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Original article

Identifying relevant determinants of in-hospital time to diagnosis for ANCA-associated vasculitis patients

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Abstract

Objectives. Diagnosing patients with ANCA-associated vasculitis (AAV) can be challenging owing to its rarity and complexity. Diagnostic delay can have severe consequences, such as chronic organ damage or even death. Given that few studies have addressed diagnostic pathways to identify opportunities to improve, we performed a clinical audit to evaluate the diagnostic phase.

Methods. This retrospective, observational study of electronic medical records data in hospitals focused on diagnostic procedures during the first assessment until diagnosis.

Results. We included 230 AAV patients from nine hospitals. First assessments were mainly performed by a specialist in internal medicine (52%), pulmonology (14%), ENT (13%) or rheumatology (10%). The overall median time to diagnosis was 13 [interquartile range: 2–49] days, and in patients primarily examined by a specialist in internal medicine it was 6 [1–25] days, rheumatology 14 [4–45] days, pulmonology 15 [5–70] days and ENT 57 [16–176] days ($P = 0.004$). Twenty-two of 31 (71%) patients primarily assessed by a specialist in ENT had non-generalized disease, of whom 14 (64%) had ENT-limited activity. Two hundred and nineteen biopsies were performed in 187 patients (81%). Histopathological support for AAV was observed in 86% of kidney biopsies, 64% of lung biopsies and 34% of ENT biopsies.

Conclusion. In The Netherlands, AAV is diagnosed and managed predominantly by internal medicine specialists. Diagnostic delay was associated with non-generalized disease and ENT involvement at presentation. Additionally, ENT biopsies had a low diagnostic yield, in contrast to kidney and lung biopsies. Awareness of this should lead to more frequent consideration of AAV and early referral for a multidisciplinary approach when AAV is suspected.

Key words: ANCA-associated vasculitis, diagnostic delay, health-care usage, patient trajectory, pauci-immune glomerulonephritis

CLINICAL SCIENCE

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Key messages

- Few studies have investigated the time to diagnosis for AAV patients and potential factors related to a prolonged time to diagnosis.
- The longest in-hospital time to diagnosis was associated with non-generalized disease and ENT involvement as a presenting symptom.
- ENT biopsies had a low diagnostic yield (34%) compared with kidney (86%) and lung biopsies (64%).

Introduction

ANCA-associated vasculitis (AAV) is a rare and complex systemic autoimmune disease affecting small vessels [1, 2]. Virtually all organs can be involved, which can lead to a plethora of symptoms in patients. Before the use of immunosuppressants, AAV was a fatal diagnosis with a 1-year mortality of >80%, whereas nowadays AAV is mainly a chronic relapsing disease [3, 4]. Improved outcomes have been achieved by optimized treatment strategies for AAV patients [5–8]. Nonetheless, diagnostic delay unfortunately remains a common phenomenon in AAV, whereas early diagnosis and treatment are important to prevent (chronic) damage and sometimes even death in AAV patients [9–11]. Few studies have addressed the relevant factors associated with early or delayed diagnosis of AAV [11, 12]. Diagnosing patients with AAV can be challenging because of its rarity, complexity and wide variety of symptoms. Patients with constitutional symptoms or a single affected organ system (especially when ANCA serology is negative) could easily be misdiagnosed as another systemic disease or as a more common, less severe disease [6, 13, 14]. Consequently, recent guidelines recommend obtaining histopathological evidence as the gold standard for confirmation of diagnosis in AAV [4, 15]. However, the diagnostic yield of a biopsy in AAV patients varies per organ or tissue from 39 to 91.5% [16, 17]. We set out to investigate the time to diagnosis and identify factors related to early diagnosis or diagnostic delay, in order to improve timely diagnosis in future AAV patients.

Methods

Study design and data collection

We performed a retrospective study in 230 AAV patients, collected from nine Dutch hospitals (three university and six non-university teaching hospitals). A detailed description of the study cohort has been published previously [18]. Briefly, the relevant patient characteristics, clinical variables, time to diagnosis, biopsies and number of involved specialisms in relationship to AAV were collected. All clinical or disease-specific definitions were physician reported and, as such, no additional interpretation of the collected data was allowed. This study was approved by our medical ethics review committee, METC-Leiden Den Haag Delft. Patients were offered the opportunity to opt out of the project.

