Use of platelet inhibitors for digital ulcers related to systemic sclerosis: EUSTAR study on derivation and validation of the DU-VASC model

Garaiman, A.; Steigmiller, K.; Gebhard, C.; Mihai, C.; Dobrota, R.; Bruni, C.; ... ; EUSTAR Collaborators

RHEUMATOLOGY

Rheumatology 2023;62:SI91–SI100
https://doi.org/10.1093/rheumatology/keac405
Advance access publication 29 July 2022

Concise report

Use of platelet inhibitors for digital ulcers related to systemic sclerosis: EUSTAR study on derivation and validation of the DU-VASC model

Alexandru Garaiman[1], Klaus Steigmiller[2], Catherine Gebhard[3], Carina Mihai[1], Rucsandra Dobrota[1], Cosimo Bruni[1,4], Marco Matucci-Cerinic[4,5,6], Joerg Henes [7], Jeska de Vries-Bouwstra [8], Vanessa Smith [9,10], Andrea Doria [11], Yannick Allanore[12], Lorenzo Dagna[5,6], Branimir Anić[13], Carlomaurizio Montecucco[14], Otylia Kowal-Bielecka[15], Mickael Martin[16], Yoshiya Tanaka [17], Anna-Maria Hoffmann-Vold [18], Ulrike Held [2], Oliver Distler [1], Mike Oliver Becker [1] and EUSTAR Collaborators

Abstract

Objective. To develop and validate the prognostic prediction model DU-VASC to assist the clinicians in decision-making regarding the use of platelet inhibitors (PIs) for the management of digital ulcers in patients with systemic sclerosis. Secondly, to assess the incremental value of PIs as predictor.

Methods. We analysed patient data from the European Scleroderma Trials and Research group registry (one time point assessed). Three sets of derivation/validation cohorts were obtained from the original cohort. Using logistic regression, we developed a model for prediction of digital ulcers (DUs). *C*-Statistics and calibration plots were calculated to evaluate the prediction performance. Variable importance plots and the decrease in *C*-statistics were used to address the importance of the predictors.

Results. Of 3710 patients in the original cohort, 487 had DUs and 90 were exposed to PIs. For the DU-VASC model, which includes 27 predictors, we observed good calibration and discrimination in all cohorts (*C*-statistic = 81.1% [95% CI: 78.9%, 83.4%] for the derivation and 82.3% [95% CI: 779.3%, 85.3%] for the independent temporal validation cohort). Exposure to PIs was associated with absence of DUs and was the most important therapeutic predictor. Further important factors associated with absence of DUs were lower modified Rodnan skin score, anti-Scl-70 negativity and normal CRP. Conversely, the exposure to phosphodiesterase-5 inhibitor, prostacyclin analogues or endothelin receptor antagonists seemed to be associated with the occurrence of DUs. Nonetheless, previous DUs remains the most impactful predictor of DUs.

Conclusion. The DU-VASC model, with good calibration and discrimination ability, revealed that PI treatment was the most important therapy-related predictor associated with reduced DU occurrence.

Key words: SSc, prognostic prediction model, digital ulcers, platelets inhibitors

[1]Department of Rheumatology, University Hospital Zurich, [2]Epidemiology, Biostatistics and Prevention Institute, Department of Biostatistics, [3]Department of Nuclear Medicine, University Hospital Zurich, Center for Molecular Cardiology, University of Zurich, Zurich, Switzerland, [4]Department of Experimental and Clinical Medicine, Division of Rheumatology, University of Florence, Scleroderma Unit, AOUC, Florence, [5]Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS San Raffaele Scientific Institute, [6]Faculty of Medicine and Surgery of the Vita-Salute San Raffaele University, Milan, Italy, [7]Centre for Interdisciplinary Clinical Immunology, Rheumatology and Autoinflammatory Diseases and Department of Internal Medicine II (Hematology, Oncology, Immunology and Rheumatology), University Hospital Tuebingen, Tuebingen, Germany, [8]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands, [9]Department of Internal Medicine, Ghent University, [10]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium, [11]Rheumatology Unit, Department of Medicine, University of Padova, Padova, Italy, [12]Department of Rheumatology A, Descartes University, APHP, Cochin Hospital, Paris, France, [13]Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, University Hospital Centre Zagreb and University of Zagreb, School of Medicine, Zagreb, Croatia, [14]Department of Rheumatology, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy, [15]Department of Rheumatology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland, [16]Internal Medicine, Poitiers University Hospital, Poitiers, France, [17]The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health Japan, Kitakyushu, Japan and [18]Department of Rheumatology, Oslo University Hospital, Oslo, Norway

Submitted 22 February 2022; accepted 11 July 2022

Correspondence to: Mike Oliver Becker, Department of Rheumatology, University Hospital Zurich, University of Zurich, Rämistrasse 100, 8006 Zurich, Switzerland.
E-mail: MikeOliver.Becker@usz.ch

CLINICAL SCIENCE

Rheumatology key messages

- We developed and validated the DU-VASC prediction model to assist the clinicians in decision-making regarding digital ulcers.
- Platelet inhibitors are the most important predictor among the included therapy predictors for the occurrence of digital ulcers.
- We encourage the use of platelet inhibitors in the management of digital ulcers.

