

## Diagnosis of Systemic Vasculitis of Autoimmune Origin in Rheumatoid Arthritis: Biopsy of Skeletal Muscle in Combination with Sural Nerve is Optimal - A Postmortem Clinicopathologic Study of 161 Patients

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### Abstract

**Aim:** The aim of this study was to determine the prevalence and severity of systemic vasculitis of autoimmune origin (A-SV) in various organs of rheumatoid arthritis (RA) patients, to find the best target of biopsy for recognition of A-SV, to ascertain the mortality due to A-SV, and clinically missed diagnosis of A-SV in RA.

**Patients and Methods:** One hundred sixty one (161) non- selected autopsy patients with RA were studied. RA was confirmed clinically according to the criteria of the American College of Rheumatology.

The causes of death and clinical diagnosis of A-SV were assessed by reviewing the clinical protocols and autopsy findings.

The prevalence and severity of vasculitis was specified histologically, based on evaluation of 12 organs (heart, lung, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal glands, skeletal muscle, peripheral nerve, skin and brain) in each of 161 patients.

The correlations between severity, mortality, and clinical diagnosis of A-SV were analyzed by Pearson's chi-squared ( $\chi^2$ ) test.

**Results and Conclusions:** A-SV was present RA in 33 (20.49%) of 161 patients. Ten (30.3%) of these 33 cases were attested as "severe", and 23 (69.7) as "mild".

Cases of systemic vasculitis of autoimmune or septic origin were histologically excluded in 125 (77.64%) of 161 RA patients.

A-SV complicated RA especially in women, with high prevalence at late onset of the disease which represented a higher risk of survival. Mild or severe A-SV complicated RA in both sexes, and at any time in the course of the disease.

Severity of A-SV not influenced the mortality or clinical diagnosis of A-SV. The mortality due to A-SV depended on the location of the affected vessels (and involved organs), and not the severity of A-SV.

A-SV may be regarded as one of the most insidious complications of RA, and proves to be one of the most likely clinically missed complications of RA.

The high prevalence of vasculitis in the skeletal muscles and peripheral nerves makes biopsy of the sural nerve (with surrounding muscles) a good target for the confirmation of suspected systemic vasculitis (with or without visible involvement of the skin).

**Keywords:** Rheumatoid Arthritis; Systemic Vasculitis of Autoimmune Origin; Cause of Death; Mortality

### Abbreviations

RA: Rheumatoid Arthritis; A-SV: Systemic Vasculitis of Autoimmune Origin; ARA: American College of Rheumatology; CoD: Cause of Death; Cl+: Clinically Diagnosed; Cl-: Clinically not Diagnosed; ND: No Data Available

### Introduction

In autoimmune diseases the vascular system is the most important target of immunological processes, manifesting themselves as vasculitis with characteristic stage dependent structural changes in blood vessels of different caliber.

Systemic vasculitis of autoimmune origin (A-SV) may be regarded as one of the basic manifestations of rheumatoid arthritis (RA) as well [1]. As Bywaters put it, "Vasculitis is RA itself [2]". In clinical practice the diagnosis of systemic vasculitis may be difficult without visible involvement of the skin.

### Objective

The aim of this study was to determine the prevalence and severity of A-SV in various organs of RA patients, to find the best target of biopsy for recognition of A-SV, to ascertain the mortality due to A-SV, and clinically missed diagnosis of A-SV in RA.

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**Patients and Methods**

At the National Institute of Rheumatology 9475 patients died between 1969 and 1992; among them 161 patients with RA, who were autopsied [1].

RA was confirmed clinically according to the criteria of the American College of Rheumatology (ACR) [3].

The causes of death and clinical diagnosis of A-SV were assessed (ascertained) by reviewing the clinical protocols and autopsy findings.

The existence (prevalence) and severity of vasculitis in various organs was determined microscopically by a detailed review of extensive histological material [4-6]. From each patient 50-100 tissue blocks of 12 organs (heart, lung, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal glands, skeletal muscle, peripheral nerve, skin and brain) were studied microscopically [1].

The correlations between severity, mortality, and clinical diagnosis of A-SV were analyzed by Pearson’s chi-squared ( $\chi^2$ ) test [7].

**Glossary of definitions [1,8]**

“**Prevalence**” concerns the presence of vasculitis in blood vessels. Prevalence of vasculitis indicates the presence of vasculitis in blood vessels of different calibers in various organs.

“**Severity**” means different degrees of inflammation (density of inflamed sections or sectors) of blood vessels in various organs. Severity of vasculitis was evaluated by semi-quantitative visual estimation on a 0 to 3 plus scale (based on the number of involved vessels per /light microscopic field x40 objective, Olympus BX51). Values of the semi-objective score system: “0” - no vasculitis, “1” - occasional blood vessels with vasculitis, “2” - less than 5 involved blood vessels, “3” - five or more involved blood vessels/microscopic field. (In case of medium size arteries or veins this corresponds to the absolute number of involved medium size vessels of a tissue sample, e.g. 5 or more than five medium size vessels/tissue sample with a x20 objective).

**Results**

Systemic vasculitis complicated RA in 36 (22.36%) of 161 patients. Three (1.86%) of them was associated with generalized lethal septic infection, which were regarded as systemic vasculitis of septic origin, and have been excluded from this study.

A-SV was present RA in 33 (20.49%) of 161 patients. Ten (30.3%) of these 33 cases were attested as “severe” (with average cumulative value of severity / RA patient with A-SV > 0.3), and 23 (69.7) as “mild” (with average cumulative value of severity/RA patient with A-SV ≤ 0.3).

Cases of systemic vasculitis of autoimmune or septic origin were histologically excluded in 125 (77.64%) of 161 RA patients.

