ORIGINAL INVESTIGATIONS

Assessment of the mortality burden of systemic sclerosis in the Russian Federation: results of a systematic review and meta-regression analysis

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Objective: *to develop a population-based mortality model for patients with systemic sclerosis (SSc) and to assess the disease burden (mortality indicators) for the Russian Federation.*

Material and methods. *A systematic review was conducted in the PubMed and Embase databases. Eleven real-world clinical practice studies were selected. Data analysis was performed in R v.4.3.0 using a random-effects meta-analysis model and meta-regression analysis. Covariates included the proportion of patients with diffuse disease and the proportion of patients with interstitial lung disease. For forecasting indicators for the Russian Federation, the proportions of patients were assumed to be 40% and 60%, respectively. Risk of bias was assessed using the ROBINS-Iv2 tool.*

Results and discussion. *Based on bivariate meta-regression analysis, SSc mortality in Russia was estimated at 26.1 deaths per 1000 patient-years (95% confidence interval, CI 17.3–39.3). The standardized mortality ratio was 4.2 (95% CI 2.6–6.5), indicating a 4.2-fold higher risk of death compared with the general population. The obtained estimates are consistent with international data and confirm the determining role of diffuse disease and lung involvement in shaping mortality.*

Conclusion. *SSc in Russia is associated with a high risk of premature mortality. The developed meta-regression model provides valid preliminary estimates of disease burden in the absence of a national registry. The results emphasize the need for early detection of lung involvement, standardized screening, and establishment of a national registry to monitor disease course and treatment effectiveness.*

Keywords: *systemic sclerosis; disease burden; meta-regression; interstitial lung disease; standardized mortality ratio; epidemiology.*
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Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by progressive fibrosis of the skin and internal organs, a limited number of pathogenetic treatment options, and a high risk of early disability and death. Current large systematic reviews indicate a global annual incidence of approximately 1.1–1.9 per 100,000 person-years (pooled estimate ~1.4/100,000). The estimated rate of new cases is about $1.1–1.3\times10^5$ new cases per year worldwide [1]. Regional differences are significant and are driven by variability in study methodology, diagnostic criteria, and diagnostic accessibility. This issue has not been studied in the Russian Federation.

Mortality in SSc remains high compared to the general population and other rheumatic diseases; the main immediate causes of death are interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), with concurrent pulmonary parenchymal involvement and PAH conferring the least favorable prognosis and highest mortality. An international epidemiological analysis of mortality for 2001–2023 revealed over 85,000 registered deaths associated with SSc, with a trend toward decreasing age-standardized mortality rates but an increase in overall rates due to the demographic changes [2]. Typical estimates of five- and ten-year survival stand at 72–75% and 62–63%, respectively. Early rapid decline in forced vital capacity (FVC) and progressive deterioration of pulmonary function tests (PFTs) are powerful independent predictors of mortality [3].

Individual predictors of poor outcome include: male sex, older age, rapid FVC decline, significant ILD, presence of PAH, and early complications, including scleroderma renal crisis (SRC). At the population level, the key variables determining the mortality burden in SSc are the proportion of patients with the diffuse form and the proportion of patients with lung involvement (ILD and/or PAH); these features correlate with the rate of organ failure and mortality, making them essential for predicting the disease burden at the national level [1, 3].

Assessment of epidemiological indicators and age structure demonstrated that SSc predominantly affects females and individuals of working age; in women, the peak incidence occurs between 30 and 50 years of age. Due to early disability and reduced work capacity, the disease causes significant loss of productive life years: cohorts of patients show high rates of job loss and exit from the labor market, the mean age of involuntary job loss is about 44 years, and the total duration of lost employment for individual patients amounts to decades. The economic burden of SSc includes significant direct medical costs and a substantial proportion of indirect costs (lost productivity); in countries with available data, total national expenditures can reach hundreds of millions of euros per year. For Russia, direct estimates of economic losses and gross domestic product (GDP) reductions associated with SSc at the population level have not been published, which deprives healthcare of tools for resource planning and early intervention [4, 5].