We collected data from the first in-hospital assessment/visit onwards. We defined the first hospital assessment/visit as the first hospital visit (either outpatient clinic patients or admitted to the hospital) for (a) symptom(s) that later in the disease course appeared to be attributable to AAV. We defined the time to diagnosis as the time between the first hospital visit and the diagnosis of AAV, which was followed by a therapeutic intervention. We classified the disease presentation as generalized disease when patients had life-threatening disease or involvement of one of the following major organs: kidneys, lungs, heart, nervous system and non-generalized disease in the event of involvement of other organ systems. We categorized the treating specialisms at the time of first presentation in the hospital and at the time of starting remission-induction therapy [19]. Results of biopsies were categorized according to the reports of the pathologists: whether the histopathological report supported the diagnosis of AAV, excluded the diagnosis of AAV or was non-specific for the diagnosis of AAV (Fig. 1).

Statistical analysis

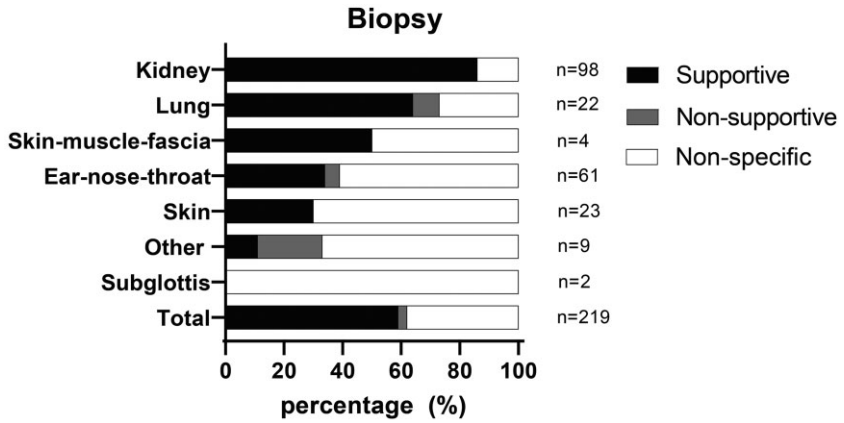
We used descriptive statistics for an overview of the patient characteristics and outcomes. The number (percentage) of variables is shown for categorical data; the mean (±S.D.) and median [interquartile range] for numerical data. A χ^2 analysis was used to compare the four quartiles of the time to diagnosis. Kaplan–Meier survival curves were plotted to compare the time to diagnosis among different specialties. All analyses were performed with IBM SPSS statistics v.25.

Results

Patient characteristics

Of 230 AAV patients (Table 1), 101 patients (44%) were female, and the median age at the time of diagnosis was 61 [IQR 49–69] years. Granulomatosis with polyangiitis (GPA) was diagnosed in 167 (73%) patients, microscopic polyangiitis (MPA) in 54 patients (23%) and eosinophilic granulomatosis with polyangiitis (eGPA) in 9 patients (4%). Antibodies PR3 were present in 139 patients (60%) and against myeloperoxidase (anti-MPO) in 76 patients (33%). Eight patients (4%) had no autoantibodies, whereas no serum antibody assay (SAA) test was performed in six patients (3%).

Fig. 1 Reported results of performed biopsies



Supportive = supported the diagnosis of ANCA-associated vasculitis (AAV). Non-supportive = excluded the diagnosis of AAV and, by definition, supported or confirmed a diagnosis other than AAV. Non-specific = neither unable to exclude the diagnosis of AAV nor was it able to support or confirm another diagnosis. *n*: number of patients.

