TITLE PAGE

Clinical outcomes of subglottic stenosis in granulomatosis with polyangiitis: results of an international multicenter observational study

CATEGORY**:** Original article

AUTHORS:

Gabriele Domenico Gallina (1), Marco Lanzillotta (1) (2), Sara Maggioni (2), Adriana Cariddi (1), Giulia Danè (3), Ayşe Nur Bayındır Akbaş (4), Askin Ates (5), Alvise Berti (6), Enrico Brunetta (7) (8), Ayse Cefle (9), Emanuele Chiara (10), Edoardo Conticini (11), Vincent Cottin (12), Paolo Delvino (13) (14), Filippo Fagni (15), Gözde Sevgi Kart Bayram (16), Ömer Karadağ (16), Gabriella Moroni (17), Sergey Moiseev (18), Sara Monti (19) (20), Tahir Sayın Öğüt (21), Pavel Nivokov (18), Roberto Padoan (22), Luca Iorio (22), Federica Davanzo (22), Michelangelo Tesi (23), Luca Quartuccio (24), Ayten Yazici (9), Marco Matucci-Cerinic (1) (2), Lorenzo Dagna (1) (2), Luca Moroni (1) (2), and the STOP-GPA Study Group.

Authors' institutions

1 Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS San Raffaele Scientific Institute, Milan, Italy

2 Università Vita-Salute San Raffaele, Milan, Italy

3 Unit of Otorhinolaryngology, IRCCS San Raffaele Hospital, Milan, Italy

4 Division of Rheumatology, Department of Internal Medicine, Pamukkale University School of Medicine, Denizli, Turkey

5 Division of Rheumatology, Department of Internal Medicine, Ankara University School of Medicine, Ankara, Turkey

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

© The Author(s) 2026. Published by Oxford University Press on behalf of the British Society for Rheumatology. All rights reserved. For permissions, please email: journals.permissions@oup.com

6 Center for Medical Sciences (CISMed), Department of Cellular, Computational and Integrative Biology (CIBIO), University of Trento, and Rheumatology Unit, S. Chiara Hospital, APSS, Trento, Italy

7 IRCCS Humanitas Research Hospital, Rheumatology and Clinical Immunology Unit, Rozzano (Milan), Italy, Humanitas.

8 Humanitas University, Rozzano (Milan), Italy.

9 Division of Rheumatology, Department of Internal Medicine, Kocaeli University School of Medicine, Kocaeli, Turkey

10 Department of Medical, Surgical and Health Sciences, University of Trieste, Italy, and Clinical Medicine and Rheumatology Unit, Cattinara University Hospital, Trieste, Italy

11 Rheumatology Unit, Department of Medicine, Surgery and Neurosciences, University of Siena

12 Department of respiratory medicine, Louis Pradel Hospital, University Lyon 1, Lyon, France.

13 School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy;

14 Rheumatology Unit, Fondazione IRCSS San Gerardo dei Tintori, Monza, Italy

15 Universitätsklinikum Erlangen, Internal Medicine 3 - Rheumatology and Immunology, Erlangen, Germany.

16 Division of Rheumatology, Department of Internal Medicine, Ankara University School of Medicine, Ankara, Turkey

17 IRCCS Humanitas Research Hospital, Nephrology and Dialysis Division, Rozzano (Milan), Italy.

18 Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscoow.

19 IRCCS Istituto Auxologico Italiano, Unit of Immunology, Allergology and Rheumatology, Milan, Italy;

20. Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

21 Division of Rheumatology, Department of Internal Medicine, Akdeniz University School of Medicine, Antalya, Turkey

22 Rheumatology Unit, Department of Medicine - DIMED, University of Padua, Padua, Italy.

23 IRCCS Meyer Children's University Hospital, Nephrology and Dialysis Unit, Firenze, Italy.

24 Division of Rheumatology, Department of Medicine, University of Udine, Azienda Sanitaria Universitaria del Friuli Centrale, Udine, Italy

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

NAME and ADDRESS of the CORRESPONDING AUTHOR for reprint request – please address correspondence to: Marco Lanzillotta (e-mail: lanzillotta.marco@hsr.it) Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS-San Raffaele Scientific Institute, via Olgettina 60, 20132, Milan, Italy. Tel: 0039-02-26434078; FAX: 0039-02-26433786

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

ABSTRACT

Objectives. Subglottic stenosis (SGS) is a challenging manifestation of granulomatosis with polyangiitis (GPA), often relapsing and poorly responsive to immunosuppressive treatment. Current guidelines lack specific recommendations for SGS management and evidence is limited. This study aimed to identify features of SGS associated with a more aggressive course and to assess the efficacy of available treatments in preventing relapses.

