%) | 7 (2.5%) | 0.065 |
| Ethnic origin | | | 0.049 |
| White | 9 (56%) | 83 (29%) | |
| North Africa | 5 (31%) | 70 (25%) | |
| Black | 0 (0%) | 59 (21%) | |
| Other | 2 (13%) | 12 (4%) | |
| Cardiovascular risk factors | | | |
| Smoker | 8 (50%) | 66 (27%) | < 0.0001 |
| Hypertension | 8 (50%) | 60 (25%) | 0.18 |
| Dyslipidemia | 1 (6%) | 34 (14%) | 0.51 |
| Diabetes mellitus | 1 (6%) | 14 (6%) | 0.33 |
| Topography of arterial lesions | | | |
| Supra-aortic branches | 13 (81%) | 213 (75%) | 0.89 |
| Thoracic aorta | 13 (81%) | 172 (61%) | 0.056 |
| Abdominal aorta | 11 (69%) | 138 (49%) | 0.088 |
| Signs/Symptoms at TA diagnosis | | | |
| Carotid tenderness | 0 (0%) | 33 (14%) | 0.20 |
| Heart failure | 2 (13%) | 12 (5%) | 0.13 |
| Myocardial infarction | 0 (0%) | 7 (5%) | 0.53 |
| Retinopathy | 0 (0%) | 14 (10%) | 0.39 |
| Stroke | 1 (7%) | 18 (8%) | 0.78 |
| Aneurysmal lesion | 13 (87%) | 189 (73%) | 0.78 |
| CRP, mg/L | 16 [8–25] | 22 [6–68] | 0.51 |
| Creatinine | 70 [64–82] | 67 [58–76] | 0.53 |
| Clinical course of TA (n = 269) | | | 0.42 |
| Acute clinical course | 7 (58%) | 140 (54%) | |
| Progressive clinical course | 5 (42%) | 117 (46%) | |
| Treatments (1st line) | | | 0.92 |
| None | 6 | 83 | |
| Corticosteroids only | 6 | 83 | |
| Immunosuppressive | 4 | 105 | |
| Biotherapies | 0 | 13 | |
| Revascularization | 2 | 18 | 0.24 |

Data are expressed as n (%) or median [interquartile].
[a] Log Rank test for Overall Survival.

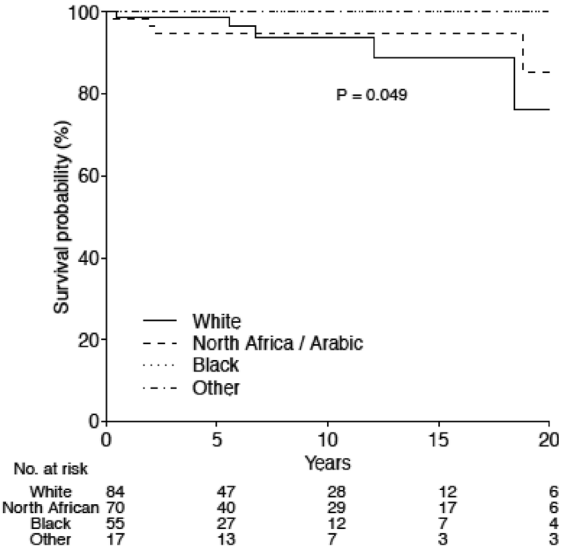
### 2.3. Statistical analysis

Continuous variables are presented as median [interquartile range, IQR], categorical variables are presented as count (percent). To compare the observed mortality with the expected mortality a standardized mortality ratio (SMR) was used. SMR is the ratio of the observed patient mortality and the mortality in the total French population with the corresponding sex and year of birth. Overall survival was defined as the time from the date of TA diagnosis and the date of death (of any cause), or last follow-up. Complication-free survival was defined as the time from the date of TA diagnosis and the date of first vascular complication, death (of any cause), or last follow-up. Survival functions were estimated using the Kaplan-Meier method. Factors associated with the time-to-event outcomes were evaluated using Cox models, with estimation of hazards ratios and their 95% confidence interval. The proportional hazards assumption was assessed with examination of Schoenfeld's residuals and Grambsch and Therneau's test. For death and complication-free survival, variables associated with the outcome at a 0.05 level were candidates for a multivariate analysis. The multivariate model selection was based on 1000 bootstrap samples drawn from the original sample with replacement. On each bootstrap sample, a variable selection using a backward stepwise selection algorithm was performed (stopping rule on p-value, with cut-off at 0.05). The final multivariate model was defined as the most frequently selected model among the 1000 bootstrap samples. A prognostic score for death and complication-free survival was then derived. It was defined as a linear predictor including a unit coefficient associated to each of the final selected variables in the multivariate model. The linear predictor was then simplified in two categories: 0 or 1 (low risk) versus 2 or 3 (high risk). The