Introduction

Digital ulcers (DUs) occur in up to 50% of patients with SSc [1]. Although the use of iloprost, phosphodiesterase-5 inhibitors (PDE-5i) or bosentan is beneficial, prevention and healing of DUs remain challenging in clinical practice [2]. In order to improve this, more important predictors and treatment approaches are needed. At the moment there are only two prediction models described in the literature: first, the Capillaroscopy Ulcers Risk Index (CSURI), which evaluated the risk of new DUs in a 3-month follow-up, and second, the clinical features, imaging, patient history—digital ulcer score (CIP-DUS), which predicts the digital ulcers based on clinical data, imaging and patient history [3, 4].

Although these two scores are performant and easy to use, both operate on imaging data, which are not always available, and do not incorporate predictors referring to therapy. Moreover, there are also several therapies, such as platelet inhibitors (PIs), that are sometimes administrated in clinical practice based on pathophysiological considerations, although formal evidence is lacking.

Thus, our first aim was to develop and validate a precise prediction model to assist clinicians in evaluating the risk for occurrence of DUs, including platelet inhibitors and exposure to vasoactive medication (DU-VASC model). As PIs appeared as significant predictors, we also assessed the incremental value of PIs in DU-VASC.

Methods

Patients and source of data

We included in our study patients aged $\geq$18 years, fulfilling the 2013 American College of Rheumatology/European League Against Rheumatism SSc classification criteria [5], enrolled in the prospective European Scleroderma Trials and Research group (EUSTAR) registry and followed up between 1 January 2013 and 24 July 2019.

Outcome

Our outcome was the occurrence of DUs at the next visit after 1 year ($\pm$3 months) of follow-up, under exposure to vasoactive therapy.

Predictors

The predictors were selected based on the available literature and clinical judgement, then introduced additively in the model: age [6], sex [6], current smoking [7], disease duration [8], modified Rodnan skin score (mRSS) [8], joint contractures [9], left ventricular ejection fraction (LVEF%) [7], dyspnoea NYHA functional class, arterial hypertension, pulmonary hypertension (PH), predicted forced vital capacity (FVC%) [8], anti-Scl-70 antibodies [6], elevation of C-reactive protein and previous occurrence of DUs [8]. To these, we added the latitude of the EUSTAR centre and the season in which the assessment was performed. The therapy predictors reflected the exposure of the patient at the previous visit to any member of specific vasoactive/vasodilating class: PIs, beta-blockers, PDE-5i, endothelin receptor antagonists (ERAs), calcium channel blockers (CCB), angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor antagonists, prostacyclin analogue and oral anticoagulants (OACs). Definitions and coding of all predictors are presented in Supplementary Tables S1 and S2, available at *Rheumatology* online.

Sample size calculations

For the justification of the sample size necessary to develop and validate the multivariable prediction model with these data, recent methods proposed by Riley *et al.* [10, 11] were used. At least 784 observations were required to develop the model using all the candidate predictors, with 124 events (at outcome prevalence of 15%). For the validation, the minimum required sample size was 591 observations with 89 events.

Missing data

Last observation carried forward imputation was used to handle missing values for variables referring to auto-antibodies. Multiple imputation was implemented to handle the rest of the missing values. The approach used here—*missForest*—operates with a random forest algorithm (50 trees). Further details on this process (e.g. included variables, imputation error and missingness) are reported in the supplementary methods (Supplementary Fig. S1, available at *Rheumatology* online) and results.

Statistical analysis

All analyses were conducted in R (version 4.0; R Foundation for Statistical Computing, Vienna, Austria) in a fully scripted manner to guarantee reproducibility.

DU-VASC development

Logistic regression was performed to develop the DU-VASC model in a derivation cohort [12] represented by all patients having their follow-up visit included in the analysis between 1 January 2013 and 16 July 2018. The remaining patients (patients having their last follow-up visit after 16 July 2018 and until 24 July 2019) were held out for external validation. These two cohorts represented the temporal set (see Supplementary Fig. S2, available at *Rheumatology* online).

DU-VASC performance

We assessed the discrimination and calibration of our model in the derivation and validation cohorts by computing *C*-statistics and assessment of calibration with calibration plots, respectively [13]. Secondary analyses were performed in two different sets of derivation/validation cohorts obtained using a random sampling (random set) and geographic split (spatial set, visits of patients followed-up in centres situated east–west from $+5^{\circ}$ longitude) of the original cohort. The size of the derivation and validation cohorts had a ratio of 2:1 in all sets. A sensitivity temporal set was also built as presented before but from a different original cohort that included also the visits of the patients where the information about exposure to PIs was missing. The missing values in this cohort were handled using the same *missForest* algorithm.

Incremental value of PIs as a predictor

Variable importance plots (VIP) provided a ranking of the predictors by their predictive power. In addition to this, we assessed the decrease in the *C*-statistics if the PI predictor was withheld [14].

Ethics

The study complies with the Declaration of Helsinki and the study protocol was reviewed and approved by the EUSTAR board (project number CP 99). Ethical approval for this study was obtained at each participating site. The participating sites are listed in the EUSTAR collaborators in Acknowledgements. All the individual centres approved the EUSTAR study and ethical/institutional approval was obtained at every participating site, according to their local ethical guidelines and EUSTAR rules. Written informed consent has been obtained from the patients (or their legally authorized representative), where appropriate.

Results

The current research is reported in accordance with the transparent reporting of the multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidance [15].