Methods. We conducted a multicenter, retrospective cohort study including GPA patients with SGS. Patients were stratified into higher relapsers (≥2 flares) and lower relapsers (≤1 flare). Clinical and treatment features were compared across groups. Univariate and multivariate analyses were conducted to identify independent predictors of relapse and multiple flares. Kaplan–Meier curves assessed time-to-relapse across regimens.

Results. Eighty-nine patients were included (30% male). Forty-eight patients (54%) were higher relapsers, with a median time-to-relapse of 36 months. Systemic immunosuppressive therapy was associated with fewer relapses (82% vs 18%, p=0.04) compared to local treatments alone. Glucocorticoids in induction regimens reduced relapse risk (86% vs 12%, p=0.03). Cyclophosphamide (CYC) was associated with the longest relapse-free survival and reduced 5-year relapse risk (OR 0.3, p=0.049). By contrast, glucocorticoid monotherapy in either induction or maintenance phase was associated with higher relapse rate (p=0.006). No specific maintenance regimen was significantly protective, though rituximab and DMARDs showed a trend toward improved outcomes.

Conclusions. Systemic immunosuppressive therapy, particularly CYC-based induction, was associated with fewer SGS relapses and prolonged relapse-free survival, while glucocorticoid monotherapy was less effective. Prospective studies are needed to optimize induction and maintenance strategies in GPA-related SGS.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

Keywords: Granulomatosis With Polyangiitis – Subglottic stenosis – Relapse – Risk factor – Treatment

Key messages:

- Systemic immunosuppression reduces SGS relapses compared to local treatment alone.
- Cyclophosphamide induction provides the longest relapse-free survival in GPA-related SGS.
- Glucocorticoid monotherapy is linked to higher relapse risk in SGS

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

INTRODUCTION

Subglottic stenosis (SGS) is an insidious manifestation of GPA[1], yet it represents the most common form of tracheobronchial involvement, with a prevalence ranging from 10% to 23%[2,3]. Subglottic stenosis consists in narrowing of the airway region bounded superiorly by the glottis and inferiorly by the trachea, typically located at the level of the cricoid cartilage—, an area particularly susceptible to stricture. SGS predominantly affects younger female patients (<30 years), and those with disease phenotypes limited to the ENT region, often ANCA negative [4].

The clinical presentation of SGS ranges from asymptomatic cases to life-threatening airway obstruction[5, 6]. Despite its inflammatory pathogenesis, GPA-related SGS has historically been poorly susceptible to immunosuppressive therapy and often local approaches, like endoscopic dilatation, are needed. Notably, SGS lesions often display indolent granulomatous or nonspecific inflammation, lack the vasculitic component, and are characterized by marked tissue fibrosis, a histopathological hallmark that reduces drugs' effectiveness and penetration[7].

Moreover, due to its chronic and fibrotic nature, SGS often relapses multiple times over the disease course, leading to substantial morbidity and a significant impact on quality of life[6, 4, 8, 9].

Although current guidelines recommend cyclophosphamide (CYC) or rituximab (RTX) combined with glucocorticoids for the treatment of GPA[10], they do not specifically address rare manifestations such as SGS[4 11, 12, 13]. Current evidence is based on small retrospective observational studies and case reports and suggests that the combination of local therapy and systemic immunosuppressants is more effective than local procedures alone[6, 9, 2, 14], but the optimal management of SGS remains undefined.

As GPA therapeutic landscape is evolving and SGS represents a difficult-to-treat manifestation, it is crucial to identify patients at risk of worse prognosis, such as higher relapse rates, and increased risk of organ damage, in order to individualize treatment approach.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

The aim of our study is to identify clinical characteristics associated with poorer outcomes in patients with SGS, and to evaluate the most effective therapeutic strategies for preventing relapses.

MATERIALS AND METHODS

Study design

This is a multicenter, retrospective, international, observational study conducted within the STOP-GPA protocol (Subglottic Stenosis and Orbital Pseudotumor in Granulomatosis with Polyangiitis). Data were collected using standardized Case Report Forms (CRFs) and centralized in a single dedicated database including variables on demography and epidemiology, disease characteristics, treatment, and clinical outcomes. Treatment options included systemic treatments and local treatment. Systemic immunosuppressive therapies included cyclophosphamide (CYC), rituximab (RTX) and DMARDs [methotrexate (MTX), azathioprine (AZA) and mycophenolate mofetil (MMF)]. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by our local ethical committee, 'Comitato Etico Territoraile Lombardia 1' (CETL1) (CET 153-2024).

We included adult patients (≥18 years) diagnosed with GPA, according to 2022 American College of Rheumatology/European Alliance of Associations of Rheumatology (ACR/EULAR) classification criteria, and Subglottic Stenosis (SGS) from 17 centers from Italy, Germany, France, Russia and Turkey, between 1981 and 2023. Patients with SGS due to other diseases were excluded.