**A. Overall survival**




**B. Survival according to ethnic origin**




**C. Survival according to tobacco smoking status**

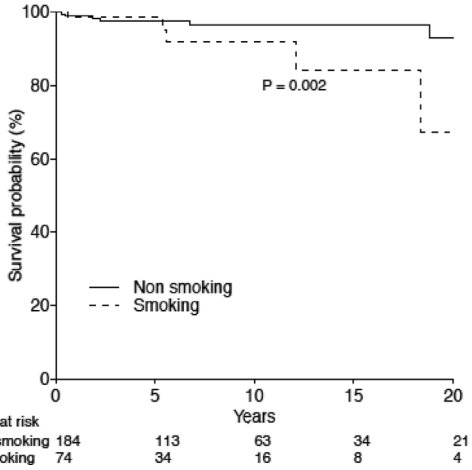



**Fig. 1. Overall survival and risk factors associated with survival.** A. Overall survival; **B.** Survival according to ethnic origin; **C.** Survival according to tobacco smoking status.

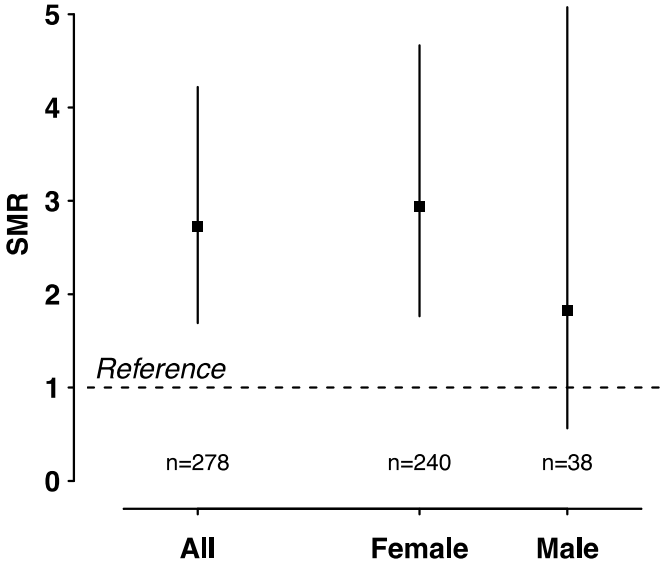



**Fig. 2.** Standardized mortality ratio (SMR).

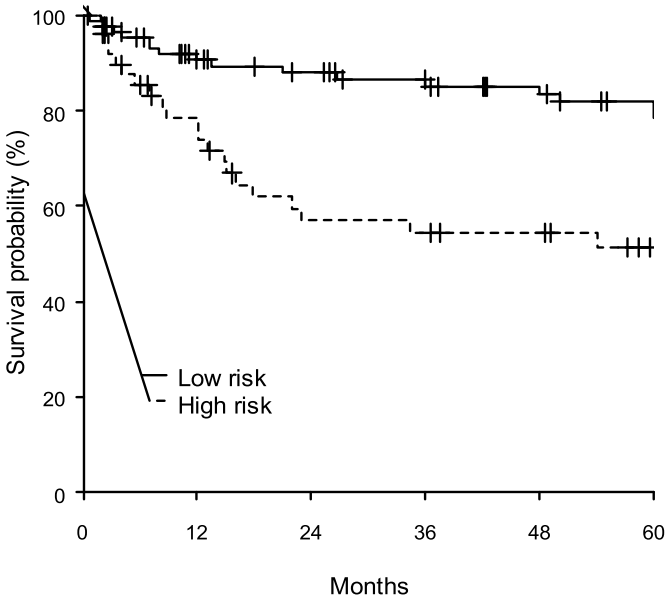



**Fig. 3.** Prognosis score for death and vascular complications.

score was validated using a resampling approach by bootstrap (N = 1000 samples). All tests were two-sided, p-values lower than 0.05 were considered as indicating significant associations. Analyses were performed using R statistical platform, version 3.0.2.