Patients

Of the 17 212 patients included in the EUSTAR registry by 24 July 2019, 8992 fulfilled our inclusion criteria (Supplementary Fig. S2, available at *Rheumatology* online). A total of 3710 patients (3169 [85.4%] women, 1668 [65.5%] of 2548 patients with available data had limited cutaneous SSc, median age 58.4 years, median disease duration 10.6 years) had at least two follow-up visits, allowing indexing of the treatment variables. Of these, 486 (13.1%) had DUs and 90 (2.4) were exposed to PIs. The derivation cohort encompassed 2473 patients, while the validation cohort had data from 1237 patients, and thus the minimal sample size requirement to develop and to validate the DU-VASC model was met. The same requirement was met also in our secondary (spatial and temporal set) or sensitivity analyses. Further clinical and therapeutic characteristics are summarized in Table 1, as well as the missing percentage for every predictor. Clinical and therapeutic characteristics for all sets after multiple imputation are presented in Supplementary Table S3, available at *Rheumatology* online.

DU-VASC development

All predictors and their association with DUs for the temporal set are presented in Fig. 1A. Model development (Supplementary Figs S3–S10, available at *Rheumatology* online), performance (Supplementary Figs S11–S12, available at *Rheumatology* online), and the performance of predictors (Supplementary Tables S4–S7, Supplementary Fig. S13, available at *Rheumatology* online) in the other sets are reported in the supplementary material and were similar in all sets. Of the therapeutic predictors, PIs, beta-blockers, CCBs and ACE inhibitors were associated negatively with presence of DUs at the next visit. Conversely, the exposure to PDE-5i, OACs, prostacyclin analogues and ERAs seemed to be associated with the occurrence of DUs at the next follow-up visits. Of the other non-therapeutic predictors, male sex, warm season at the time of assessment and a higher FVC% were associated with absence of DUs at the next follow-up visit, while previous DUs, anti-Scl-70 ab positivity, PH, higher mRSS, higher latitude of the centre, presence of joint contractures, a longer disease duration, elevated CRP and presence of arterial hypertension were associated with occurrence of DUs at the next follow-up visit. The DU-VASC formula to compute the probability of DU occurrence is shown in the Supplementary Results, available at *Rheumatology* online.

DU-VASC performance

C-Statistics were consistent across derivation and validation cohorts in the temporal set: 81.1% (95% CI: 78.9%, 83.4%) and 82.3% (95% CI: 79.36%, 85.3%), respectively (Fig. 1B). These values correspond to a good discrimination ability of the model, suggesting no data overfitting. The calibration of the DU-VASC model was also good and consistent across cohorts (Fig. 1C).

Table 1 Patients' characteristics

Characteristics	Overall ($n = 3710$)	Missing, *n* (%)	Derivation ($n = 2473$)	Validation ($n = 1237$)
Age, median (IQR), years	58.4 (48.8–67.7)	0 (0)	58.5 (48.9–67.8)	58.1 (48.6–67.6)
Sex: female, *n* (%)	3169 (85.4)	0 (0)	2092 (84.6)	1077 (87.1)
Disease subset: limited cutaneous SSc, *n* (%)	1668 (65.5)	1162 (31.3)	1117 (66.7)	551 (63)
Current smoking: yes, *n* (%)	19 (0.9)	1481 (39.9)	11 (0.7)	8 (1.1)
Latitude, median (IQR), degrees	47.4 (43.8–50.9)	0 (0)	47.6 (43.8–50.9)	47.4 (44.8–50.6)
Time since RP onset, median (IQR), years	5.5 (3.1–12.9)	3675 (99.1)	5.5 (2.7–12.7)	7.1 (3.9–14)
Season: warm, *n* (%)	1837 (49.5)	0 (0)	1288 (52.1)	549 (44.4)
Disease duration, median (IQR), years	10.6 (5.6–17)	616 (16.6)	10.3 (5.5–16.5)	11 (5.9–18.2)
Digital ulcers: yes, *n* (%)	487 (13.1)	0 (0)	339 (13.7)	148 (12)
Pitting scars on fingertips: current, *n* (%)	1011 (30.5)	391 (10.5)	686 (30.9)	325 (29.5)
Arterial hypertension: yes, *n* (%)	752 (21)	133 (3.6)	513 (21.7)	239 (19.7)
mRSS, median (IQR)	4 (2–9)	360 (9.7)	4 (2–10)	4 (0–8)
Joint contractures: yes, *n* (%)	938 (26.5)	170 (4.6)	642 (27.1)	296 (25.3)
Dyspnoea stage III–IV: yes, *n* (%)	391 (10.5)	0 (0)	267 (10.8)	124 0
LVEF %, median (IQR)	61 (60–65)	1485 (40)	61 (60–65)	60 (60–65)
Pulmonary hypertension: yes, *n* (%)	329 (13.3)	1242 (33.5)	242 (15.2)	87 (9.9)
FVC, median (IQR), % predicted	96 (80–111)	1002 (27)	96 (79–111)	95 (81–110)
DLCO/SB, median (IQR), % predicted	68 (54–80)	1253 (33.8)	67 (53–80)	69 (54–81)
Malabsorption syndrome: yes, *n* (%)	94 (3.5)	1019 (27.5)	73 (4.3)	21 (2.1)
ANA positive: yes, *n* (%)	3537 (95.3)	0 (0)	2342 (94.7)	1195 (96.6)
ACA positive: yes, *n* (%)	1447 (39)	0 (0)	998 (40.4)	449 (36.3)
Anti-RNA polymerase III positive: yes, *n* (%)	273 (7.4)	0 (0)	167 (6.8)	106 (8.6)
Anti-Scl-70 positive: yes, *n* (%)	1221 (32.9)	0 (0)	830 (33.6)	391 (31.6)
CRP, elevation: yes, *n* (%)	785 (24.6)	525 (14.2)	512 (24.1)	273 (25.8)
Any platelet inhibitor: yes, *n* (%)	90 (2.4)	0 (0)[a]	64 (2.6)	26 (2.1)
Any oral anticoagulant: yes, *n* (%)	98 (2.6)	263 (7.1)[a]	81 (3.3)	17 (1.4)
Any B-blocker: yes, *n* (%)	137 (3.7)	313 (8.4)[a]	104 (4.2)	33 (2.7)
Any prostacyclin analogue: yes, *n* (%)	400 (10.8)	434 (11.7)[a]	282 (11.4)	118 (9.5)
Any PDE-5 inhibitor: yes, *n* (%)	159 (4.3)	313 (8.4)[a]	108 (4.4)	51 (4.1)
Any endothelin receptor antagonist: yes, *n* (%)	229 (6.2)	468 (8.7)[a]	176 (7.1)	53 (4.3)
Any Ca-blocker: yes, *n* (%)	553 (14.9)	772 (20.1)[a]	393 (15.9)	160 (12.9)
Any ACE/angiotensin receptor inhibitor: yes, *n* (%)	353 (9.5)	245 (6.6)[a]	262 (10.6)	91 (7.4)