Endpoint

The primary endpoint was SGS relapse, defined as endoscopic demonstration of narrowing of the airway space with or without worsening symptoms, necessitating local intervention and/or escalation of systemic treatment as per clinical judgement. Secondary endpoint was time-to-relapse.

Statistical Analysis

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

Demographic and clinical characteristics were analyzed to investigate potential predictors of relapse. We assessed whether demographic and clinical data or specific treatments influenced relapse risk and whether time to relapse differed based on the treatment received. Patients were also stratified into two groups based on the number of relapses (0–1: "lower relapsers [Lr]" vs. ≥2: "higher relapsers [Hr]") for additional analyses. Patients with less than 6 months of follow-up after SGS diagnosis were excluded from the analyses.

For comparisons between categorical variables, Chi-square or Fisher's exact tests were used. Continuous variables were presented as median and interquartile range and compared using Mann–Whitney U tests or Kruskal–Wallis tests, as appropriate.

Survival analysis for relapse-free survival was performed using Kaplan–Meier curves, and differences between groups were assessed with the log-rank test. Data were censored at 5 years to preserve proportionality assumptions. A sub-analysis at 12 months was conducted to explore the early effect of induction regimens. Cox proportional hazards regression analysis was used to explore factors associated with time to relapse, with results expressed as hazard ratios (HR) and 95% confidence intervals (CI).

RESULTS

Study population

We enrolled a total of 96 patients with GPA and SGS. Mean prevalence of SGS among all GPA cohorts was 7% (± 4.2). The analyzed cohort included 89 patients who had a follow-up since SGS onset of at least six months. Sixty-two were females (70%), with a median age of 34 years at GPA diagnosis and 37 years at SGS onset. SGS was the first manifestation of GPA in 42 patients (47%), while in the remaining cases SGS became clinically evident after a median of 42 months from GPA diagnosis (IQR: 17-100). Concomitant endobronchial stenoses were detected in 15 patients (17%). ANCA were positive in 60 patients (67%) with a predominance of anti-PR3 over anti-MPO (82% vs

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

18%), and negative in 25 (27%); in 5 patients ANCA status was not known. Histological samples from the SGS lesion were available in 31 patients (35%); among them, granulomas were found in 13 cases (42%), vasculitis in 6 (19%), while the remaining specimens showed nonspecific inflammatory changes. Median follow up was 83 months (IQR: 45-163). Further demographic and clinical characteristics are detailed in **Table 1 and Supplementary Table S1 and S2.**

Eighty patients (90%) received systemic immunosuppressive therapy for SGS, while 56 (63%) also underwent local procedures such as endoscopic dilatation, laser therapy, and/or glucocorticoid injections; 14 (16%) needed tracheostomy placement. Nine patients (10%) were treated with local therapies alone. Among systemic therapies employed for SGS relapse, cyclophosphamide was the most commonly used induction of remission agent (40%), followed by conventional DMARDs (30%) and RTX (26%). Systemic glucocorticoids (GCs) were used in 65% of patients, either in combination or as monotherapy (8%). For maintenance treatment, DMARDs were employed most frequently (62%), followed by RTX (34%). Glucocorticoids were part of the maintenance regimen in 56% of patients.

Outcomes

Forty-eight patients (54%) experienced at least one SGS relapse, with a median time-to-relapse (TTR) of 36 months (IQR: 21-98). In ten patients (21%) SGS relapse co-occurred with systemic vasculitis ones. Nineteen patients (21%) were “higher relapsers” (Hr), whereas 70 patients (79%) were “lower relapsers” (Lr).

We first analyzed potential risk factors for SGS relapse by comparing relapsers and non-relapsers. No demographic or clinical characteristics were significantly associated with relapse risk, except for patients who presented with SGS as the initial manifestation of GPA, who had a lower likelihood of relapse (25% Hr vs. 54% Lr; p = 0.04). Regarding treatment, patients receiving systemic treatment for SGS were less prone to relapse compared to those managed with local interventions alone (82% Lr vs 18% Hr, p=0.04). Among local interventions, endoscopic dilatation was associated with a risk

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

of frequent relapses (p=0.02). Among patients receiving immunosuppressive therapies, the concomitant use of local procedures led to numerically less relapses (45% Lr vs 15% Hr, p=0.09).

The use of GCs as part of the induction regimen was associated not only with a reduced risk of relapse but also with a reduced risk of developing multiple relapses during disease course (percentage of patients receiving GC as induction in Lr: 86% vs Hr: 12%, p = 0.03), compared with patients treated without GCs. Notably, the use of intravenous glucocorticoid pulses did not show a significant impact on relapse risk. Mean oral GCs dose was 33 mg/day (±19). There was no significant difference in terms of relapse rate between high (> 33 mg) vs low (< 33 mg) dose of GCs.