Demographics, onset and duration of diseases complicated by A-SV are summarized in table 1.

| Sex                 | Number of Autopsies | Average age in years at death | Range (in years) | Age at onset of disease | Disease duration (in years) |
|---------------------|---------------------|-------------------------------|------------------|-------------------------|-----------------------------|
| RA patients         | 161                 | 65.32                         | 88 - 16          | 50.83                   | 14.43                       |
| Female              | 116                 | 64.95                         | 87 - 16          | 50.19                   | 14.79                       |
| Male                | 45                  | 66.29                         | 88 - 19          | 52.57                   | 13.46                       |
| With A-SV           | 33                  | 67.15                         | 83 - 32          | 56.90                   | 11.68                       |
| Female              | 21                  | 67.19                         | 82 - 32          | 59.05                   | 10.47                       |
| Male                | 12                  | 67.08                         | 83 - 53          | 53.50                   | 13.58                       |
| “Severe” A-SV       | 10                  | 67.80                         | 82 - 58          | 55.22                   | 13.67                       |
| Female              | 7                   | 69.00                         | 82 - 58          | 55.17                   | 15.67                       |
| Male                | 3                   | 65.75                         | 78 - 58          | 55.33                   | 9.67                        |
| “Mild” A-SV         | 23                  | 66.87                         | 83 - 32          | 57.59                   | 10.86                       |
| Female              | 14                  | 66.29                         | 80 - 32          | 60.85                   | 8.08                        |
| Male                | 9                   | 67.78                         | 83 - 52          | 52.89                   | 14.89                       |
| Without A-SV - S-SV | 125                 | 65.02                         | 88 - 16          | 49.04                   | 15.45                       |
| Female              | 94                  | 64.82                         | 87 - 16          | 48.08                   | 16.03                       |
| Male                | 31                  | 65.65                         | 88 - 19          | 52.21                   | 13.54                       |

**Table 1:** Sex, average age (range), onset and duration of 161 RA in patients with or without A-SV.

Comparing the age, sex, onset of RA, and duration of disease at the time of death, RA started later and led to death earlier in patients with A-SV, especially in female patients; the difference was significant.

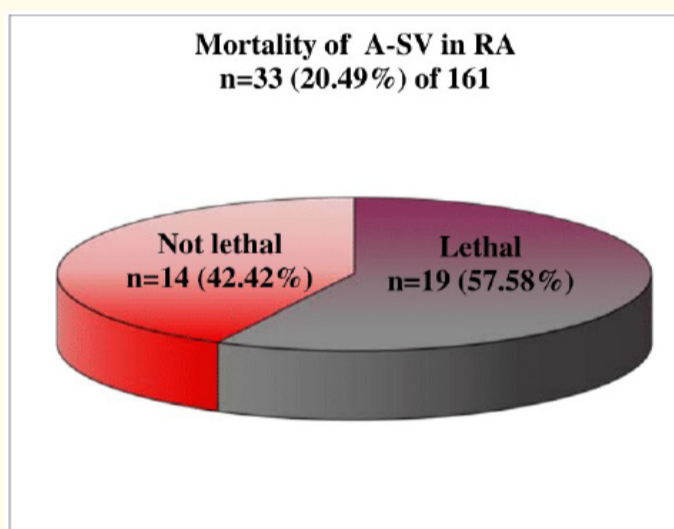
There was no significant correlation in survival time of male and female patients with severe and mild A-SV; severity of A-SV did not reduce significantly the survival time of vasculitic patients.

The statistical correlation between female and male RA patients with A-SV (n = 33 of 161) and without A-SV (n = 125 of 161), furthermore between patients with severe A-SV (n = 10 of 33) and mild A-SV (n = 23 of 33), regarding the onset of RA, disease duration and survival time is summarized in table 2.

| RA patients - p <                                       | Total (Females and Males) |                  |                  | Females |                  |                  | Males   |                  |                  |
|---|---------------------------|------------------|------------------|---------|------------------|------------------|---------|------------------|------------------|
|   | Avg Age                   | Disease duration | Onset of disease | Avg Age | Disease duration | Onset of disease | Avg Age | Disease duration | Onset of disease |
| With A-SV (n=33) versus without A-SV (n = 125)          | 0,345                     | 0,086            | 0,016            | 0,391   | 0,015            | 0,000            | 0,747   | 0,993            | 0,862            |
| With severe A-SV (n = 10) versus without A-SV (n = 125) | 0,384                     | 0,599            | 0,202            | 0,260   | 0,931            | 0,184            | 0,935   | 0,572            | 0,807            |
| With mild A-SV (n = 23) versus without A-SV (n = 125)   | 0,502                     | 0,086            | 0,031            | 0,685   | 0,001            | 0,000            | 0,665   | 0,808            | 0,938            |
| With severe A-SV (n = 10) versus mild A-SV (n = 23)     | 0,806                     | 0,482            | 0,667            | 0,566   | 0,108            | 0,297            | 0,732   | 0,523            | 0,860            |

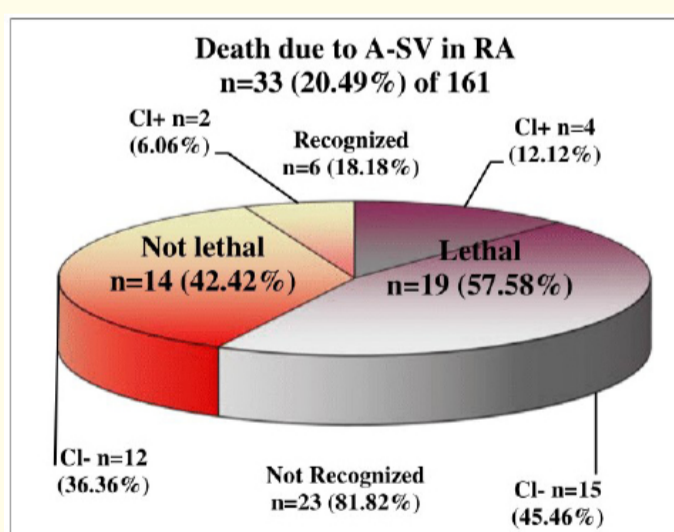
**Table 2**

The prevalence, severity, mortality and clinical diagnosis of A-SV based on 12 organs of 33 RA patients are summarized in table 3 and illustrated with figure 1.



**Figure 1a:** (Mortality of A-SV).

A-SV was fatal in 19 (57.58 %), and not fatal in 14 (42.42 %) of 33 patients.



**Figure 1b:** (Relationship between mortality and clinical recognition of A-SV).

Lethal vasculitis was clinically recognized in 4 of 19 fatal cases (12.12 % of 33), and in 2 of 14 non-fatal cases (6.06 % of 33).