Table 1 Patient characteristics

Characteristics	
Age at diagnosis, median [IQR], years	61 [49–69]
Female, *n* (%)	101 (44)
Ethnicity, *n* (%)	
Caucasian	218 (95)
Asian	1 (0.4)
Other	11 (5)
Clinical diagnosis, *n* (%)	
GPA	167 (73)
MPA	54 (24)
eGPA	9 (4)
SAA, *n* (%)	
Anti-PR3	139 (60)
Anti-MPO	76 (33)
Both negative	8 (4)
Not performed	6 (3)
Median in-hospital time to diagnosis, median [IQR], days	13 [2–49]
Symptoms, *n* (%)	
Constitutional	122 (53)
Cutaneous	21 (9)
Mucous membranes/eyes	20 (9)
ENT	99 (43)
Pulmonary	79 (34)
Cardiovascular	4 (2)
Abdominal	9 (4)
Renal	101 (44)
Nervous system	33 (14)
Other	5 (2)

c-ANCA: cytoplasmic ANCA; eGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; IQR: interquartile range; MPA: microscopic polyangiitis; p-ANCA: perinuclear ANCA; SAA: serum antibody assay.

One hundred and twenty-two patients (53%) had constitutional symptoms, 101 patients (44%) renal symptoms, 99 patients (43%) ENT symptoms and 79 patients (34%) pulmonary symptoms. To a lesser extent, the following organ systems were involved: nervous system (14%), skin (9%), mucous membranes/eyes (9%), abdomen (4%), cardiovascular (2%) and other (2%). The estimated glomerular filtration rate (eGFR) was <60 ml/min in 111 patients (48%), and proteinuria was detectable (>0.15 g/24 h) in 79 patients (34%). Overall, 166 patients (72%) had generalized disease. The median time to diagnosis was 13 [IQR 2–49] days.

Involved specialisms at diagnosis and at remission-induction therapy

The first assessment for AAV symptoms of these patients after presentation in a hospital for AAV symptoms was performed by specialists in internal medicine (52%), pulmonology (14%), ENT (13%), rheumatology (10%), neurology (4%), ophthalmology (3%), immunology (1%), surgery (0.4%) and other specialties (4%) (Table 2). After diagnosis, a shift was observed at the time of initiating remission-induction therapy, which was mainly instituted by specialists in internal medicine (73%) and rheumatology (21%), and less so by specialists in immunology (3%), ENT (2%), pulmonology (2%), neurology (0.4%) and ophthalmology (0.4%).

Biopsies

Diagnostic procedures to confirm or establish the diagnosis of AAV via histopathology were performed in 187 patients (81%; total number of biopsies: 219; Fig. 1). The organ distribution of biopsies was as follows: 98 kidney (45%), 61 ENT (28%), 23 skin (11%), 22 lung (10%), 9 other (4%), 4 skin–muscle–fascia (2%) and 2 in the

Table 2 Specialist involvement at presentation and initiating remission-induction therapy

Specialists	At presentation [*n* (%)]	Remission-induction therapy [*n* (%)]
Internal medicine	119 (52)	167 (73)
Rheumatology	24 (10)	49 (21)
Immunology	2 (1)	6 (3)
Dermatology	0 (0)	0 (0)
ENT	31 (13)	5 (2)
Pulmonology	33 (14)	5 (2)
Neurology	8 (4)	1 (0.4)
Ophthalmology	6 (3)	1 (0.4)
Gastroenterology	0 (0)	0 (0)
Surgery	1 (0.4)	0 (0)
Other	9 (4)	6 (3)

n: number of patients; Other: cardiology, urology and paediatrics.

subglottic region (1%). Biopsies of other organs consisted of different anatomical locations: palatum molle ($n=3$), tongue ($n=1$), orbita ($n=1$), conjunctiva ($n=1$), myocardium ($n=1$), anal mucosa ($n=1$) and peripheral nerve ($n=1$). Findings were reported as supportive in 129 (59%), non-supportive in 7 (3%) and non-specific in 83 (38%) biopsies. A supportive histopathology result was most frequently reported for kidney (86%) and lung (64%) biopsies. Conversely, non-specific (i.e. neither supportive nor non-supportive) findings were reported most frequently for skin (70%), other locations (67%) and ENT (61%) biopsies.

Time to diagnosis

Detailed information enabling the calculation of the time to diagnosis was available for 194 patients. The median time to diagnosis was 13 [IQR 2–49] days. Forty-seven patients were diagnosed within 2 days (first quartile), 50 patients between 2 and 12 days (second quartile), 49 patients between 13 and 49 days (third quartile) and 48 patients after 49 days (fourth quartile). The most frequent symptoms in all four quartiles were constitutional, ENT, pulmonary and renal symptoms (25–63%; Table 3). Inherent to these results, we observed that in all four quartiles mainly specialists from internal medicine, pulmonology, ENT and rheumatology were involved in the first assessment (Table 3).