Induction treatment with CYC was associated with the highest SGS relapse-free survival at 5 years (67%, p=0.006) (**Figure 1**), while the group treated with GCs alone showed a 100% relapse rate at 36 months. Relapse-free survival at 5 years after induction with RTX and DMARDs was 52% and 32%, respectively. These findings were confirmed in the multivariable Cox regression analysis (table 2), in which CYC was the only immunosuppressant significantly protective against the risk of subsequent relapses after the first one (HR 0.33; 95% CI 0.1-0.99; p = 0.049), followed by a possible trend for GCs (p=0.059), when adjusted for sex and age. A sub-analysis of the first 12 months after induction treatment, showed a significant difference between CYC versus DMARDs or RTX, in which the last one was associated with higher relapses (p= 0.02). Regarding maintenance therapy (**Figure 2**), patients receiving GCs alone were more prone to early relapse (median time-to-relapse - RTX: 49 months, DMARDs: 56 months, GCs: 25 months). Nonetheless, no regimen reached statistical significance (relapse rate – RTX: 50%, DMARDs: 50%, GCs: 86%; p = 0.06). No specific treatment regimen was associated with more than one relapse in the multivariate regression analysis.

DISCUSSION

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

Treatment of GPA has evolved over recent decades with the adoption of CYC and RTX for induction of remission, dramatically changing the disease course[10, 15]. However, limited evidence is available regarding the optimal management of difficult-to-treat manifestations such as SGS. Immunosuppressive therapy alone has historically shown limited efficacy in SGS (ranging from 20% to 26% across various studies), often necessitating multiple endoscopic procedures[16].

In this study, we tried to identify patients at risk to develop more relapses and, consequently, organ damage and to evaluate the best treatments to prevent flares. We found that patients treated with systemic immunosuppressive therapy had better outcomes in term of SGS relapses. In particular, the use of glucocorticoids (GCs) as part of induction treatment was associated with a lower risk of relapse and fewer relapses overtime. Among immunosuppressants, induction regimens with cyclophosphamide were associated with the best time-free-survival, opposite from patients treated only with GCs, which had the worst outcomes. The efficacy of RTX is evident only at 5 years, probably reflecting the cumulative effect of multiple treatment courses.

Langford et al., in 1996, demonstrated the effectiveness of endoscopic dilation techniques and intralesional steroid injections in the treatment of isolated SGS, in the absence of immunosuppressive therapy. This raised the hypothesis of an independent course of SGS from systemic vasculitis[6]. The 2015 study by Terrier et al. showed good efficacy of endoscopic dilation, laser therapy, and local steroid injections compared to systemic therapy alone in reversing SGS, although with high treatment failure rates due to relapses between 1 and 5 years. Among immunosuppressive agents, only high-dose steroids (>30 mg/day) were associated with better response rates, while no significant differences were observed between other agents[9].

In 2023, the study by Moroni et al. showed a significant superiority of systemic immunosuppressive treatment combined with local therapy when compared to endoscopic treatment alone. In particular, both steroid therapy and induction regimens based on CYC or RTX, unlike MTX, were associated with lower relapse rates (78% with CYC and 70% with RTX did not need any dilatation during their

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

follow-up after first episode of SGS). However, there was no significant difference in time-to-relapse (TTR) among the different immunosuppressants[2].

In 2024, the study by Aden et al. showed that maintenance therapy with RTX, when administered after local laser therapy, was associated with fewer relapses compared to patients treated with other immunosuppressive agents. However, none of the latter received cyclophosphamide in this study. No significant differences were observed in TTR[14]. In addition, a recent study from Torres et al highlighted a longer interval between endoscopic airway interventions in patients receiving RTX [16].

Considering the above, the approach currently best supported by scientific evidence for the treatment of SGS in GPA consists of endoscopic management of the lesion using balloon dilation, intralesional steroid injection, combined with immunosuppressive treatment. Endoscopic procedures have proven more effective when performed after some time has passed since diagnosis and initiation of immunosuppressive therapy[3].

Although tracheostomy rates in our cohort may appear high, they align with published frequencies of up to 40% in GPA-associated SGS, especially in earlier reports, in patients presenting with severe or fixed stenosis, and in tertiary referral settings that tend to manage more complex airway disease[17]. Our data confirms that SGS often follows a relapsing course, in the absence of systemic immunosuppression. Interestingly, patients who developed SGS as the initial manifestation of GPA experienced fewer relapses during follow-up. This finding contrasts with prior hypotheses suggesting that early SGS presentation might indicate a more aggressive disease course. A potential explanation is that early onset of SGS may prompt earlier diagnosis and systemic therapeutic intervention, which could improve disease control and limit recurrence. Additionally, when SGS is the first sign of GPA, patients may be monitored more closely from the outset, allowing for timely adjustments in treatment that prevents flares. These findings suggest that early recognition and prompt management of SGS may positively impact the disease trajectory.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

Importantly, systemic glucocorticoids therapy emerged as a protective factor against SGS relapse in the induction phase, supporting their central role in initial management. Steroid pulses did not show any benefit in our study, however, high quality studies addressing the correct initial dose of GC to treat SGS are warranted.