Therapy for SSc is comprehensive, taking into account the dominant manifestations, and aims to slow fibrosis progression, control inflammation, prevent vascular complications, and maintain quality of life and work capacity. For SSc and associated ILD, the effectiveness of immunosuppressants (cyclophosphamide, mycophenolate mofetil) and antifibrotic drugs (nintedanib) has been demonstrated; recent randomized clinical trials have shown that nintedanib therapy slows the decline in FVC. Biologic agents (rituximab, tocilizumab, etc.) and autologous hematopoietic stem cell transplantation are used in certain carefully chosen categories of patients with rapidly progressive disease. Standard drug classes (calcium channel blockers, angiotensin-converting enzyme inhibitors, prostanoids, phosphodiesterase-5 inhibitors, etc.) are used for the treatment of vascular complications (Raynaud's phenomenon, digital ulcers) and PAH. To achieve the optimal benefit-risk ratio of therapy in each clinical case a multidisciplinary approach and treatment personalization are required [6–8].

Despite numerous studies on the clinical manifestations, causes of death, and prognostic factors in SSc in various populations, systematic population-based estimates of mortality and economic burden for the Russian Federation are absent in official statistical reports, where SSc is included in the combined group "systemic connective tissue disorders" under ICD-10 Class XIII. This complicates the formalization of national mortality rates, determination of the level of disability nationwide, and calculation of the impact of SSc on GDP and the DALY (Disability-Adjusted Life Years) metric. At the same time, it is known that early detection of ILD and PAH, and adequate therapy modification, contribute to the preservation of lung function and work capacity [3, 5]. Given this, the creation of a standardized SSc registry is warranted for assessing survival, as well as direct and indirect costs [2, 8, 9].

However, as a preliminary assessment of the SSc burden in Russia, a population model linking the main predictors of death, namely diffuse form prevalence and lung involvement, adapted to Russian realities can be used. Such a model can be a meta-regression, which is an extension of meta-analysis that quantitatively links differences in outcome effects between studies with their population or methodological characteristics. In practice, for SSc this means that overall and standardized mortality rates along with standard errors are extracted from published studies, and the proportions of diffuse form (%DF) and lung involvement (%ILD) in the population are included as covariates. In the model, the dependent variable is the logarithm of mortality, and the coefficients for % dcSSc or % ILD indicate how many times (in relative terms) mortality changes with a change in the proportion of the respective phenotype. The output of meta-regression provides an interpretable quantitative relationship and allows the prediction of expected mortality for Russia given fixed values of % dcSSc and % ILD. A similar approach has been used in similar studies [1, 10].

The objective of the study is to develop a population-based mortality model for patients with SSc and estimate the disease burden for the Russian Federation.

Material and methods. A systematic review was conducted based on a search strategy dated May 14, 2025 (*Appendix 1*)[1] in the medical databases PubMed and Embase. The data obtained from the search (data extraction) included patient characteristics and study design features, based on which clinical and methodological heterogeneity were assessed, as well as the main outcomes – crude mortality rate (CMR)[2] and standardized mortality ratio (SMR).

SMR was calculated as the ratio of observed deaths to expected deaths: SMR = O/E. The standard error (SE) of the SMR was defined as $1/\sqrt{O}$, where O is the number of observed deaths. CMR was calculated as the ratio of the number of deaths to the sum of patient-years of follow-up: CMR = deaths / person-years. The standard error of the CMR was calculated using the following formula:

$$SE(CMR) = \sqrt{[CMR \times (1 - CMR) / \text{person-years}]}.$$

In cases where SMR was provided separately for men and women, the overall SMR for the entire cohort was obtained as a weighted average by sex proportions.

The risk of bias (RoB) was assessed using the RoBINS-Iv2 tool [11].

Systematic review, data extraction, and RoB assessment were performed independently by two investigators followed by result synchronization. A third investigator was involved to resolve disagreements.