The median time to diagnosis in patients with generalized disease was 9 [IQR 1–43] days versus 22 [3–73] days in non-generalized disease ($P=0.094$). The median time to diagnosis in patients primarily assessed by specialists from internal medicine was 6 [1–25] days, rheumatology 14 [4–45] days, pulmonology 15 [5–70] days and ENT 57 [16–177] days ($P=0.004$; Fig. 2).

Given that the fourth quartile encompassed 48 patients who were diagnosed with AAV after >49 days, we performed a more in-depth analysis in this group. We focused on the most frequent symptoms and the specialties mainly involved and compared the fourth quartile with the first three quartiles ($n=146$; data not shown). No significant difference was observed between the first three quartiles and the fourth quartile with respect to generalized and non-generalized disease ($P=0.167$), ENT ($P=0.359$), pulmonary ($P=0.109$) and renal symptoms ($P=0.179$). Nevertheless, there was a significant difference in constitutional symptoms (60% *vs* 29%, $P<0.001$). More patients who were assessed primarily by internal medicine specialists were diagnosed in the first three quartiles in comparison to the fourth quartile (55% *vs* 33%, $P=0.010$). The opposite was shown for patients who were assessed primarily by ENT specialists (8% *vs* 29%, $P<0.001$). Of note, from all 31 patients primarily assessed by ENT specialists, 22 (71%) had non-generalized disease, of whom 14 (64%) patients had ENT-limited disease. Ten of 14 patients with ENT-limited disease were diagnosed in the fourth quartile. Looking from another perspective, we found a total of 21 patients with ENT-limited disease, primarily assessed by specialists from ENT ($n=14$), internal medicine ($n=5$) and pulmonology ($n=2$). Only 1 of 21 patients was diagnosed without performing an SAA test or biopsy.

Forty-eight biopsies were performed in 45 of 48 patients (94%) in the fourth quartile (Table 3), of which 24 biopsies (50%) showed supportive, 23 (48%) non-specific and 1 (2%) non-supportive findings (data not shown). Most of the biopsies were taken from an ENT area ($n=19$) and kidneys ($n=16$) and, to a lesser extent, from the lung ($n=6$), skin ($n=4$), other ($n=2$) or the subglottic region ($n=1$). Supportive results were reported in 12 of 16 (75%) kidney, 3 of 6 (50%) lung, 1 of 2 (50%) other and 8 of 19 (42%) ENT biopsies, whereas non-specific findings were reported in all skin and subglottic biopsies and in 10 of 19 (53%) ENT, 3 of 6 (50%) lung, 1 of 2 (50%) other and 4 of 16 (25%) kidney biopsies.

Given that ENT biopsies most often yielded non-specific findings, both in the fourth quartile and in the total group of patients, we also performed a sub-analysis of this. ENT biopsies were performed in 59 patients; 19 of 59 (32%) patients had supportive, 3 of 59 (5%) non-supportive and 37 of 59 (63%) non-specific findings as result of the ENT biopsies. Fifteen of 37 patients with non-specific findings of ENT biopsies

TABLE 3 Presenting symptoms, specialisms at first presentation and biopsies divided over four quartiles of the time to diagnosis