## 3. Results

### 3.1. Characteristics of the study population

We identified 318 patients fulfilling international criteria for TA, including 259 (86%) women (Table 1). Median age at diagnosis was 36 [interquartile range 25–47] years. Ethnic origins were Caucasian/White (n = 87, 37%), North-Africa (n = 73, 31%), Black (n = 56, 24%), and other (*i.e.* Asian, Indian, Middle-East) (n = 17, 7%). At diagnosis, 36%, 35%, and 30% of patients were classified as Ishikawa's group I, II, and III, respectively. The most frequent presentation was Numano type V (i.e. involvement of the entire aorta and its branches). The median time from symptom onset to TA diagnosis in our cohort was 0.8 [0–3.9] year. Most patients were treated with steroids (n = 283, 89%) and/or immunosuppressive therapies (n = 196, 66%).

### 3.2. Differences according to gender and ethnic origin

There was no difference in gender repartition according to ethnic origin. Men tended to be more frequently smokers (42% vs. 26%, p = 0.07) (Table 1). At diagnosis, male gender was associated with cardiac insufficiency (14% vs. 9%, p = 0.034), but less frequent aneurysmal lesions (51% vs. 76%, p = 0.005).

Comparison according to ethnic origin is presented in Table 1. White patients were more frequently smokers, were older at TA diagnosis and had less frequently hypertension. Supra-aortic vessels involvement varied according to ethnicity (p = 0.012), Black patients being the least affected by this localization (68%) at diagnosis.

### 3.3. Mortality

During a median follow-up of 6.1 [2.8–13.0] years, 16 (5%) patients died (Table 2). There was no difference in the death rate according to the year of TA diagnosis [Number of death/number at risk: 1970–1984, 5/18, HR (95% CI) 1; 1985–1999, 4/59, HR 3.15 (0.45–22.0), p = 0.25; 2000–2014, 7/223, HR 7.29 (0.63–84.8), p = 0.11]. Death causes were mesenteric ischemia (n = 4, 25%), aortic aneurysm rupture (n = 4, 25%), sudden death (n = 3, 19%), septic shock (n = 3, 19%), pulmonary embolism (n = 1, 6%), and cardiogenic shock (n = 1, 6%). One, five, and ten years' overall survival were 98.9% [95%CI: 97.8–100], 98.1% [96.4–99.8], and 96.1% [93.4–98.9%], respectively (Fig. 1). Factors associated with mortality were ethnic origin (Overall survival at 5 years: Caucasians 93.9% [87.1–100] vs. North Africa/Middle East 94.8% [89.2–100] vs. Black 100%, p = 0.049), p = 0.049, and tobacco smoking (91.8 [96.2–99.7] vs. 96.4% [82.9–100] p < 0.0001) (Table 2). One hundred and twenty-six patients had at least one vascular complication. The 1-, 5-, and 10-years complication free survival was 90% (95%CI: 86.6–93.6), 69.9% (64.3–76.0), and 53.7% (46.8–61.7), respectively. The overall SMR was 2.73 [CI 95% 1.69–4.22] (Fig. 2). The SMR was 2.94 [1.76–4.67] for women and 1.82 [0.56–5.08] for men.

### 3.4. Prognostic score of vascular complications and death

Progressive disease course at diagnosis (p = 0.017), thoracic aorta involvement (p = 0.009), and retinopathy (p = 0.002) were independently associated with death and complication free survival in multivariate analysis. A prognostic score was elaborated based on this final adjusted model, as a linear predictor with a unit coefficient associated to each of the three final selected variables (progressive disease course, thoracic aorta involvement and retinopathy). The linear predictor was then simplified in two categories: 0 or 1 (low risk, corresponding to the absence of any of the 3 selected factors or presence of one factor at diagnosis, respectively) versus 2 or 3 (high risk, corresponding to the presence of 2 or 3 factors). The probability of death and complication free survival in the low risk vs. high risk groups at one and five years was 90.7% (95%CI: 84.7–97.1) vs. 78.6% (67.6–91.4) at one year, and 78.4% (69.4–88.6) vs. 51.5% (38.3–69.2) at 5 years (p = 0.001) (Fig. 3).