Statistical analysis of the data was conducted using the R software v.4.3.0 environment and included the assessment of statistical heterogeneity, as well as publication bias using Egger's test For the classical meta-analysis, random-effects models were selected (Hunter—Schmidt estimator with small sample correction). A leave-one-out sensitivity analysis was also performed.

Assessment of the role of internal organ involvement was performed using meta-regression analysis. Covariates were the proportions of patients with diffuse skin involvement and ILD.Prediction of CMR and SMR values for Russia was modeled with proportions of patients with the diffuse form and lung involvement equal to 40% and 60%, respectively [12, 13]. Two approaches were used in meta-regression: univariate and bivariate. In the latter, an assumption was made about the correlation between outcomes $\rho = 0.7$ [14].

Results. Based on the systematic review, 11 real-world evidence studies (*Appendices 2, 3*) in English were selected.

The included studies demonstrate high methodological heterogeneity: enrollment years range from the mid-20th century to

[1]Appendices 1–8 to this article are available on the journal's website: https://mrj.ima-press.net/mrj

[2]In Russian literature, the equivalent of CMR is the overall mortality rate (OMR)

the early 2000s, cohort sizes range from several dozen to >1,000 patients [number of subjects ≈ 21–1012; patient-years (PY) ≈ 481.8–12,890.4], and sample types include registries and samples from hospital and specialized centers. The minimum follow-up period for SSc patients was 10 years (3 studies) [18, 24, 25], the maximum was 40 years (1 study) [19], the remaining studies assessed the efficacy endpoint (survival) over a period of 14 to 30 years (6 studies) [15–17, 19, 21–23]. In 6 studies, concomitant SSc therapy was used [15–17, 19, 23, 24]; in 5 studies, there was no information on therapy [18, 20–22, 25].

The total number of participants in the selected studies was 4,003, with a mean of 364 participants per study. The minimum number of participants was 79 (in the study by C.P. Simeyn et al. [16]), and the maximum was 1012 (C. Ferri et al. [17]).There is significant clinical heterogeneity in the study cohorts: the proportion of women was 66–92%, mean age was mostly 45–50 years, and there were age subgroups over 65 years. On average, disease duration reaches 7 years, the minimum disease duration is presented in the study by C.P. Simeyn et al. [16] – 4.5 years, and the maximum – in the study by L. Scussel-Lonzetti et al. [18] – 9.3 years (for women). The total number of patients with limited form of SSc is 1,468, with diffuse cutaneous SSc – 623. The proportion of the diffuse form across subgroups ranges approximately from 3% to 76%, lung involvement from 25% to >80% in individual cohorts. Data on antibodies, disease duration, and age at onset are either incomplete or missing in several studies. A detailed description of the patient population characteristics in the selected studies is provided in Appendix 4.

Data preparation for analysis and extraction of primary outcomes included a number of measures related to insufficient and heterogeneous reporting of population descriptions and study results. The extracted outcomes are presented in *Appendix 5*.

Processing and reconstruction of patient follow-up (FU) duration metrics were carried out as follows. If only the mean FU per group was reported in the publication, the total cumulative FU (PY) was calculated as mean FU Ч number of patients in the corresponding group. If FU was reported by subgroups (e.g., by disease form), the total PY was obtained as the sum of PY across the subgroups This procedure was applied to studies by C. Ferri et al. [17], A.J. Geirsson et al. [19], C. Perez-Bocanegra et al. [20], R. Hesselstrand et al. [21]. In the absence of an explicit FU value, but with the presence of a Kaplan–Meier survival curve, individual patient data were reconstructed using the method of P. Guyot et al. [26] followed by calculation of total PY (applied to data from L. Scussel-Lonzetti et al. [18]). For retrospective studies in the absence of FU, the latter was considered equal to the mean disease duration at the end of follow-up; in the study by P. Hissaria et al. [22], the mean disease duration at death was used.

Adjustment of the distribution of SSc subtypes in the study by C. Ferri et al. [17] was performed according to the following rule:

limited = limited + intermediate × 0.95; diffuse = diffuse + intermediate × 0.05.