In our cohort, the mean starting dose of glucocorticoids was 33 mg/day. We did not observe significant differences in relapse rates based on the initial steroid dose; however, the study was not designed to determine the optimal glucocorticoid dosage, and available data on this topic were limited. Based on these findings, initiating treatment with a dose of approximately 30 mg/day, as suggested by the previous mentioned study, may represent a reasonable therapeutic approach[4]. From a pathogenetic standpoint, the rapid anti-inflammatory effect of GCs can modify the early progression trajectory during the first few months and result in less airway narrowing in the long term. However, steroid monotherapy is inadequate, as evidenced by a 100% relapse rate in this subgroup, highlighting the necessity for combination regimens. Among immunosuppressants, induction regimens based on CYC, compared to RTX or DMARDs, and maintenance regimen based on DMARDs or RTX, compared with GCs alone, has shown the best effect in maintaining prolonged SGS relapse-free survival. CYC induction showed longest time-free-survival both at 12 months and 5 years. This can have to do with the pathogenesis of the granulomatous infiltration where a cytotoxic agent (CYC) might target the cells involved more efficiently than RTX.

A major strength of our study is the sample size since it is, to our knowledge, the largest cohort of patients with SGS in the context of GPA reported to date. Moreover, patients were enrolled from multiple international centers, increasing the external validity and relevance of our findings.

Nonetheless, this study has several limitations. First, we lacked data on the severity of SGS, limiting our ability to draw definitive conclusions regarding the role of local procedures in more severe cases and the use of DMARDs in milder forms. Second, as an observational study, patients may have received additional or intercurrent treatments during the disease course or for other GPA

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

manifestations, potentially confounding our findings. By contrast, patients undergoing endoscopic dilatation had more relapses, likely reflecting more severe or symptomatic disease. Another limitation is the limited granularity of data regarding endobronchial stenosis, which was not systematically documented across participating centers and therefore should be interpreted with caution. Furthermore, the retrospective design constrained our ability to reconstruct precise DMARDs dosing and treatment strategies. In addition, pulmonary function tests were not consistently available, preventing their inclusion in the relapse definition. Ultimately, as a multicentric study, the results may be influenced by possible regional differences between different disease phenotype and therapeutic approaches among different countries.

About possible future perspectives, a small 2021 study showed potential benefit from sirolimus therapy in SGS. This drug, known for its anti-inflammatory and anti-proliferative effects, acts on the mTOR receptor, offering a rationale for inhibiting fibrosis within subglottic lesions—unlike conventional immunosuppressants[18]. We don't have sufficient data to evaluate efficacy of avacopan in our cohort. In the future it may prove useful in the treatment of SGS, due to its glucocorticoid-sparing effect [19].

CONCLUSIONS

In conclusion, our findings indicate that all patients with SGS should receive systemic glucocorticoids as part of the initial treatment. However, steroid monotherapy and only local procedures are insufficient as they are associated with early relapse and should be combined with an immunosuppressive agent to reduce the risk of recurrence of SGS. For patients with severe disease requiring induction regimens, cyclophosphamide may be preferred, as it was associated with a longer time-to-relapse. In contrast, for milder forms of GPA or for SGS occurring in the context of a more systemic but less aggressive disease, rituximab may be an appropriate choice.

Further studies with larger cohorts and randomized controlled trials (RCTs) will allow for a better understanding of this rare manifestation of GPA. Moreover, the refinement of diagnostic techniques

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

capable of quantifying the extent of inflammation and fibrosis may enable the selection of more effective therapeutic strategies and the personalization of treatment based on individual disease characteristics.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author, subject to approval by the local ethics committee.

FUNDING STATEMENT

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

DISCLOSURES

The authors have declared no conflicts of interest.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

ACKNOWLEDGEMENTS: STOP-GPA Study Group (Collaborators)