There was no significant correlation between clinical diagnosis of A-SV and mortality ( $\chi^2 = 0.0017, p < 0.96$ )

**Figure 1a and 1b:** Mortality of vasculitis and relationship between mortality and clinical recognition of A-SV.

|    | Pr n <sup>o</sup> /y       | Sex | Heart | Muscle | Lung  | Pancreas | Kidney | G-I   | Spleen | AG    | Nerve | Liver | Skin  | Brain | M & N | Avg/  | Total | CoD | Cl+/- |
|----|----------------------------|-----|-------|--------|-------|----------|--------|-------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-----|-------|
| 1  | 123/86                     | f   | 0,00  | 0,00   | 0,50  | 0,00     | 0,00   | 0,00  | 0,00   | 0,00  | 0,00  | 0,00  | 0,00  | 0,00  | 0,00  | 0,042 | 0,50  | CoD | Cl-   |
| 2  | 40/89                      | m   | 0,00  | 0,50   | 0,00  | 0,00     | 0,00   | 0,00  | 0,00   | 0,00  | 0,00  | 0,00  | 0,00  | 0,00  | 0,25  | 0,042 | 0,50  |     | Cl-   |
| 3  | 146/91                     | m   | 0,33  | 0,00   | 0,00  | 0,00     | 0,00   | 0,00  | 0,00   | 0,00  |       | 0,00  | 0,17  | 0,00  | 0,00  | 0,045 | 0,50  |     | Cl+   |
| 4  | 41/90                      | f   | 0,33  | 0,00   | 0,00  |          | 0,00   | 0,00  |        | 0,00  |       | 0,00  | 0,17  | 0,00  | 0,00  | 0,056 | 0,50  |     | Cl-   |
| 5  | 90/85                      | f   | 0,00  | 0,33   | 0,00  | 0,00     | 0,50   | 0,00  | 0,00   | 0,00  | 0,00  | 0,00  | 0,00  | 0,00  | 0,17  | 0,069 | 0,83  |     | Cl-   |
| 6  | 87/90                      | f   | 0,67  | 0,00   | 0,17  | 0,00     | 0,00   | 0,00  | 0,00   | 0,00  | 0,00  | 0,17  | 0,00  | 0,00  | 0,00  | 0,083 | 1,00  |     | Cl-   |
| 7  | 144/92                     | f   | 0,00  | 0,33   | 0,00  | 0,00     | 0,00   | 0,33  | 0,00   | 0,00  | 0,00  | 0,33  | 0,00  | 0,00  | 0,17  | 0,083 | 1,00  | CoD | Cl-   |
| 8  | 20/80                      | f   | 0,33  |        |       |          | 0,00   | 0,17  |        |       |       | 0,00  |       | 0,00  |       | 0,100 | 0,50  |     | Cl+   |
| 9  | 43/85                      | m   | 0,00  | 0,33   | 0,00  | 0,33     | 0,50   | 0,00  | 0,00   | 0,00  | 0,17  | 0,00  | 0,00  | 0,00  | 0,25  | 0,111 | 1,33  |     | Cl-   |
| 10 | 119/85                     | f   | 0,00  | 0,00   | 1,33  | 0,00     | 0,00   | 0,00  | 0,00   | 0,00  | 0,00  | 0,00  | 0,00  | 0,00  | 0,00  | 0,111 | 1,33  | CoD | Cl-   |
| 11 | 65/90                      | f   | 0,33  | 0,00   | 0,00  | 0,00     | 0,17   | 0,17  | 0,00   | 0,17  | 0,17  | 0,00  | 0,33  | 0,00  | 0,08  | 0,111 | 1,33  | CoD | Cl-   |
| 12 | 25/85                      | f   | 0,00  | 0,00   | 1,83  | 0,00     | 0,00   | 0,00  | 0,00   | 0,00  | 0,00  | 0,00  | 0,00  | 0,00  | 0,00  | 0,153 | 1,83  | CoD | Cl-   |
| 13 | 295/88                     | m   | 0,67  | 0,00   | 0,33  | 0,00     | 0,00   | 0,00  | 0,50   | 0,00  | 0,00  | 0,33  | 0,00  | 0,00  | 0,00  | 0,153 | 1,83  | CoD | Cl-   |
| 14 | 285/89                     | m   | 1,17  | 0,00   | 0,00  | 0,00     | 0,00   | 0,00  | 0,67   | 0,00  | 0,00  | 0,00  | 0,00  | 0,00  | 0,00  | 0,153 | 1,83  | CoD | Cl-   |
| 15 | 221/91                     | f   | 0,17  | 0,00   | 0,00  | 0,00     | 0,50   | 0,00  | 0,00   |       | 1,17  | 0,00  | 0,00  | 0,00  | 0,58  | 0,167 | 1,83  | CoD | Cl-   |
| 16 | 279/87                     | f   | 0,17  | 0,33   | 0,17  |          | 0,17   | 0,00  | 0,00   | 0,33  | 0,67  | 0,00  |       | 0,00  | 0,50  | 0,183 | 1,83  | CoD | Cl-   |
| 17 | 395/76                     | f   | 1,67  | 0,00   | 0,33  | 0,17     | 0,00   | 0,00  | 0,00   | 0,00  |       | 0,00  |       | 0,00  | 0,00  | 0,217 | 2,17  | CoD | Cl+   |
| 18 | 20/70                      | f   | 0,50  | 0,67   | 0,00  | 0,00     | 0,33   | 0,17  | 0,50   | 0,00  |       | 0,00  | 0,33  | 0,00  | 0,67  | 0,227 | 2,50  | CoD | Cl-   |
| 19 | 81/70                      | m   | 0,17  |        | 0,00  |          | 0,67   |       | 0,17   | 0,50  |       | 0,17  |       | 0,00  |       | 0,238 | 1,67  | CoD | Cl-   |
| 20 | 312/87                     | m   | 1,00  | 0,00   | 0,33  | 0,00     | 0,33   | 0,00  | 1,00   | 0,00  | 0,17  | 0,00  |       | 0,00  | 0,08  | 0,258 | 2,83  | CoD | Cl-   |
| 21 | 175/82                     | m   | 0,00  | 0,33   | 0,00  |          | 0,83   |       |        | 0,50  |       | 0,00  | 0,50  | 0,00  | 0,33  | 0,271 | 2,17  |     | Cl-   |
| 22 | 275/87                     | m   | 1,50  | 0,67   | 0,00  | 0,00     | 0,00   | 0,17  | 0,00   | 0,33  | 0,33  | 0,00  |       | 0,00  | 0,50  | 0,273 | 3,00  | CoD | Cl+   |
| 23 | 243/87                     | f   | 1,00  | 0,83   | 0,00  | 0,17     | 0,00   | 0,00  | 0,33   | 0,83  | 0,17  | 0,17  | 0,00  | 0,00  | 0,50  | 0,292 | 3,50  |     | Cl-   |
| 24 | V/A                        | f   | 0,00  | 0,00   | 1,50  | 0,17     | 0,17   |       |        |       | 0,00  |       |       |       | 0,00  | 0,306 | 1,83  | CoD | Cl-   |
| 25 | 288/73                     | f   | 0,00  |        | 0,00  |          | 0,17   | 1,33  | 0,33   | 0,17  |       | 0,33  |       | 0,17  |       | 0,313 | 2,50  |     | Cl-   |
| 26 | 227/89                     | f   | 1,17  | 0,83   | 0,50  | 0,00     | 0,33   | 0,00  | 0,33   | 0,00  | 0,33  | 0,50  | 0,00  | 0,00  | 0,58  | 0,333 | 4,00  | CoD | Cl-   |
| 27 | 114/71                     | f   | 1,50  |        |       |          | 0,00   |       |        |       |       | 0,00  |       | 0,00  |       | 0,375 | 1,50  |     | Cl-   |
| 28 | 194/88                     | f   | 0,33  | 0,83   | 0,67  |          | 0,67   | 0,00  | 0,00   | 0,67  | 0,00  | 0,67  | 0,17  | 1,00  | 0,42  | 0,455 | 5,00  | CoD | Cl+   |
| 29 | 174/72                     | m   | 0,00  |        | 0,33  | 1,33     | 1,50   | 1,00  | 0,00   | 1,50  |       | 0,00  |       | 0,00  |       | 0,630 | 5,67  |     | Cl-   |
| 30 | 240/88                     | f   | 2,50  | 0,67   | 0,50  | 0,83     | 0,00   | 0,83  | 0,83   |       | 0,50  | 0,50  | 0,00  | 0,00  | 0,58  | 0,651 | 7,17  | CoD | Cl-   |
| 31 | 36/86                      | m   | 0,50  | 1,00   | 0,00  | 1,00     | 1,50   | 0,83  | 1,00   | 0,33  | 0,83  | 0,83  | 0,17  | 0,00  | 0,92  | 0,667 | 8,00  |     | Cl-   |
| 32 | 14/92                      | f   | 0,17  | 0,83   | 2,00  | 1,00     | 1,33   | 0,83  | 1,67   | 0,33  | 0,17  | 0,17  | 0,33  | 0,17  | 0,50  | 0,750 | 9,00  |     | Cl-   |
| 33 | 110/80                     | f   | 2,50  | 2,00   | 0,33  | 3,00     | 0,67   | 2,67  | 0,83   | 2,17  | 1,17  | 2,67  | 0,00  | 0,00  | 1,58  | 1,500 | 18,00 | CoD | Cl+   |
|    |                            |     |       |        |       |          |        |       |        |       |       |       |       |       |       |       |       |     |       |
|    |                            |     |       |        |       |          |        |       |        |       |       |       |       |       |       |       |       |     |       |
|    | Count                      |     | 33    | 28     | 31    | 25       | 33     | 29    | 28     | 28    | 23    | 32    | 23    | 32    | 28    | 33    | 33    | 19  | 6     |
|    | Total                      |     | 19    | 11     | 11    | 8        | 10     | 9     | 8      | 8     | 6     | 7     | 2     | 1     | 9     | 9     |       |     |       |
|    | Avg Severity of A-SV/Organ |     | 0,566 | 0,375  | 0,349 | 0,320    | 0,313  | 0,293 | 0,292  | 0,280 | 0,254 | 0,214 | 0,094 | 0,042 | 0,310 | 0,285 |       |     |       |
|    | Missed samples             |     | 0     | 5      | 2     | 8        | 0      | 4     | 5      | 5     | 10    | 1     | 10    | 1     | 5     |       |       |     |       |
|    | Without Vasculitis         |     | 11    | 13     | 16    | 16       | 16     | 18    | 16     | 16    | 11    | 20    | 15    | 29    | 10    |       |       |     |       |
|    | With Vasculitis            |     | 22    | 15     | 15    | 9        | 17     | 11    | 12     | 12    | 12    | 12    | 8     | 3     | 18    |       |       |     |       |
|    | Prevalence of A-SV/Organ   |     | 66,67 | 53,57  | 48,39 | 36,00    | 51,52  | 37,93 | 42,86  | 42,86 | 52,17 | 37,50 | 34,78 | 9,38  | 64,29 |       |       |     |       |