This approximation is based on the results of the study by S. Jacobsen et al. [23], in which patients with SSc were divided into groups depending on the limited or diffuse form, as well as on the involvement of body segments (fingers, limbs, trunk). CJD Zarafonetis et al. [24] assumed that all patients had the limited form of the disease.

The mid-cohort year was calculated as the arithmetic mean between the year of start and the year of enrollment/observation end in the study: mid_cohort = (year_start + year_end) / 2.

During data extraction, it was found that studies by C. Bryan et al. [25], R. Hesselstrand et al. [21], and A.J. Geirsson et al. [19] mentioned a certain proportion of patients with lung involvement at baseline (pulmonary fibrosis, etc.), but the proportions themselves were not reported in the articles. To impute missing values for the percentage of lung involvement, the meta-analysis by M. Elhai et al. [27] was used (as a data source and as a modeling framework for predicting missing values). The model was built as a mixed-effects meta-regression. Fixed effects were the % of deaths from pulmonary cause and PY FU; the random effect was the country where the study was conducted. Based on this model, predictions were obtained for missing % lung involvement values. Subsequently, in the study by R. Hesselstrand et al. [21], patients with lung involvement were divided into groups – with limited and diffuse forms of SSc according to their size.

The risk of bias (RoB) assessment of 11 non-randomized studies using the RoBINS-I tool (*Appendix 6*) revealed moderate or serious risk in each work. Five studies received an overall rating of "serious risk" [17, 19, 20–22], six – "moderate risk" [15, 16, 18, 23–25]; none of the studies were rated as having low risk of bias. The most problematic domain in all studies was bias due to confounding factors. The studies by C. Perez-Bocanegra et al. [20] and A.J. Geirsson et al. [19] did not apply multivariate analysis, which does not allow distinguishing the independent contributions of age, SSc type, and organ involvement. R. Hesselstrand et al. [21], when studying the biomarker thrombospondin-5, limited themselves to adjustment only for age, without considering SSc type and severity of skin fibrosis. A serious limitation of the work by C. Ferri et al. [17] was the high risk of bias due to deviations from intended interventions: combining data from three centers over 44 years (1955–1999) covers fundamentally different eras of SSc treatment, while the observation period was not included in the analytical model. A significant problem in the study by P. Hissaria et al. [22] was incomplete data. Information on gastrointestinal and cardiac involvement was incomplete and excluded from the analysis. Autoantibody testing was performed in only 47% of patients, and capillaroscopy in 16%, limiting the reliability of conclusions about serological predictors of survival.

The risk of bias in patient selection for the study was moderate in most works. The domains of intervention classification, outcome measurement, and selection of the reported result demonstrated predominantly low risk across all studies, which is explained by the objectivity of the outcome (death was verified through state registries) and the use of classification criteria for SSc.

The meta-analysis was performed using a random-effects model (Hunter-Schmidt estimator with small sample correction). Figure 1 shows publication bias plots, Figures 2–3 show forest plots of the meta-analysis with heterogeneity assessment.

As seen in Figures 1–3, moderate publication bias and pronounced statistical heterogeneity were detected for both outcomes.

As the meta-regression analysis results, the estimates of CMR and SMR for Russia were obtained (Table 1). The results of the sensitivity analysis are presented in Appendix 8.

Given that the bivariate approach is more powerful, it was used as the primary result. Thus, mortality due to SSc in Russia is estimated at 26.1 (95% CI 17.3–39.3) cases per 1,000 patient-years, which is 4.2 (95% CI 2.6–6.5) times higher than the general population mortality.