## 4. Discussion

In the present study, we report the long term mortality in a cohort of 318 patients with TA. We analyzed the main causes of death and the SMR in our TA patients. We defined high risk patients for death and vascular complications according to a multivariate model. The most striking conclusions drawn by this study are 1) the overall mortality of 5% after a median follow-up of 6.1 years, 2) the 2.7 times higher

mortality in TA patients as compared to age-sex match healthy controls, 3) we developed a prognosis score that allow classifying patients as low or high risk to death or vascular complication.

Female dominance in TA patients has been consistently reported in previous studies. In this study, the female-to-male ratio was 6.6:1, which is in range with other ratios reported in European and Asian countries (4.3–10.5:1) [9,10,15–17]. Women had a lower prevalence of cardiac insufficiency but more frequent aneurysms lesions. Other studies have reported differences in TA disease localization according to gender [4]. Watanabe et al. have reported that male were older (median, 43.5 years) and had more localized abdominal lesions than women TA patients [7]. However, we did not find any gender differences according to TA localization in the present study.

Eighty one percent of deaths were directly attributable to a cardiovascular complication, mainly mesenteric ischemia and aortic aneurysm rupture. The remaining 20% of deaths were related to infectious complications during the course of the disease. With SMR, we reported a higher mortality than expected for the French population of same gender and age. These results are consistent with previous reports revealing that TA patients had a lower survival rate than those determined for the age-gender-matched general population and that cardio-vascular complications were the main cause of death in TA patients [10,18]. Interestingly, the SMR was higher in women than in men (2.94 vs 1.82).

Caucasian patients had a significantly higher mortality than other ethnic groups. However, they were older at TA diagnosis and more frequently smokers which may impact on mortality. On the other hand, the prevalence of hypertension was lower in Caucasians. Ethnic differences have been reported in TA. In a comparative study between TA patients from Japan, Korea, and India, Japanese patients had more frequently lesions at the aortic arch and/or its branches, while most lesions in Korean and Indian patients were at the abdominal aorta [5]. In a Norwegian study, Asian and African origin was significantly associated with abdominal aorta and renal arteries involvement compared to Caucasians [6]. In our study, we found that Black patients had less frequent supra-aortic vessels involvement.

Older studies have reported higher mortality, possibly reflecting an improvement in management of TA, including the use of biological therapies [19]. A population-based study in Korea reported a 5-year survival of 94.6% [10]. In this study, most TA patients were diagnosed after 45 years and the highest incidence was in the 65–69 years old group. In a Chinese cohort of 810 TA patients, 12 patients died during follow-up, mainly from cardio-vascular diseases [18]. This lower incidence of mortality may be explained by a shorter time of follow-up (median of 3.2 years) than in our study.

We developed a simple prognosis score based on three variables associated with complication-free survival in a multivariate model: progressive disease course, thoracic aorta involvement, and retinopathy. In patients classified as high risk, treatment intensification and close monitoring might be recommended to prevent these complications. All these three parameters are easily found at diagnosis and during TA follow-up. TA related retinopathy is not infrequent but may be underdiagnosed [20,21]. A complete ophthalmologic evaluation with fluoresceine angiography may be useful in TA patients.

We acknowledge some limitations in our study. This is a retrospective study over a long time period. Angiographic techniques have changed significantly over time and may affect the assessment of disease activity. However, in our cohort, 74% of patients were diagnosed after 2000, when CT-scan, MRI and ultrasonography were available for assessment of disease activity. Since TA is a rare disease, especially in Caucasian countries, we believe this study could add to the current knowledge on the disease. Factors identified as associated with mortality were determined in univariate analysis. Because of a low death-rate, it was not possible to determine whether these factors were independently associated with mortality alone. Nevertheless, we were able to develop a prognostic score for complication-free survival and death.

In conclusion, this French nationwide study of TA patients shows an overall mortality of 5% after a median follow-up of 6.1 years. The mortality rate at 5 and 10 years was of 1.9% and 3.9%, respectively. Caucasians patients and smokers were associated with mortality in TA. The mortality rate was 2.7 times higher in TA patients as compared to age-sex match healthy controls. We developed a simple and useful prognosis score to identify patients at risk for vascular complication or death.

## Conflict of interest disclosures

None.

## Permissions information

All illustrations and figures in the manuscript are entirely original and do not require reprint permission.

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