1. Veli Cobankara, MD, Division of Rheumatology, Department of Internal Medicine, Pamukkale University School of Medicine, Denizli, Turkey
2. Veli Yazisiz, MD,Division of Rheumatology, Department of Internal Medicine, Akdeniz University School of Medicine, Antalya, Turkey
3. Emine Uslu, MD; Division of Rheumatology, Department of Internal Medicine, Ankara University School of Medicine, Ankara, Turkey
4. Servet Akar, MD, Division of Rheumatology, Department of Internal Medicine, Katip Çelebi University School of Medicine, Izmir, Turkey
5. Hasan Kocaayan, MD; Division of Rheumatology, Department of Internal Medicine, Katip Çelebi University School of Medicine, Izmir, Turkey
6. Hamit Kucuk, MD, Division of Rheumatology, Department of Internal Medicine, Gazi University School of Medicine, Ankara, Turkey
7. Rıza Can Kardaş, MD ; Division of Rheumatology, Department of Internal Medicine, Gazi University School of Medicine, Ankara, Turkey
8. Timucin Kasifoglu, MD, Division of Rheumatology, Department of Internal Medicine, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey
9. Reşit Yıldırım, MD; Division of Rheumatology, Department of Internal Medicine, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey
10. Muhammed Emin Kutlu, MD; University of Health Sciences Turkey, Faculty of Medicine Bakırköy Dr. Sadi Konuk Education and Training Hospital, Department of Rheumatology, Istanbul, Turkey
11. Fatos Onen, MD,Division of Rheumatology, Department of Internal Medicine, Dokuz Eylul University School of Medicine, Izmir, Turkey
12. Tuba Demirci, MD; Division of Rheumatology, Department of Internal Medicine, Dokuz Eylul University School of Medicine, Izmir, Turkey
13. Mehmet Engin Tezcan, MD; University of Health Sciences Turkey, Faculty of Medicine, Kartal Dr. Lütfi Kırdar City Hospital Department of Rheumatology, Istanbul, Turkey
14. Duygu Şahin, MD; University of Health Sciences Turkey, Faculty of Medicine, Kartal Dr. Lütfi Kırdar City Hospital Department of Rheumatology, Istanbul, Turkey
15. Ahmet Omma,MD; University of Health Sciences Turkey, Faculty of Medicine, Ankara Bilkent City Hospital, Department of Rheumatology, Ankara, Turkey
16. Pınar Akyüz Dağlı, MD; University of Health Sciences Turkey, Faculty of Medicine, Ankara Bilkent City Hospital, Department of Rheumatology, Ankara, Turkey
17. Alessandra Milanesi: 1. Department of Internal Medicine and Therapeutics, Università di Pavia, Pavia, Italy; 2. Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.
18. Elena Treppo - Division of Rheumatology, Department of Medicine, University of Udine, Azienda Sanitaria Universitaria del Friuli Centrale, Udine, Italy.
19. Giacomo Emmi, Department of Medical, Surgical and Health Sciences, University of Trieste, Italy, and Clinical Medicine and Rheumatology Unit, Cattinara University Hospital, Trieste, Italy.
20. Stefano Viscardi, Division of Thoracic Surgery, IRCCS San Raffaele Scientific Institute, Milan, Italy.
21. Umberto Tanzini, Unit of Otorhinolaryngology, IRCCS San Raffaele Hospital, Milan, Italy
22. Apostolos Karligkiotis, Unit of Otorhinolaryngology, IRCCS San Raffaele Hospital, Milan, Italy
23. Pierpaolo Lattanzi, Unit of Otorhinolaryngology, IRCCS San Raffaele Hospital, Milan, Italy
24. Salvatore Carrabino, Unit of Otorhinolaryngology, IRCCS San Raffaele Hospital, Milan, Italy
25. Roberto Bortolotti, Unit of Rheumatology, Santa Chiara Regional Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento, Italy.
26. Francesco Peyronel, IRCCS Meyer Children's University Hospital, Nephrology and Dialysis Unit, Firenze, Italy
27. Marco Fornaro University of Bari , Rheumatology Unit, Bari , Italy.
28. Camille Taille Hôpital Bichat, Service de Pneumologie, Paris, France

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

29. Gregory Pugnet Department of Internal Medicine and Clinical Immunology, CHU Toulouse Rangueil, Toulouse, France.
30. Biancamaria Venerandi, Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS San Raffaele Scientific Institute, Milan, Italy

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

REFERENCES

1. Kitching AR, Anders HJ, Basu N, Brouwer E, Gordon J, Jayne DR, et al. ANCA-associated vasculitis. *Nat Rev Dis Primers*. 2020;6:71.

2. Moroni, L, Giudice L, Lanzillotta M, Cariddi A, Ramirez AG, Bozzolo EP. et al. Role of systemic immunosuppression on subglottic stenosis in granulomatosis with polyangiitis: Analysis of a single-centre cohort. *Eur J Intern Med* 2023;114, 108–112.

3. Catano J, Uzunhan Y, Paule R, Dion J, Regent A, Legendre P. et al. Presentation, Diagnosis, and Management of Subglottic and Tracheal Stenosis During Systemic Inflammatory Diseases. *Chest.* 2022;161:257-265..

4. Girard C, Charles P, Terrier B, Bussonne G, Cohen P, Pagnoux C et al. Tracheobronchial stenoses in granulomatosis with polyangiitis (Wegener's): A Report on 26 Cases. *Medicine (Baltimore*). 2015;94:e1088

5. Aravena C, Almeida FA, Mukhopadhyay S, Ghosh S, Lorenz RR, Murthy SC et al. Idiopathic subglottic stenosis: A review. *J Thorac Dis*. 2020;12:1100-1111

6. Langford CA, Sneller MC, Hallahan CW, Hoffman GS, Kammerer WA, Talar-Williams C et al, et al. Clinical features and therapeutic management of subglottic stenosis in patients with Wegener's granulomatosis. *Arthritis Rheum*. 1996;39:1754-60.