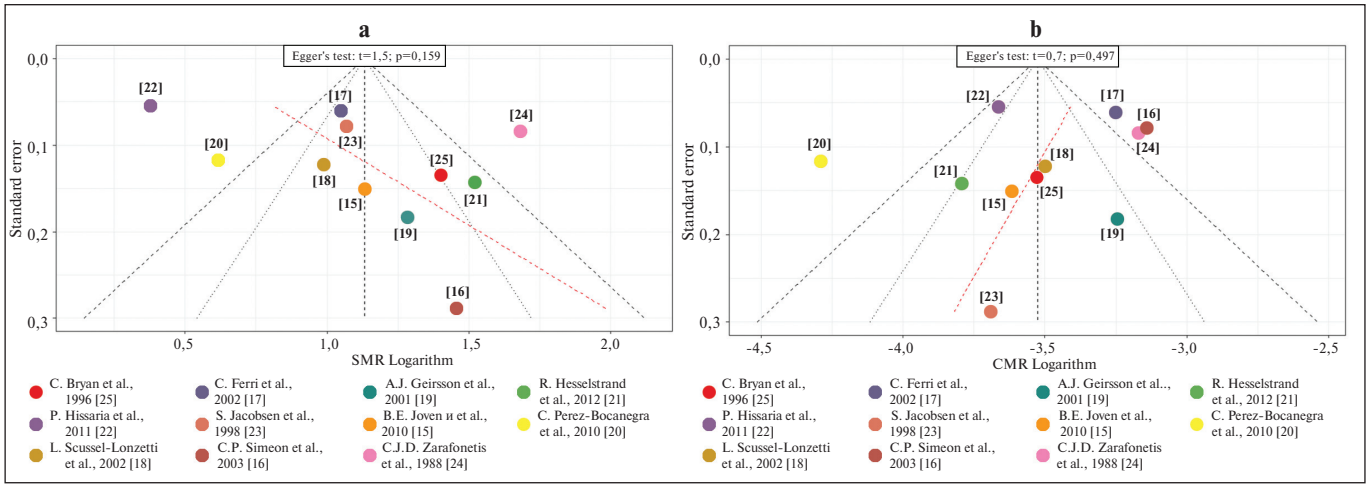

Fig. 1. *Assessment of publication bias: a – SMR (standardized mortality ratio); b – CMR (crude mortality rate)*

The results of the leave-one-out sensitivity analysis are presented in *Appendix 7*. According to this analysis, no studies were identified that create significant distortions in the pooled results for both outcomes: upon sequential exclusion of each study, SMR fluctuates between 2.9 and 3.3, and annual CMR between 28 and 32 per 1,000 patients. This indicates the robustness of the central conclusion about a significant increase in mortality in SSc (approximately threefold excess risk by SMR and ~2.8–3.2% annual mortality), and also that there is no single study drastically changing the point estimate. The largest decrease in heterogeneity (I^2) for SMR (to 87.6%) is observed when excluding data from P. Hissaria et al. [22], indicating the contribution of this cohort to overall variability. For annual CMR, the most noticeable change in I^2 (to 83.7%) and an increase in the point estimate occur when excluding the results obtained by C. Perez-Bocanegra et al. [20], reflecting the clinical and demographic features of this cohort (21% elderly patients, 73.8% patients with lung involvement) and its relatively larger weight compared to other studies. In most scenarios, I^2 remains very high (>85–90%), indicating real and substantial inter-study heterogeneity, rather than the influence of a single outlier.

The sensitivity analysis revealed critical sources of uncertainty. Refusing from FU reconstruction led to an increase in CMR and SMR estimates and a widening of confidence intervals: 29.5 (95% CI 14.1–61.6) and 5.8 (95% CI 3.0–11.3), respectively, indicating a high sensitivity of the estimates to the method of calculating total PY and confirming that reporting FU is one of the key requirements for a reliable mortality estimate. Excluding the imputation of lung involvement proportion also led to a significant increase in uncertainty and a shift in point estimates, highlighting the dependence of the conclusion on assumptions about missing data: using an external model [27] to predict missing values facilitates the inclusion of more studies but introduces model dependence and a potential source of systematic bias. Sensitivity to the exclusion of individual studies was generally moderate: removing the works with the largest contribution (studies [17] and [22]) changed estimates within the confidence interval of the main model. Overall, the results indicate a consistent direction of the effect (increased mortality with a higher proportion of severe phenotypes), but with a pronounced dependence of magnitude and uncertainty on the method of FU reconstruction and the strategy for handling missing covariates.