**Table 3:** Prevalence and severity of A-SV in 33 (20.49 %) of 161 RA patients.

Arranged according to the increased values of severity/patients (from up to down), and decreased values of severity /organs (from left to right)

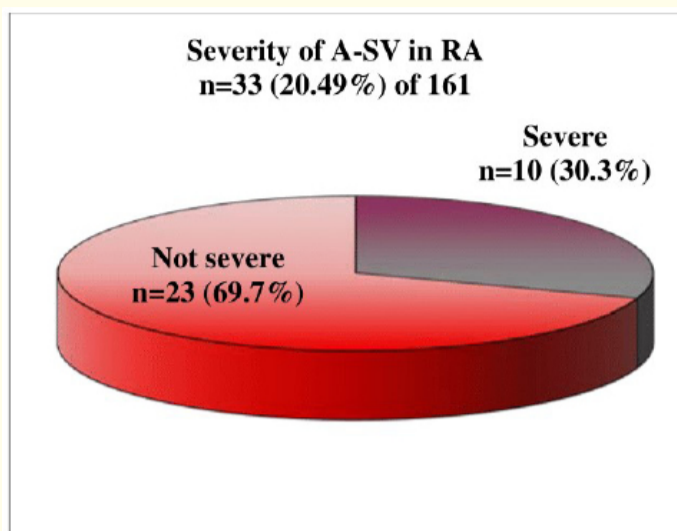
**Glossary to table 3**

Pr n<sup>o</sup>/y: Protocol number/year; CoD: Cause of Death; Cl+: Clinically diagnosed A-SV in 6 (18.18%) of 33 patients; clinically recognized 4 of 19 lethal cases due to A-SV, and 2 of 14 not lethal cases; Cl-: Clinically not diagnosed A-SV in 27 (81.82%) of 33 patients; clinically not recognized 15 of 19 lethal cases, and 12 of 14 not lethal cases); AG: Adrenal gland; G-I: Gastrointestinal tract; f: Female; m: Male