[a]Definitions of organ manifestations according to EUSTAR. Highest missingness among the variables used to build the respective summary variable. ACA: anti-centromere antibodies; ACE: angiotensin-converting enzyme; DLCO/SB: diffusing capacity of the lung for carbon monoxide/single breath; FVC: forced vital capacity; HRCT: high resolution CT; IQR: interquartile range; LVEF: left ventricular ejection fraction; mRSS: modified Rodnan skin score; PDE-5: phosphodiesterase-5; RNA: ribonucleic acid; Scl70: anti-Scl70 antibodies, anti-topoisomerase I antibodies.

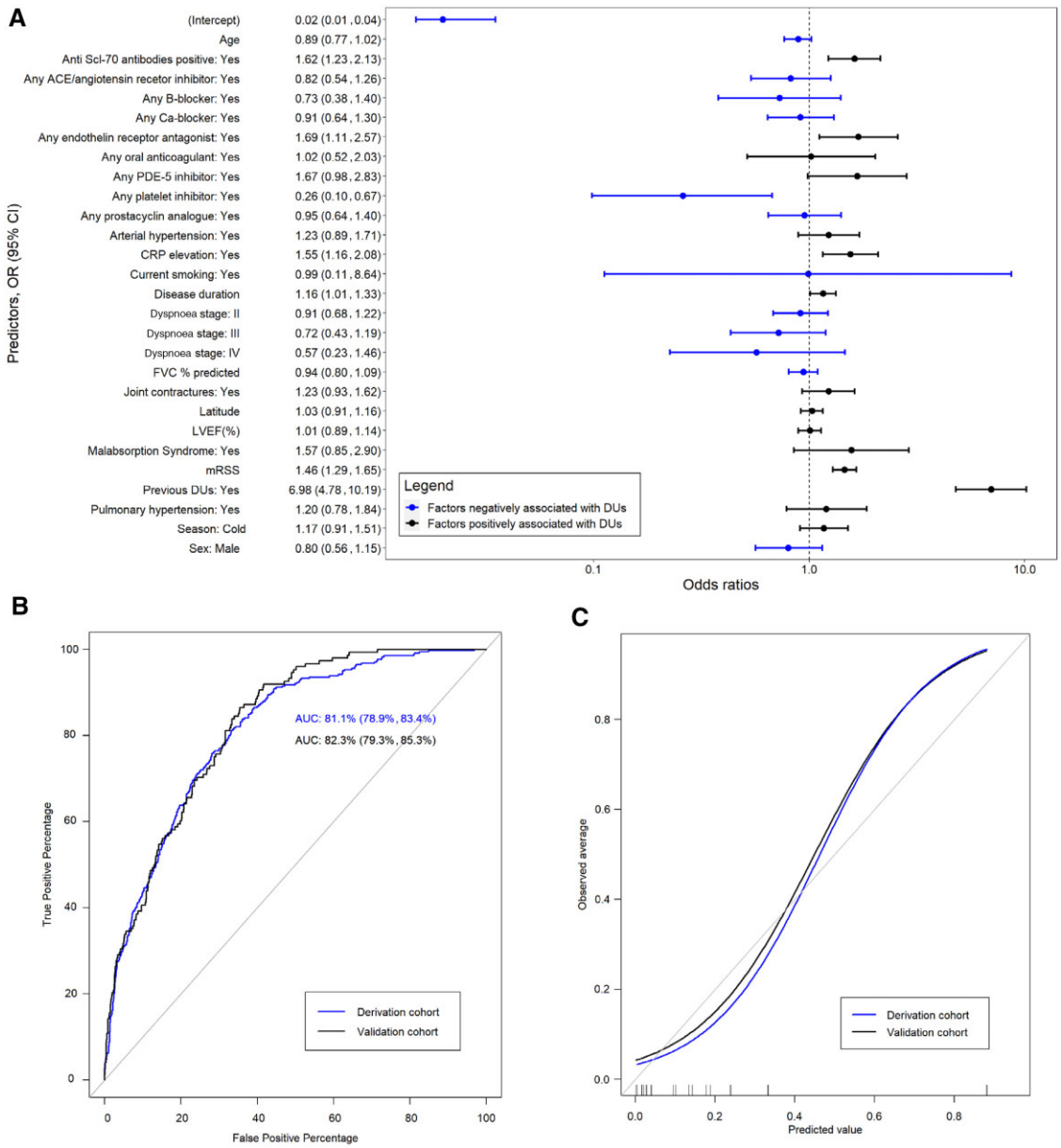
Incremental value of the PIs as predictor