Study limitations and discussion. The SSc mortality estimates obtained in this study for the Russian Federation are 26.1 (95% CI: 17.3--39.3) cases per 1,000 patients per year and an SMR of 4.2 (95% CI: 2.6--6.5), which is generally consistent with international understanding of high SSc mortality and falls within the range of published estimates for large cohorts and meta-analyses. In the systematic review and meta-analysis by the French group, the pooled SMR for SSc was 3.45, and in their own French multicenter cohort – 5.73, demonstrating a wide but clinically plausible range of estimates depending on study design, sample structure, and observation period [27]. Thus, our calculated SMR value of 4.2 lies between these figures and does not contradict the current literature. Additionally, it should be noted that according to results from large international cohort studies, mortality in SSc is mainly determined by cardiopulmonary complications, primarily the extent of pulmonary fibrosis and the presence of PAH, and to a lesser extent by cardiac involvement and SRC [28–30]. This aligns well with our chosen meta-regression structure, where the proportions of patients with lung involvement and the diffuse form were used as the main population predictors of mortality.

However, direct comparison with Russian publications is limited by the absence of national epidemiological studies. Available isolated Russian studies are mainly devoted to the pattern of organ involvement, quality of life, patient routing, and ILD progression, rather than direct estimation of population mortality [31, 32]. There are isolated works noting survival at different time periods depending on the initial disease severity and therapy received. For example, the study by N.G. Guseva [33] analyzed survival at 5, 10, and 15 years after disease onset in 262 patients treated at the Institute of Rheumatology in 1960–1980, showing largely the natural history of SSc. Thus, an adverse outcome was noted in the acute course of SSc (2/3 of patients died in the first 2 years of the disease), while in the chronic course, 5-year survival was 93%, 10-year – 87%, 15-year – 85%, except for patients with PAH [33]. In the work by L.A. Garzanova et al. [34], tolerability of rituximab therapy and survival were evaluated in 151 SSc patients enrolled from 2008 to 2020, over a period of 5.6±2.6 years. Over the entire observation period, 17 (11%) deaths were recorded (2/100 patient-years; 95% CI 1.3–3.2). It was noted that most patients died from the progression of insufficiency of vital organ

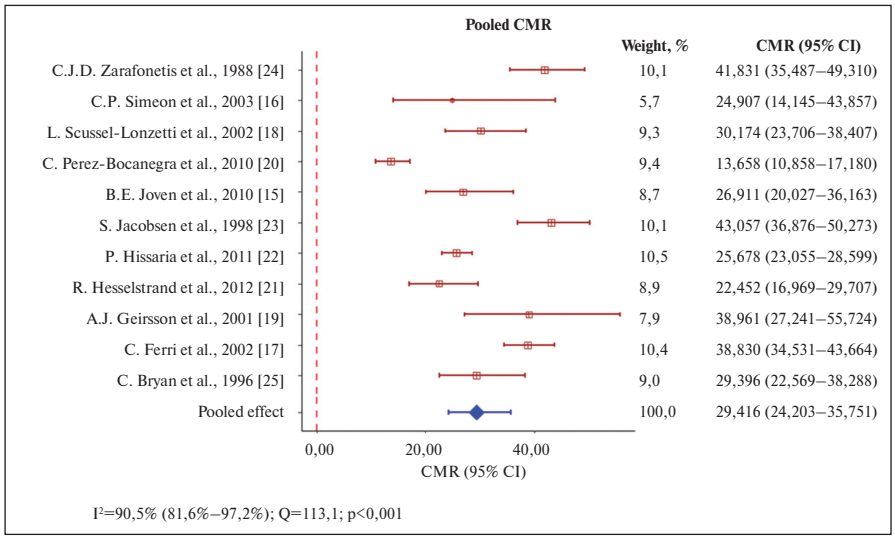

Fig. 2. *Forest plot with assessment of statistical heterogeneity for CMR, deaths per 1000 patients*