	Total ($n = 194$)	First quartile ($n = 47$)	Second quartile ($n = 50$)	Third quartile ($n = 49$)	Fourth quartile ($n = 48$)	*P*-value
Symptoms at presentation in hospital, *n* (%)						
Constitutional	101 (52)	29 (62)	27 (54)	31 (63)	14 (29)	0.002
Cutaneous	16 (8)	2 (4)	6 (12)	6 (12)	2 (4)	0.260
Mucous membranes/eyes	15 (8)	1 (2)	6 (12)	4 (8)	4 (8)	0.336
ENT	78 (40)	16 (34)	19 (38)	21 (43)	22 (46)	0.655
Pulmonary	67 (35)	13 (28)	23 (46)	19 (39)	12 (25)	0.102
Cardiovascular	4 (2)	0	1 (2)	3 (6)	0	0.112
Abdominal	9 (5)	5 (11)	3 (6)	1 (2)	0	0.068
Renal	89 (46)	29 (62)	27 (54)	15 (31)	18 (38)	0.007
Nervous system	29 (15)	4 (9)	6 (12)	11 (22)	8 (17)	0.245
Other	3 (2)	1 (2)	1 (2)	1 (2)	0	0.800
Generalized	144 (74)	36 (77)	42 (84)	34 (69)	32 (67)	0.198
Non-generalized	50 (26)	11 (23)	8 (16)	15 (31)	16 (33)	
Specialisms at first presentation, *n* (%)						
Internal medicine	96 (49)	31 (66)	31 (62)	18 (37)	16 (33)	0.001
Rheumatology	21 (11)	6 (13)	4 (8)	8 (16)	3 (6)	0.366
Immunology	2 (1)	1 (2)	0	1 (2)	0	0.559
Dermatology	0	0	0	0	0	–
ENT	26 (13)	4 (9)	1 (2)	7 (14)	14 (29)	0.001
Pulmonology	32 (16)	5 (11)	10 (20)	7 (14)	10 (21)	0.485
Neurology	8 (4)	2 (4)	1 (2)	5 (10)	0	0.065
Ophthalmology	5 (3)	0	1(2)	3 (6)	1 (2)	0.283
Gastroenterology	0	0	0	0	0	–
Surgery	1 (0.5)	0	1 (2)	0	0	0.408
Other	8 (4)	1 (2)	2 (4)	1 (2)	4 (8)	0.367

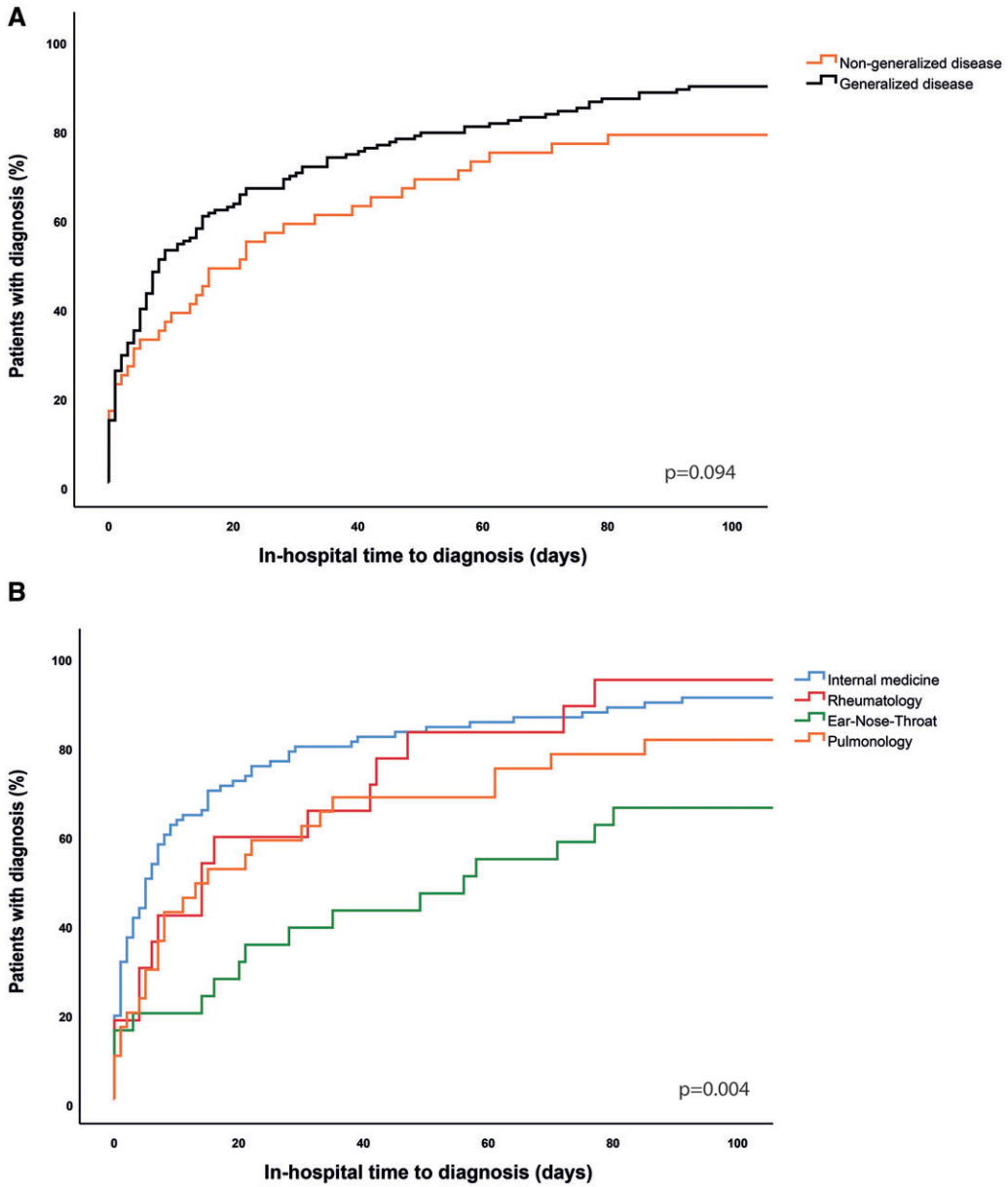
	Total ($n = 161$)	First quartile ($n = 34$)	Second quartile ($n = 42$)	Third quartile ($n = 40$)	Fourth quartile ($n = 45$)	*P*-value
Biopsies, *n* (%)						
Organs						
Kidney	83 (52)	25 (74)	28 (67)	14 (35)	16 (36)	0.006
Lung	18 (11)	0	5 (12)	7 (18)	6 (13)	0.076
Skin–muscle–fascia	4 (2)	1 (3)	1 (2)	2 (5)	0	0.572
ENT	49 (30)	7 (21)	5 (12)	18 (45)	19 (42)	0.002
Skin	19 (12)	3 (9)	8 (19)	4 (10)	4 (9)	0.382
Other	9 (6)	0	3 (7)	4 (10)	2 (4)	0.273
Subglottis	2 (1)	0	0	1 (3)	1 (2)	0.568
Total	184	36	50	50	48	