In the VIPs, the PIs ranked highest among the therapeutic predictors, first among the predictors negatively associated with DUs, and among therapy predictors, regardless of which derivation/validation set was considered (Supplementary Fig. S13, available at *Rheumatology* online). Accordingly, when new models were built by subsequently removing one therapy predictor, we observed the largest drop in the *C*-statistic when PIs were withheld from the original model (Supplementary Table S4, available at *Rheumatology* online).

Discussion

We developed and validated a well performing prognostic prediction model for the occurrence of DUs, which integrates well-known factors associated with the occurrence of DUs and vasoactive therapy predictors—the DU-VASC model. The performance of DU-VASC was similar to other currently available scores predicting DUs [3, 4]. The different type of predictor data selected for the prediction of DUs in CSURI and CIP-DUS (i.e. imaging data)—which are not available in the EUSTAR registry—prevented us from fitting CSURI or CIP-DUS in our data and comparing performances directly. DU-VASC is, however, not intended to replace CSURI or CIP-DUS, but rather to help the clinician to predict the occurrence of DUs based on predictors or data that are already available and are usually collected at every follow-up visit of a patient in any EUSTAR centre, taking into consideration also therapy predictors, in particular the PIs. CIP-DUS or CSURI can only be used where imaging data are available.

Fig. 1 Model presentation



(**A**) Forest plot displaying the association of the outcome (occurrence of DUs) with every predictor on an exponential scale. (**B**) ROC curves displaying the discrimination ability of the fitted model in the derivation and validation cohorts, respectively. The area under the curve (AUC) is given with the 95% confidence intervals. (**C**) Calibration plots of the model in the derivation cohort and in the validation cohort. On the *x*-axis, the model's predicted probability of the occurrence of DUs is plotted against the observed risk of presence of DUs on the *y*-axis (0 = absence of DUs, 1 = presence of DUs). The diagonal line represents perfect prediction, meaning that the predicted risk is the same as the observed risk across the whole range. Ideally, the lines obtained should lie exactly over the diagonal line. ACE: angiotensin converting enzyme; AUC: area under receiver operating characteristic curve (*C*-statistic); DU: digital ulcer; FVC: forced vital capacity; LVEF: left ventricular ejection fraction; mRSS: modified Rodnan skin score; OR: odds ratio; PDE-5: phosphodiesterase-5; ROC: receiver operating characteristic.

In the assessment of the incremental value of therapy predictors in our model, the exposure to PIs was ranked the highest among the therapy predictors. Interestingly, the exposure to prostacyclin analogues, ERAs or PDE-5i, which proved their benefit in randomized clinical trials, seemed to be associated in our study with occurrence of DUs [2, 16–20]. In fact, in real life the use of these three drugs or of their combination in the management of

DUs is beneficial. These conflicting findings might be explained by the fact that these therapies were already started at previous visits to heal/prevent DUs or the therapy was initiated due to PH. Notably, their incremental predictive value ranked below the one for PIs in the variable importance plot and the *C*-statistic drop was smaller when these three regimens were removed from the full model.

Our study has several limitations. First, owing to the study design, it was not possible to distinguish between different treatment indications or the nature/origin of DUs. Second, the exclusion of the observations with missing values in PIs and presence of DUs might have resulted in a selection bias. However, the results in the sensitivity analysis hold together and selection bias was negligible because of the large size of the EUSTAR cohort.

Another important limitation is the definition of the outcome itself: in the EUSTAR database this was dichotomous and recorded in two consecutive visits, with a 12 months interval, which did not allow exploration of the real clinical course of DU occurrence and healing. Unfortunately, the EUSTAR dataset does not allow further tracking of individual DUs at various visits, and neither does it record if the total number of ulcers decreased or increased between visits, or how their severity varied. In general, patients with severe and chronic or recurrent DUs might be those who were more prone to be on prostacyclin analogues, PDE-5i or ERAs. However, shorter follow-up time intervals than 12 months are exceptional in the EUSTAR dataset. Nonetheless, being able to distinguish between absence and presence of DUs at the next follow-up visit is a valuable gain offered by the DU-VASC. Finally, the large amount of missing data in variables referring to other types of vascular diseases (such as atherosclerosis, peripheral arterial disease or diabetes) prevented us from using them as predictors. Despite the limitations, our study has several strengths. We used the largest possible dataset with observations from tertiary centres from Europe, Asia and America, thereby reducing the risk of overfitting or misleading results from too small sample sizes. Moreover, previous models (i.e. CSURI or CIP-DUS) were not derived and validated with the same methodological rigour as DU-VASC: sample size considerations, shrinkage, external validation into a large cohort, accuracy and calibration assessment or transparent reporting according to TRIPOD.

In conclusion, our study showed that the exposure to PIs is a relevant predictor for absence of DUs. However, the effect size of the use of PIs for the digital ulcers was not addressed in this study. In fact, in this study we modelled the risk of DU occurrence and not the size of effectiveness of PIs on DUs. Therefore, this model is meant to assist the clinician with decision-making. For the use of PIs for the management of DUs, treatment effectiveness of PIs would need to be addressed in prospective studies and randomized controlled trials.