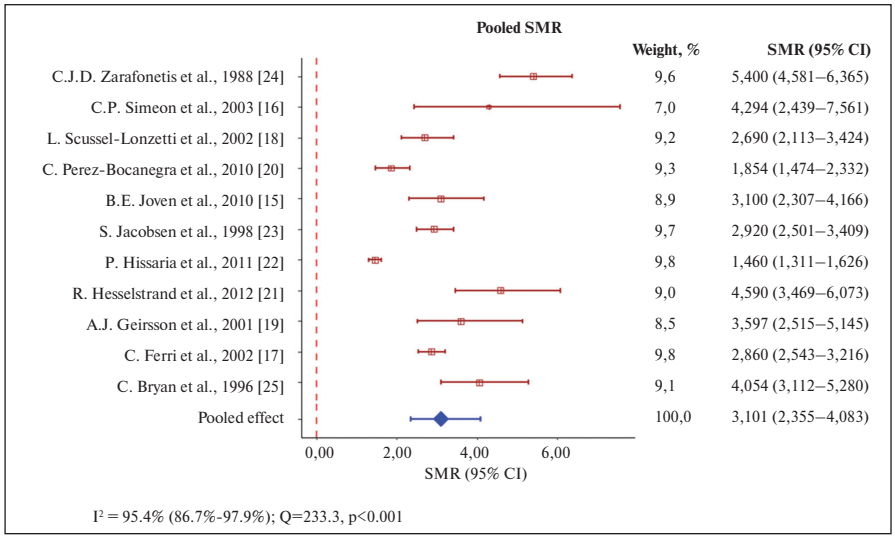

Fig. 3. *Forest plot with assessment of statistical heterogeneity for SMR*

functions that had occurred before the start of rituximab treatment. However, these data should be interpreted considering the characteristics of the study patient group: the predominance of the diffuse form and ILD with baseline severe reduction in lung diffusion capacity, high disease activity, and a number of other visceral involvement (cardiac and renal involvement), implying an initially poor prognosis Nevertheless, these works provide only a general idea of SSc mortality in Russia.

Thus, the absence of pronounced discrepancies between our model estimate and estimates obtained from foreign cohorts should be considered rather as an indirect sign of its clinical plausibility, rather than as complete verification using Russian data.

Considering the obtained mortality estimate and the predominance of fatal cardiopulmonary complications, the view of the limited social significance of SSc should be reconsidered. It is obvious that approaches to the management of SSc patients require systematic improvement in early diagnosis, screening for ILD and pulmonary hypertension, timely initiation of pathogenetically based therapy, and standardization of patient routing.

Despite the validity and clinical interpretability of the constructed model, the creation of a standardized database is a promising and useful step. The meta-regression model, even with a clinically adequate prediction, is by definition limited by the aggregated nature of the data and does not replace individual analysis of disease course, causes of death, time-to-event, and response to therapy. To understand what such a database should look like, it is advisable to look at existing international platforms. The most significant is EUSTAR, the largest international SSc database, including a standardized minimum data set and allowing analysis of mortality, target organ progression, and risk factors for adverse outcomes. The EUSTAR mortality analysis included over 11,000 patients, with a median follow-up of 2.3 years [27, 35]. A significant advantage of EUSTAR is the systematic collection of a wide range of disease characteristics, allowing not only cohort description but also the construction of prognostic models. More recent works based on EUSTAR data demonstrate the possibility of analyzing individual SSc phenotypes, trajectories of organ involvement, and outcomes in large samples with prospective follow-up [36–41].

The Spanish RESCLE registry is a national multicenter cohort created to assess survival, causes of death, and prognostic factors; it covers 14 centers, and its analysis showed the independent prognostic role of age at onset, disease phenotype, presence of ILD and/or PAH, and SRC [42] Its key value lies in the fact that it reflects the national rather than international characteristics of care provision and thereby allows for the assessment of mortality and risk factors in relation to a single healthcare system.