**Remarks to table 3**

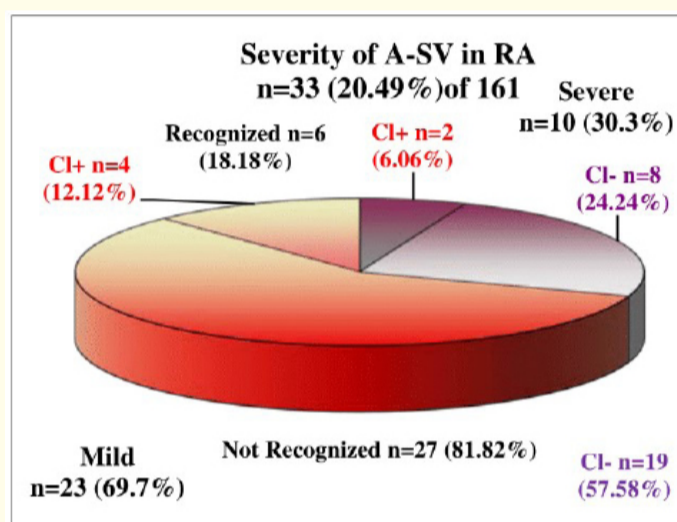
Vasculitis was not present in every organ and existed with different severity in 33 RA patients with A-SV (consequently the "prevalence" and "severity" in various organs are different).

Some tissue samples of 12 organs were not available for evaluation (consequently the "total value" of "severity" in these patients with A-SV is lower).



**Figure 1c:** (Severity of vasculitis)

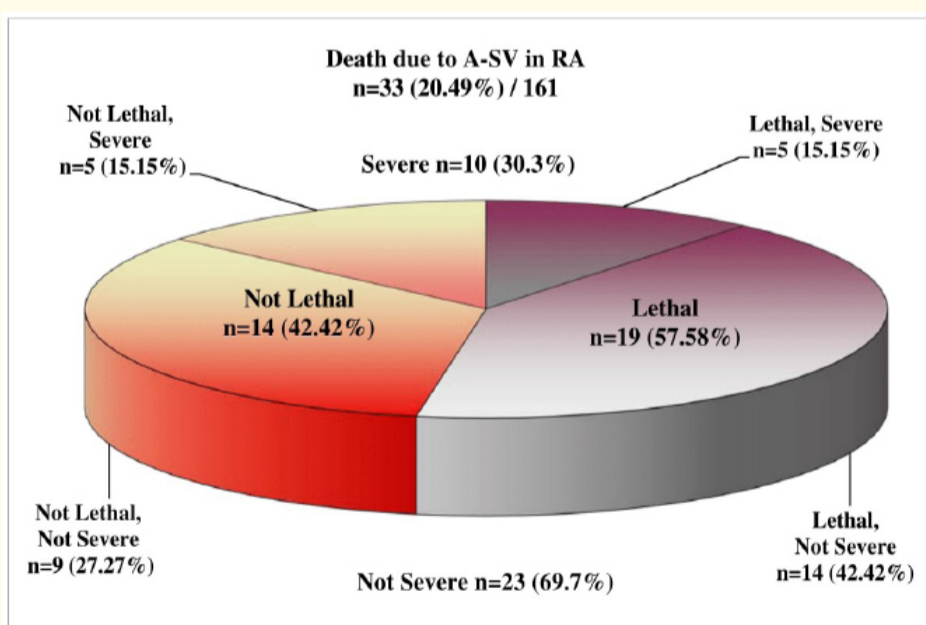
Ten patients (30.3 %) of 33 had severe (with average cumulative value of severity/RA patient with A-SV > 0.30), and 23 (69.7 %) of 33 had a mild degree of A-SV (with average cumulative value of severity/RA patient with A-SV ≤ 0.30)



**Figure 1d:** (Relationship between severity and clinical recognition of A-SV).

Vasculitis was clinically recognized in 2 of 10 patients with severe A-SV, and in 4 of 23 with mild A-SV. There was no significant correlation between the clinical diagnosis of A-SV and severity ( $\chi^2 = 0.0976$ ,  $p < 0.75$ ).

**Figure 1c and 1d:** Severity of A-SV and relationship between severity and clinical recognition of A-SV.



SV led directly to death in 19 (11.87 of 161 and 57.58 % of 33) patients.

Severe A-SV had a direct causal role in the death in 4 of 19, and mild A-SV in 15 of 19 cases. There was no significant correlation between severity of SV and mortality ( $\chi^2 = 0.3371$ ,  $p < 0.56$ ).

**Figure 1e:** Relationship between mortality and severity of vasculitis.

A-SV was lethal in 19 (57.58%), and not lethal in 14 (42.42%) of 33 cases (Figure 1a). Lethal vasculitis was clinically recognized in 4 of 19 fatal (12.12% of 33), and recognized in 2 of 14 not fatal (6.06% of 33) cases and (Figure 1b). There was no significant correlation between the clinical diagnosis of A-SV and mortality ( $\chi^2 = 0.0017$ ,  $p < 0.96$ ).

Ten patients (30.3%) of 33 had severe (with average cumulative value of severity/RA patient with A-SV  $> 0.30$ ), and 23 (69.7%) of 33 had a mild degree of A-SV (with average cumulative value of severity/RA patient with A-SV  $\leq 0.30$ ) (Figure 1c). A-SV was clinically recognized in 6 (18.18%) of 33 patients; out of them with severe vasculitis in 2 of 10, and mild in 4 of 23 cases. There was no significant correlation between the clinical diagnosis of A-SV and severity ( $\chi^2 = 0.0976$ ,  $p < 0.75$ ) (Figure 1d).

SV led directly to death in 19 (11.87 of 161 and 57.58% of 33) patients.