Acknowledgements

EUSTAR collaborators: Dr Silvia Bellando Randone and Gemma Lepri (Section of Rheumatology, Department of Medicine, University of Florence, Florence, Italy), Dr Ulrich Walker (Department of Rheumatology, Unispital Basel, Basel, Switzerland), Prof. Florenzo Iannone (Rheumatology Unit-DiMIMP, School of Medicine, University of Bari, Bari, Italy), Dr Suzana Jordan (Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland), Prof. Radim Becvar (Institute of Rheumatology, 1st Medical School, Charles University, Praha, Czech Republic), Dr Ewa Gindzienska-Sieskiewicz and Dr Katarzyna Karaszewska (Department of Rheumatology and Internal Diseases, Medical University of Bialystok, Bialystok, Poland), Prof. Maurizio Cutolo (Research Laboratory and Division of Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy), Giovanna Cuomo (Dipartimento Medicina Clinica e Sperimentale 'F-Magrassi' II Policlinico U.O. Reumatologia, Napoli, Italy), Dr Elise Siegert (Department of Rheumatology, Charité University Hospital, Berlin, Germany), Dr Simona Rednic (Clinica Reumatologie, University of Medicine and Pharmacy 'Iuliu Hatieganu' Cluj, Cluj, Romania), Dr Jérome Avouac and Dr Carole Desbas (Rheumatology A dpt, Paris 5 University Cochin Hospital, Paris, France), Dr Roberto Caporali and Dr Lorenzo Cavagna (Unita' Operativa e Cattedra di Reumatologia, IRCCS Policlinico S Matteo, Pavia, Italy), Dr Patricia E. Carreira (Servicio de Reumatología, Hospital 12 de Octubre, Madrid, Spain), Dr Srdan Novak (Department of Rheumatology and Clinical Immunology, Internal medicine, Rijeka, Croatia), Prof. László Czirják (Department of Immunology and Rheumatology Faculty of Medicine, University of Pécs, Pecs, Hungary), Dr Michele Iudici (Rheumatology Unit, Geneva University Hospitals, Geneva, Switzerland), Prof. Eugene J. Kucharz (Department of Internal Medicine and Rheumatology, Medical University of Silesia, Katowice, Poland), Dr Elisabetta Zanatta (Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Padova, Padova, Italy), Dr Bernard Coleiro ('Stella Maris', Balzan, Malta), Prof. Gianluca Moroncini (Clinica Medica, Università Politecnica delle Marche & Azienda Ospedali Riuniti, Ancona, Italy), Prof. Dominique Farge Bancel (Department of Internal Medicine Hopital Saint-Louis, Paris, France), Prof. Paolo Airò (Spedali Civili di Brescia Servizio di Reumatologia Allergologia e Immunologia Clinica, Brescia, Italy), Dr Roger Hesselstrand (Department of Rheumatology, Lund University Hospital, Lund, Sweden), Asst Prof. Mislav Radic (Department of Internal Clinic, Clinical Hospital of Split, Split, Croatia), Prof. Alexandra Balbir-Gurman (B. Shine Rheumatology Unit, Rambam Health Care Campus, Rappaport Faculty of Medicine, Technion, Haifa, Israel), Prof. Nicolas Hunzelmann (Universitätshautklinik Köln, Köln, Germany), Dr Raffaele Pellerito (Ospedale Mauriziano, Centro di Reumatologia, Torino, Italy), Dr Alessandro Giollo (Università degli Studi di Verona, Dipartimento di Medicina Clinica e Sperimentale, Reumatologia-Medicina Interna B, Verona, Italy), Dr Jadranka Morovic-Vergles (Division of Clinical Immunology and Rheumatology,