The French multicenter cohort included 625 patients followed from 2000 to 2013 with subsequent information collection until 2016; it provided some of the most detailed data on survival, SMR, and prognostic factors, including age, SSc phenotype, presence of SRC, PAH, and PFT parameters in the patient [28]. Thus, each of the existing registries demonstrates that the greatest value is not simply administrative

Table 1. CMR and SMR estimates for Russia, 95% CI

Parameter	Univariate approach	Bivariate approach
Annual CMR per 1,000 patients	26,0 (17,2–39,2)	26,1 (17,3–39,3)
SMR	4,2 (2,6–6,5)	4,2 (2,6–6,5)

databases, but standardized clinical platforms that allow simultaneous recording of disease phenotype, severity of internal organ involvement, patient routing, treatment, and the entire range of medical and social outcomes.

As a Russian example, we can cite the registry of children with rheumatic diseases at a specialized center based at the Morozov Hospital in Moscow, which by 2025 included 67 patients with SSc. The creation of this registry made it possible to identify shortcomings in the regulatory framework governing preferential drug provision for SSc patients and to propose a number of measures to improve the work of the pediatric rheumatology service [42].

A logical next step in studying the problem could be not only its validation using Russian data but also the institutionalization of systematic information collection. The creation of a regional or (ideally) national registry, structured according to the model of international platforms and adapted to Russian clinical practice, will allow us to fully trace the entire patient journey – from disease onset and diagnosis to treatment selection, monitoring of complications, and outcomes – and thereby ensure a real improvement in the quality of medical care for SSc patients in Russia.

This study has several limitations. Aggregated (study-level) meta-regression has a number of limitations that significantly affect the interpretation of results. First, ecological bias: associations at the cohort level may not reflect individual risks, so conclusions about a causal relationship between phenotype and mortality are population-based. Second, high heterogeneity by enrollment time, cohort type (registry studies and data collection based on medical organizations), diagnostic criteria, and completeness of reporting (differences in definition and verification of lung involvement, incomplete antibody data, FU) increased the uncertainty of mortality estimates, widening their confidence intervals. Third, FU reconstruction was performed based on the assumption of its uniform distribution among patients. Fourth, the use of external meta-analysis to impute missing proportions of patients with lung involvement creates a potential circular effect and increases the dependence of the conclusion on the choice of the model source (M. Elhai et al. [26]). Finally, the bivariate model assumes a correlation of $\rho=0.7$, taken from a foreign study [14]. Fifth, the small number of selected studies and the large number of missing data in population descriptions did not allow the inclusion of important variables such as the proportions of patients with anticentromere antibodies and anti-topoisomerase-1 antibodies, PFT data, and treatment received. Nevertheless, the obtained clinically sound estimates and generally satisfactory sensitivity analysis results support the validity of the model.

Conclusion. The conducted systematic review and bivariate meta-regression showed that the CMR for SSc in Russia significantly exceeds the general population rate and amounts to 26.1 (95% CI 17.3–39.3) cases per 1,000 patient-years, and the SMR reaches 4.2 (95% CI 2.6–6.5). The obtained estimates are in good agreement with international data on the poor prognosis of SSc and confirm the determining role of severe disease phenotypes, primarily the diffuse form and ILD, in shaping the population mortality burden. Clinically, this underscores the need for early identification of high-risk patients, standardized screening for ILD and PAH, and timely referral to specialized centers.

Despite a number of limitations of the initial data, we managed to develop and implement a methodologically correct, transparent, and robust meta-regression model that provided interpretable and practically significant mortality estimates for Russia, supported by multi-step sensitivity analyses and a bivariate approach. This allows it to be considered a valid tool for preliminary population-based mortality assessment in the absence of population data on SSc in the Russian Federation. At the same time, the results of the study indicate the need to create a standardized registry system, which would allow assessing not only mortality but also the pattern of organ involvement, patient routing, treatment effectiveness, and loss of real-world work capacity.

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