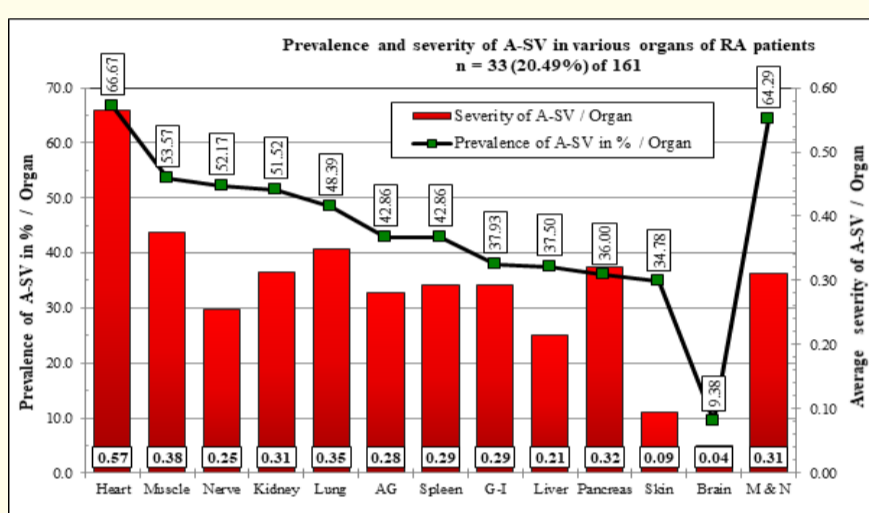
Severe A-SV had a direct causal role in the death in 4 of 19, and mild A-SV in 15 of 19 cases. There was no significant correlation between severity of SV and mortality ( $\chi^2 = 0.3371$ ,  $p < 0.56$ ) (Figure 1e).

The prevalence of A-SV was the highest in the heart, skeletal muscle, peripheral nerve and kidneys, (66.67 - 51.52%), it was moderate in the lungs, spleen, adrenal glands, gastrointestinal tract, liver, pancreas and the skin, (48.39 - 34.78%), and least frequent in the brain (9.38%).

Comparing the prevalence and severity of A-SV there was a slight difference between them in order of peripheral nerve, pancreas, adrenal gland, G-I tract, lung and kidneys.

The prevalence of A-SV in the peripheral (sural) nerves and surrounding skeletal muscle together was nearly as high as the prevalence of A-SV in the heart.

Figure 2 demonstrates the average prevalence and severity of A-SV in various organs in comparison with the average prevalence and severity of A-SV in skeletal muscle and sural nerves together.



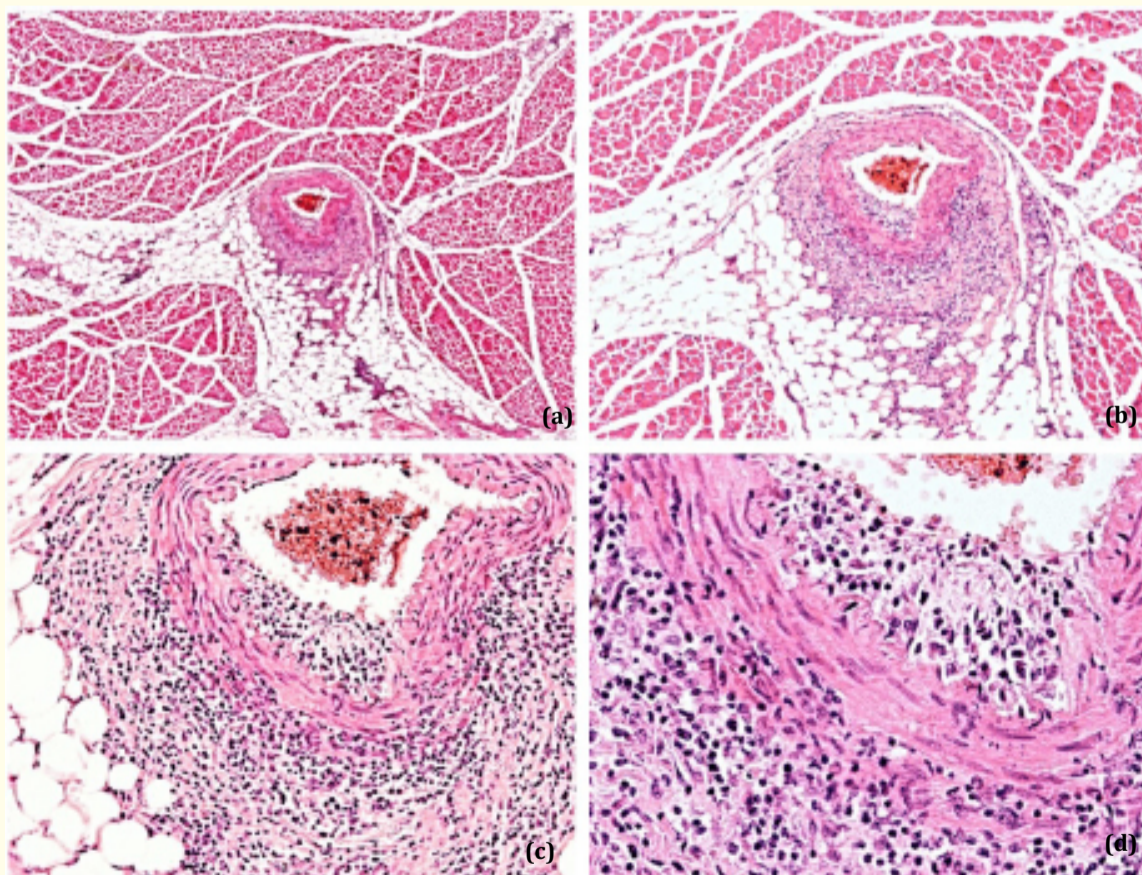
**Figure 2:** Prevalence and severity of A-SV in various organs. (Arranged according to the decreasing values of prevalence)

**Remark to figure 2**

The prevalence and the severity of A-SV are different aspects of the same phenomenon, usually running parallel to each other in different vessels of various organs.

The average prevalence of A-SV in the peripheral (sural) nerves (52.17%) and surrounding skeletal muscle (53.57%) together (64.29%) were nearly as high as the prevalence of A-SV in the heart (66.67%).