subsequently also underwent a biopsy of another organ, which eventually yielded supportive findings in 9 patients (6 kidney, 2 lung and 2 skin biopsies).

Discussion

In the present study, we have investigated the diagnostic trajectories of patients with AAV in university or major teaching hospitals in The Netherlands. We observed that patients frequently presented with generalized disease, in whom renal and pulmonary symptoms were usually present, whereas a smaller group presented with non-generalized disease mainly consisting of constitutional and ENT symptoms. Most patients were assessed primarily by specialists from internal medicine, ENT, pulmonology and rheumatology. Non-generalized disease and ENT involvement as presenting symptoms were associated with a significant diagnostic delay. Additionally, ENT biopsies had a very low diagnostic yield, in contrast to kidney and lung biopsies, which led to confirmation of diagnosis in the majority of cases.

Fig. 2 Kaplan–Meier curve of the time to diagnosis



(**A**) Time to diagnosis in all patients with generalized disease (black) *vs* non-generalized disease (orange). (**B**) Time to diagnosis in all patients assessed primarily by specialists from internal medicine (blue), rheumatology (red), ENT (green) and pulmonology (orange).

Our cohort consisted mainly of patients with generalized disease, mostly accompanied by constitutional, renal, pulmonary and/or ENT symptoms. As expected and in concordance with the presenting symptoms, most patients were assessed primarily by internists, rheumatologists, pulmonologists and ENT specialists, which was also observed in a recent study [20]. Of note, after the first assessment, we observed a shift from pulmonologists and ENT specialists to internists and rheumatologists to initiate remission-induction therapy. These data are informative for triage of suspected AAV patients or ENT patients with limited disease or constitutional symptoms who could benefit from early referral to a specialist in internal medicine and/or rheumatology.