Department of Internal Medicine, Dubrava University Hospital, Zagreb, Croatia), Prof. Christopher Denton (Centre for Rheumatology, Royal Free and University College London Medical School, London, UK), Prof. Nemanja Damjanov (Institute of Rheumatology Belgrade, Belgrade, Serbia), Dr Ann-Christian Pecher (University Hospital Tuebingen, Center for Interdisciplinary Rheumatology, Immunology and Autoinmmune Diseases [INDIRA], Tuebingen, Germany), Dr Vera Ortiz Santamaria (Rheumatology, Granollers General Hospital, Barcelona, Spain), Dr Stefan Heitmann (Department of Rheumatology, Marienhospital, Stuttgart, Germany), Dr Dorota Krasowska (Department of Dermatology, Venereology and Pediatric Dermatology, Medical University of Lublin, Lublin, Poland), Prof. Paul Hasler (Kantonsspital Aarau, Rheumaklinik und Institut für Physikalische Medizin und Rehabilitation, Aarau, Switzerland), Prof. Ivan Foeldvari (Hamburger Zentrum für Kinder- und Jugendrheumatologie Kompetenz-Zentrum für Uveiits und Sklerodermie im Kindes- und Jugendalter, Hambrug, Germany), Dr Maria João Salvador (Rheumatology Department, Hospitais da Universidade, Coimbra, Portugal), Dr Bojana Stamenkovic (Institute for prevention, treatment and re-habilitation rheumatic and cardiovascular disease Niska Banja, Niska Banja, Serbia), Dr Carlo Francesco Selmi (Division of Rheumatology and Clinical Immunology Humanitas Clinical and Research Center, Milano, Italy), Prof. Lidia P. Ananieva (VA Nasonova Institute of Rheumatology, Moscow, Russia), Dr Ariane Herrick (Hope/Hospital University of Manchester, Rheumatic Diseases Centre, Clinical Sciences, Salford, UK), Prof. Ulf Müller-Ladner (Lehrstuhl für Innere Medizin mit Schwerpunkt Rheumatologie der Justus-Liebig-Universität Giessen, Abteilung für Rheumatologie und Klinische Immunologie, Bad Nauheim, Germany), Raffaele De Palma (Clinica di Medicina Interna ad Orientamento Immunologico e Medicina, Genova, Italy), Dr Merete Engelhart (Department of Rheumatology, University Hospital of Gentofte, Hellerup, Denmark), Dr Gabriela Szücs (Third Department of Medicine, Rheumatology Division, University of Debrecen, Medical Center, Debrecen, Hungary), Dr Carlos de la Puente (Servicio de Reumatología, Hospital Ramon Y Cajal, Madrid, Spain), Dr Øyvind Midtvedt, Dr Torhild Garen and Dr Håvard Fretheim (Department of Rheumatology, Rikshospitalet University Hospital, Oslo, Switzerland) Prof. Eric Hachulla (Department of Internal Medicine Hôpital Claude Huriez, Lille, France), Dr Valeria Riccieri (Dipartimento di Medicina Interna e Specialità Mediche, 'Sapienza', Università di Roma, Rome, Italy), Dr Ruxandra Maria Ionescu (Department of Rheumatology—St Maria Hospital, Carol Davila University of Medicine and Pharmacy Bucharest, Bucharest, Romania), Dr Ana Maria Gheorghiu (Department of Internal Medicine and Rheumatology Clinic, Ion Cantacuzino Clinical Hospital, Bucharest, Romania), Prof. Cord Sunderkötter (Department of Dermatology, University of Münster, Münster, Germany), Prof. Jörg Distler (Department of Internal Medicine 3, Universitätsklinikum Erlangen, Erlangen, Germany), Dr Francesca Ingegnoli (Division of Rheumatology, Istituto Gaetano Pini, Department of Clinical Sciences & Community Health, Milano, Italy), Prof. Luc Mouthon (Department of Internal Medicine of Pr Loïc Guillevin, Hôpital Cochin, Paris, France), Dr Francesco Paolo Cantatore (U.O. Reumatologia-Università degli Studi di Foggia Ospedale 'Col. D'Avanzo', Foggia, Italy), Dr Susanne Ullman (Department of Dermatology D-40, University Hospital of Copenhagen, Copenhagen, Denmark), Dr Maria Rosa Pozzi (Dipartimento di Medicina, Ospedale San Gerardo, Monza, Italy), Dr Kilian Eyerich (Department of Dermatology and Allergy of the TU Munich, Munich, Germany), Prof. Piotr Wiland (Department of Rheumatology and Internal Diseases, Wroclaw University of Medicine, Wroclaw, Poland), Dr Marie Vanthuyne (Université Catholique de Louvain, Louvain, Belgium), Dr Juan Jose Alegre-Sancho (Hospital Universitario Dr Peset, Valencia, Spain), Dr Kristine Herrmann (Division of Rheumatology, Department of Medicine III, and Department of Dermatology, University Medical Center Carl Gustav Carus, Technical University of Dresden, Dresden, Germany), Dr Ellen De Langhe (University Hospital Leuven, Department of Rheumatology and Laboratory Tissue Homeostasis and Disease, Skeletal Biology and Engineering Research Center, KU Leuven, Belgium), Dr Marko Baresic and Dr Miroslav Mayer (Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, University of Zagreb, School of Medicine, University Hospital Center Zagreb, Zagreb, Croatia), Prof. Sule Yavuz (Deptartament of Rheumatology, University of Marmara, Istanbul, Turkey), Dr Brigitte Granel (Service de Médecine Interne Hôpital Nord de Marseille, Marseille, France), Dr Carolina de Souza Müller (Hospital de Clinicas da Universidade Federal do Parana, Curitiba, Parana, Brazil), Dr Svetlana Agachi (Department of Rheumatology, Republican Clinical Hospital, Chisinau, Republic of Moldova), Dr Simon Stebbings (Department of Medicine, School of Medicine, University of Otago, Dunedin, New Zealand), Dr D'Alessandro Mathieu and Dr Alessandra Vacca (I Chair of Rheumatology, University of Cagliari-Policlinico Universitario, Monserrato, Italy), Prof. Kamal Solanki (Waikato University Hospital, Hamilton, New Zealand), Dr Douglas Veale (Department of Rheumatology, Bone and Joint Unit, St Vincent's University Hospital, Dublin, Ireland), Dr Esthela Loyo and Dr Carmen Tineo (Reumatologia e Inmunologia Clinica Hospital Regional Universitario Jose Ma Cabral y Baez Clinica Corominas, Santiago, Dominican Republic), Dr Mengtao Li (Department of Rheumatology Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China), Prof. Edoardo Rosato (Sapienza Università di Roma, Dipartimento di Medicina Clinica, UOC di Medicina Interna e Nutrizione Clinica-Scleroderma Unit, Università La Sapienza, Policlinico Umberto I, Roma, Italy), Dr Fahrettin Oksel and Dr Figen Yargucu (Department of Internal Medicine, Faculty of