7. Taylor SRJ, Salama AD, Joshi L, Pusey CD, Lightman SL. Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis. *Arthritis Rheum*. 2009;60:1540–1547.

8. Aries PM, Hellmich B, Voswinkel J, Both M, Nolle B, Holl-Ulrich K et al. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. *Ann Rheum Dis*. 2006;65:853–858.

9. Terrier B, Dechartres A, Girard C, Jouneau S, Kahn JE, Dhote R, et al. Granulomatosis with polyangiitis: Endoscopic management of tracheobronchial stenosis: Results from a multicentre experience. *Rheumatology (Oxford)*. 2015;54:1852-7.

10. Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, Blockmans D, Cid MC. et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. *Ann Rheum Dis*. 2023;83:30-47

11. Kim YJ, Malm IJ, Mener DJ, Kim J, Seo P. Otolaryngological progression of granulomatosis with polyangiitis after systemic treatment with rituximab. *Otolaryngol Head Neck Surg.* 2014;150:68-72

12. Marroquín-Fabián E, Ruiz N, Mena-Zúñiga J, Flores-Suárez LF. Frequency, treatment, evolution, and factors associated with the presence of tracheobronchial stenoses in granulomatosis with polyangiitis. Retrospective analysis of a case series from a single respiratory referral center. *Semin Arthritis Rheum*. 2019;48:714-9

13. Swain SK, Sahu MC, Parida JR. Wegener's granulomatosis causing subglottic stenosis: Experiences at a tertiary care hospital of the Eastern India. *J Taibah Univ Med Sci*. 2016;11:211-6.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

14. Aden AA, Awadallah AS, XIE KZ, Wallerius KP, O'Byrne TJ, Bowen AJ, et al. Medical Maintenance Therapy Following Laser Excision in Patients With Granulomatosis With Polyangiitis (GPA)-Associated Subglottic Stenosis. *Otolaryngol Head Neck Surg*. 2024;171:180-7.15. Kronbichler A, Bajema IM, Bruchfeld A, Mastroianni Kirsztajn G, Stone JH. Diagnosis and management of ANCA-associated vasculitis. *Lancet*. 2024;403683-98.

16. Torres SJ, Neevel AJ, Ford JA, Kashat L, Hogikyan ND, Kupfer RA, et al. Immunosuppression and Surgery-Free Interval in Granulomatosis With Polyangiitis Airway Stenosis. Laryngoscope. 2025. doi: 10.1002/lary.70249

17. Taylor CS, Calyburgh DR, Rosenbaum JT, Schindler JS. Clinical manifestations and treatment of idiopathic and Wegener granulomatosis-associated subglottic stenosis. *JAMA Otolaryngol Head Neck Surg*. 2013;139:76-81

18. Poo SX, Pepper RJ, Onwordi L, Ghufoor K, Sandhu G, Salama AD. Sirolimus use in patients with subglottic stenosis in the context of granulomatosis with polyangiitis (GPA), suspected GPA, and immunoglobulin G4-related disease. *Scand J Rheumatol*. 2021;50:52-7.

19. Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the Treatment of ANCA-Associated Vasculitis. *N Engl J Med*. 2021;384:599-609.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

Table 1. **Clinical and demographic characteristics of the whole cohort and of higher relapsers (Hr) compared to lower relapses (Lr).** Abbreviations: Hr: higher relapsers; Lr: lower relapsers; GPA: granulomatosis with polyangiitis; ANCA: anti-neutrophil cytoplasmic antibodies; PR3: Proteinase 3; MPO: myeloperoxydase; BVAS: Birmingham Vasculitis Activity Score; SGS: subglottic stenosis; CYC: Cyclophosphamyde; RTX: Rituximab; DMARDS: Disease-modifying antirheumatic drugs; GCs: Glucocorticoids.