As previously reported in various studies, the time from onset of symptoms to diagnosis in AAV patients could amount to several months and sometimes even years [11, 12, 20, 21]. Patients with delayed commencement of treatment caused by delayed diagnosis are likely to suffer from more chronic organ damage [10]. AAV is a complex disease, and most patients have general symptoms or solely complaints of affected organ systems that would

also match with other diseases, which can lead to incorrect or delayed diagnosis [13]. In all four quartiles of the time to diagnosis, patients often had constitutional, ENT, pulmonary and/or renal symptoms, illustrating how challenging the diagnosing of AAV can be for physicians. We did not observe a significant difference between generalized and non-generalized disease; the longest time to diagnosis was observed in patients assessed primarily by ENT specialists. In the fourthquartile, 71% (10 of 14) had ENT-limited disease at presentation, which poses a challenge to establish a complex, systemic diagnosis of AAV upon the first presenting symptoms [12, 22]. On top of this, 9 of 15 (60%) [ENT ($n = 5$), lung ($n = 1$), skin ($n = 1$), subglottic region ($n = 1$) and other ($n = 1$)] biopsies in this group showed non-specific findings. Importantly, in most cases the diagnostic delay in ENT-limited AAV will not lead to life-threatening situations. However, this can be associated with chronic damage and long-term morbidity owing to tissue destruction, imposing an important disease burden on AAV patients [23].

Obtaining histopathological evidence from affected organs in combination with clinical and laboratory findings is usually considered as the gold standard to confirm diagnosis in AAV, especially in ANCA-negative patients. It is not uncommon in clinical practice that more than one organ is affected and can be targeted for a diagnostic biopsy. Indeed, guidelines recommend biopsies in affected organs, taking into account the invasiveness and accompanying risk of complications of the biopsy procedure [4]. Physicians often have to choose which organ or tissue is most suitable for a diagnostic biopsy in patients suspected of AAV with several affected organs. Our study demonstrated that the highest yield of findings contributing to diagnoses was obtained from kidney biopsies (86%) and lung biopsies (73%). Biopsies from other organs or tissues were predominantly non-specific for the diagnosis of AAV. Therefore, these data provide important information for clinicians' considerations to balance the yield of a biopsy against the risks of this procedure. Our data can help to support physicians to attain informed consent for a kidney or lung biopsy with higher risks of complication in relationship to potentially less valuable biopsies from other locations with a low risk of complications. Of note, it was not the aim and design of this study to assess the sensitivity or specificity of biopsies in AAV patients.

Several limitations of this study should be mentioned. First, owing to the study design, this study was not carried out to identify causal associations of in-hospital diagnostic delay. In this retrospective study, we adopted the disease characteristics as they were reported by physicians (and did not perform additional checks on diagnostic or classification criteria.) Second, owing to analysis of electronic medical records only in hospitals and lack of documentation about the patient trajectory before referral to a hospital, we could only study the patient trajectory inside the hospital. Consequently, data of patient and general practitioner delays are missing, which could also play a significant role in diagnostic delay. Third, we cannot draw conclusions on the contribution of an SAA on the time to diagnosis, because we did not collect the exact timing of this test. However, one can plausibly assume that an SAA is performed when the clinician considers AAV as a (differential) diagnosis. In that scenario, the time to diagnosis would be influenced mainly by the time before testing.

Conclusion

From the present clinical audit study, it can be concluded that the longest time to diagnosis is observed in patients with non-generalized disease, especially in ENT-limited disease with biopsy results that did not contribute to establishing the AAV diagnosis. In general, AAV patients are diagnosed and managed by internal medicine specialists in The Netherlands, and with respect to tissue biopsies the highest yield was obtained from kidney and lung biopsies to establish diagnosis in AAV.

Our study raises awareness that diagnostic delay occurs mainly in patients with ENT-limited disease and that the yield of biopsies differs between certain organs and/or tissues. Therefore, we advocate more frequent consideration of AAV as a diagnosis in patients with ENT symptoms and the early referral of patients for a multidisciplinary approach when AAV is suspected in cases that are difficult to diagnose. Additionally, conducting SAA tests more often in patients with ENT symptoms might be a simple and inexpensive improvement, of which the effects should be studied in another follow-up study. It could also be helpful to choose an organ or tissue for biopsy with a high probability of obtaining histological evidence; for example, in our study the kidney and lung biopsies had the highest yield. These suggestions might help to reduce the diagnostic delay and ensure timely commencement of proper treatment, which might prevent organ damage or even death in these patients.

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A full list of ARCH study group members can be found in Supplementary Data S1, available at *Rheumatology Advances in Practice* online.

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Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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