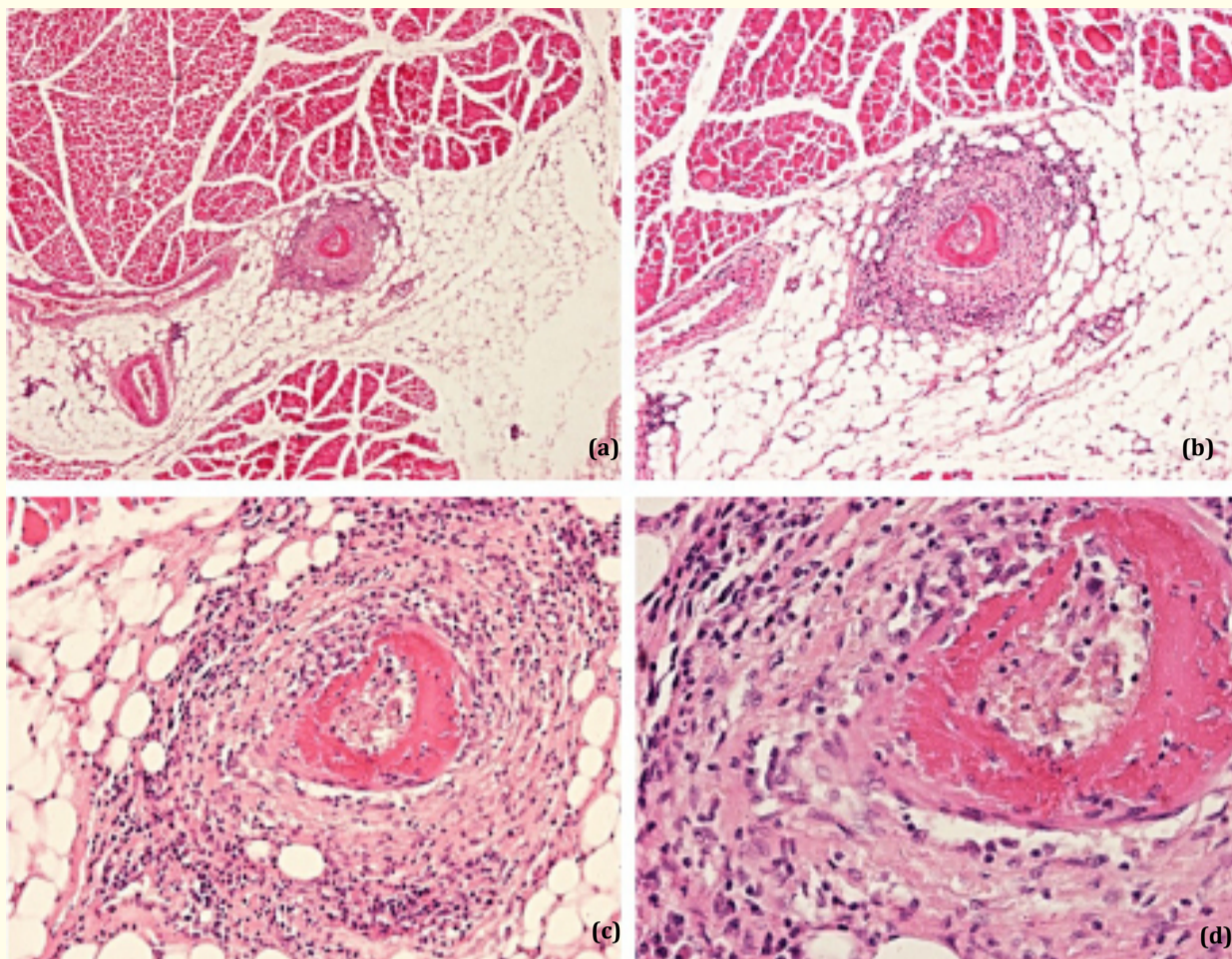
Figures 3a-d demonstrates different types of A-SV in the frequently involved peripheral (sural) nerve and surrounding muscles.