	Total	Hr	Lr	p-value
N (%)	89 (100)	19 (21)	70 (79)	
Sex				
Female (%)	62 (70)	13 (21)	49 (79)	0.79
Male (%)	27 (30)	6 (22)	21 (78)	
Age at GPA diagnosis (years, median - IQR)	34 (23-45)	29 (18-39)	34 (25-46)	0.12
ANCA (%)	60 (67)	12 (20)	48 (80)	0.3
PR3 (%)	44 (49)	9 (20)	29 (80)	
MPO (%)	12 (18)	3 (25)	18 (75)	
BVAS at GPA diagnosis (median - IQR)	10 (6-15)	6 (3-10)	10 (6-13)	0.08
SGS as first GPA manifestation (%)	42 (47)	5 (25)	37 (54)	**0.04**
Systemic therapy (%)	80 (90)	14 (18)	66 (82)	**0.04**
Induction regimen				
CYC (%)	36 (40)	5 (14)	31 (86)	0.13
RTX (%)	23 (26)	2 (9)	21 (91)	0.06
DMARDs (%)	27 (30)	7 (26)	20 (74)	0.59
GCs in induction regimens (%)	58 (65)	7 (12)	51 (86)	**0.03**
Maintenance regimen				
RTX (%)	30 (34)	4 (13)	26 (87)	0.18
DMARDs (%)	55 (62)	10 (18)	45 (82)	0.29
GCs in maintenance regimens (%)	50 (56)	7 (14)	43 (86)	0.86
Local therapy	56 (63)	17 (30)	39 (70)	**0.03**
Endoscopic dilatation (%)	37 (42)	13 (35)	24 (65)	**0.02**
Laser therapy (%)	8 (9)	3 (38)	5 (62)	0.7
GCs infiltration (%)	13 (15)	4 (31)	9 (69)	0.5
Tracheostomy	14 (16)	2 (10)	12 (17)	0.5

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026

Table 2. Multivariable analysis showing the association of different treatment with higher relapsers (Hr) and lower relapses (Lr). Abbreviation*:* CYC: Cyclophosphamyde; RTX: Rituximab; DMARDS: Disease-modifying antirheumatic drugs; GCs: Glucocorticoids.

	Hr vs Lr: Induction regimen		**Hr vs Lr: maintenance regimen**	
Variable	**HR (CI)**	**p-value**	**HR (CI)**	**p-value**
CYC	**0.33 (0.1-0.99)**	**0.049**	**-**	**-**
RTX	2.46 (0.42-14.56)	0.3	0.47 (0.08-2.47)	0.37
DMARDs	2.25 (0.72-7.23)	0.16	0.58 (0.13-2.63)	0.48
GCs	0.33 (0.1-1)	0.059	3.12 (0.9-11.2)	0.083
Age	0.98 (0.95-1.02)	0.34	1.97 (0.96-1.02)	0.62
Sex	1.69 (0.55-5.17)	0.36	1.9 (0.67-5.76)	0.2

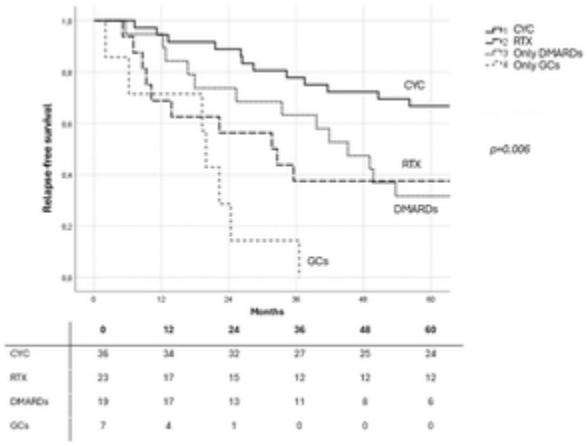
Figure 1. 5-years relapse risk after stratified by induction therapy. Abbreviations: CYC: Cyclophosphamyde; RTX: Rituximab (continuous line); DMARDS: Disease-modifying antirheumatic drugs (dashed line); GCs: Glucocorticoids (dotted line).

ALT TEXT: Kaplan–Meier plot illustrating differences in 5-year relapse-free survival among patients receiving different induction therapy strategies, with divergence of curves over time indicating varying relapse risks.

Figure 2. 5-years relapse risk stratified by maintenance therapy. Abbreviations: CYC: Cyclophosphamyde; RTX: Rituximab (continuous line); DMARDS: Disease-modifying antirheumatic drugs (dashed line); GCs: Glucocorticoids (dotted line).

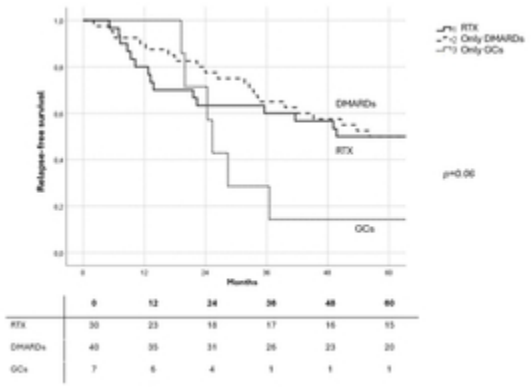
ALT TEXT: Kaplan–Meier plot illustrating differences in 5-year relapse-free survival among patients receiving different maintenance therapy strategies, with divergence of curves over time indicating varying relapse risks.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026



25x18mm (300 x 300 DPI)

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026



22x16mm (300 x 300 DPI)

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keag107/8496286 by Policlinico S. Matteo PV user on 27 February 2026