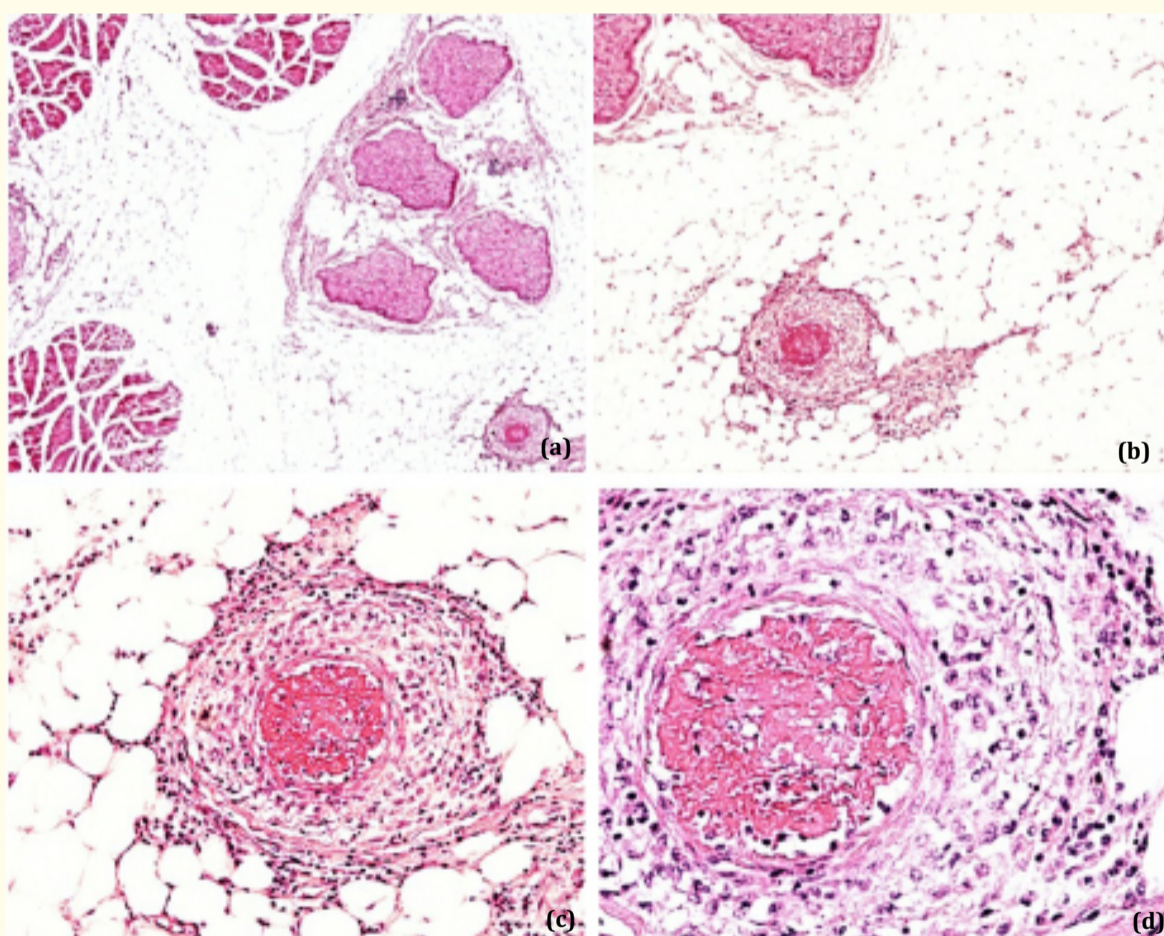
**Figure 3a-d:** RA, skeletal muscle

Small artery, non-specific, subacute-subchronic vasculitis with granulomatous proliferation of intima (a) HE, x20, (b) same as (a) x40, (c) same as (a) x100, (d) same as (a) x200

(The original magnification corresponds to the 24x36 mm transparency slide – the correct height: weight ratio is 2:3).



**Figure 4a-d:** RA, skeletal muscle  
Small artery, subacute vasculitis with fibrinoid necrosis  
(a) HE, x 20, (b) same as (a) x40, (c) same as (a) x100, (d) same as (a) x200



**Figure 5a-d:** RA, skeletal muscle and peripheral nerve (Sural nerve)  
Small artery and arteriole, granulomatous subacute vasculitis with thrombosis  
(a) HE, x 20, (b) same as (a) x40, (c) same as (a) x100, (d) same as (a) x200

## Discussion

The role of systemic vasculitis in mortality of RA is generally accepted [9-11], and the opinion of Genta., *et al.* still holds true: “rheumatoid vasculitis ... remains an important complication of RA that needs to be promptly recognized and treated” [12].

Early recognition of A-SV seems to be difficult, because the cardiovascular system is the primary target, and vasculitis precedes the clinical symptoms. As Fassbender said ‘the arterial disease dominates the clinical symptoms’ [13].

Prognostic and therapeutical consequences of A-SV have to be confirmed by definitive means. The clinical diagnosis of vasculitis is established mostly by visible skin involvement.

In a clinical and laboratory study of 50 RA patients with systemic rheumatoid vasculitis Scott., *et al.* found that skin biopsies taken usually for rashes were positive for rheumatoid arteritis in 16 of 19 patients [14].

“Ideally, a biopsy or an angiogram would be the best, but often the diagnosis rests upon the clinical picture. In general, blind biopsies are not helpful” [15].

Modern classifications concluded that ‘a definitive diagnosis of vasculitis should be made upon biopsy of involved tissue’ [16,17]. The involved organs are not necessarily representing optimal targets of biopsy or are not always easily accessible (brain, heart, etc.), and the diagnosis of A-SV may be delayed.

Flipo., *et al.* prefer labial salivary gland biopsy to assess rheumatoid vasculitis with predictive value [18], and according to Voskuyl., *et al.* the muscle biopsy specimen is specific and reliable in ruling out rheumatoid vasculitis [19].

According to our best knowledge a detailed analysis regarding the prevalence and severity of A-SV and its relationship to mortality and clinical diagnosis has not been available in the literature. Likewise missing is a detailed assessment of the optimal target of biopsy for the histological diagnosis of A-SV, based on comparison of 12 organs.

In our autopsy population there was no correlation between the severity or mortality and clinical diagnosis of A-SV. The mortality due to A-SV depended on the location of the affected vessels (and involved organs), and not on the severity of A-SV. For example, mild A-SV involving the brain may be lethal; on the other hand, severe vasculitis of the skin may not be life-threatening.

The clinical diagnosis of vasculitis was established mostly by visible skin involvement. The involvement of the skin was fairly moderate (0.094 of theoretical maximal value of 3), and only one third (34.74%) of patients with A-SV showed vasculitis of the skin at death. A-SV was clinically recognized in about one fifth of cases (6 of 33), representing only 18.18% of post-mortem found vasculitis (“tip of the iceberg”). A-SV with lethal outcome was clinically recognized in 4 of 19 (21.05%), and was missed in 15 of 19 (78.95%) patients. Systemic vasculitis proved to be one of the most likely clinically missed complications of RA. In case of A-SV 15 of 19 (78.95%), in case of septic infection 13 of 24 (54.16%) and in case of AA amyloidosis 8 of 17 (47.05%) of complications with lethal outcome have not been recognized clinically [1].

Late clinical recognition of A-SV limits the success of possible therapy, carries a worse prognosis and may be the cause of sudden and unexpected death [8]. The high prevalence of vasculitis in the skeletal muscles and peripheral nerves makes biopsy of the sural nerve (with surrounding muscle) a good target for the confirmation of suspected systemic vasculitis (with or without visible involvement of the skin).

Sural nerve biopsy is a minor surgical procedure in comparison for example with a biopsy of the temporal artery in suspected giant cell arteritis (cranial or temporal arteritis). The risk of surgical complications (peripheral sensory neuropathies like paraesthesia, hypoesthesia, or dysesthesia) is minimal.

## Conclusions

A-SV may complicate RA especially in women, with a high prevalence at late onset of the disease which may represent a higher risk of survival. Mild or severe A-SV may complicate RA in both sexes, and at any time in the course of the disease.

Severity of A-SV does not influence the mortality or clinical diagnosis of A-SV. The mortality due to A-SV depends on the location of the affected blood vessels (and involved organs), and not on the severity of A-SV.

A-SV may be regarded as one of the most insidious complications of RA, and proves to be one of the most likely clinically missed complications of RA.

The high prevalence of vasculitis in the skeletal muscles and peripheral nerves makes biopsy of the sural nerve (with surrounding muscle) a good target for the confirmation of suspected systemic vasculitis (with or without visible involvement of the skin).



## **Conflict of Interest**

No conflict of interest.

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