Medicine, Division of Rheumatology, Ege University, Izmir, Turkey), Dr Cristina-Mihaela Tanaseanu (Clinical Emergency Hospital St Pantelimon, Bucharest, Romania), Prof. Rosario Foti (A.O.U. Policlinico Vittorio Emanuele La U.O. Di Reumatologia A.O.U. Policlinico V.E. Catania, Centro di Riferimento Regionale Malattie Rare Reumatologiche, Catania, Italy), Prof. Codrina Ancuta (Division of Rheumatology and Rehabilitation, GR. T. Popa Center for Biomedical Research, European Center for Translational Research, 'Grigore T. Popa' University of Medicine and Pharmacy Rehabilitation Hospital, Iasi, Romania), Prof. Britta Maurer (Department of Rheumatology and Clinical Immunology/Allergology Inselspital, University of Bern, Bern, Switzerland), Dr Jacob van Laar (James Cook University Hospital Marton Road, Middlesbrough, UK), Prof. Marzena Olesinska (Department of Connective Tissue Disease, Institute of Rheumatology, Warsaw, Poland), Dr Cristiane Kayser (Universidade Federal de São Paulo—Disciplina de Reumatologia, São Paulo, Brasil), Dr Nihal Fathi (Assiut and Sohage University Hospital, Rheumatology Department Assiut University Hospital, Assiut, Egypt), Dr Paloma García de la Peña Lefebvre and Dr Jorge Juan Gonzalez Martin (Hospital Universitario Madrid Norte Sanchinarro, Madrid, Spain), Dr Jean Sibilia (University Hospital of Strasbourg, Department of Rheumatology, Hôpital de Hautepierre, Service de Rhumatologie, Strasbourg, France), Dr Ira Litinsky (Department of Rheumatology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel), Prof. Francesco Del Galdo (Scleroderma Programme, Institute of Molecular Medicine, Division of Musculoskeletal Diseases, University of Leeds, Leeds, UK), Dr Lesley Ann Saketkoo (Tulane University Lung Center, Tulane/University Medical Center Scleroderma and Sarcoidosis Patient Care and Research Center, New Orleans, USA), Dr Eduardo Kerzberg (Osteoarticular Diseases and Osteoporosis Centre Pharmacology and Clinical Pharmacological Research Centre School of medicine—University of Buenos Aires Rheumatology and Collagenopathies Department Ramos Mejía Hospital, Buenos Aires, Argentina), Dr Washington Bianch and Dr Breno Valdetaro Bianchi (Department of Rheumatology-Santa Casa da Misericórdia do Rio de Janeiro, Brasil), Dr Ivan Castellví (Hospital de la Santa Creu i Sant Pau, Barcelona, Spain), Dr Massimiliano Limonta (USSD Reumatologia, Ospedali Riuniti di Bergamo, Bergamo, Italy), Dr Doron Rimar (Rheumatology Unit Bnai Zion Medical Center, Haifa, Israel), Dr Maura Couto (Unidade de Reumatologia de Viseu, Centro Hospitalar Tondela-Viseu, Portugal), Dr François Spertini (Department of Rheumatology, Clinical Immunology and Allergy, Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland), Dr Antonella Marcoccia (Capillaroscopic Unit—Sandro Pertini Hospital, Roma, Italy), Dr Sarah Kahl (Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Innere Medizin/ Rheumatologie/Immunologie Rheumaklinik Bad Bramstedt, Bad Bramstedt, Germany), Dr Ivien M. Hsu (UMDNJ-Scleroderma Program Clinical Research Center, Robert Wood Johnson University Hospital, New Brunswick, USA), Dr Thierry Martin (Clinical Immunology Internal Medicine, National Referral Center for Systemic Autoimmune Diseases, Strasbourg, France), Dr Sergey Moiseevand and Dr Pavel Novikov (Clinic of Nephrology, Internal and Occupational Diseases, Moscow, Russia), Prof. Lorinda S. Chung (Department of Dermatology Stanford University School of Medicine, Stanford, USA), Dr Tim Schmeiser (Krankenhaus St Josef, Wuppertal-Elberfeld, Germany), Dr Dominik Majewski (Department of Rheumatology and Internal Medicine, Poznan University, Poznan, Poland), Prof. Zbigniew Zdrojewski (Department of Internal Medicine, Connective Tissue Diseases and Geriatrics, University Clinical Centre, Medical University of Gdansk, Gdansk, Poland), Dr Julia Martínez-Barrio (Department of Rheumatology, Gregorio Marañón Univeristy Hospital, Madrid, Spain), Dr Vera Bernardino (Unidade de Doencas Autoimunes—Hospital Curry Cabral, Centro Hospitalar Lisboa Central, Lisboa, Portugal), Prof. Gabriela Riemekasten (Universitätsklinik Lübeck, Lübeck, Germany), Prof. Yair Levy (Meir Medical Center, Kfar-Saba, Israel), Dr Elena Rezus (Division of Rheumatology & Rehabilitation, University of Medicine and Pharmacy 'Grigore T. Popa' Iasi, Rehabilitation Hospital, Iasi, Romania), Dr Omer Nuri Pamuk (Trakya University Medical Faculty, Department of Internal Medicine, Division of Rheumatology, Edirne, Turkey), Prof. Piercarlo Sarzi Puttini (University Hospital Luigi Sacco, Milan, Italy), Prof. Hadi Poormoghim (Scleroderma Study Group, Department of Rheumatology, Firoozgar Hospital, Tehran, Iran), Prof. Ina Kötter (Asklepios Clinic Altona, Medical Department 4, Rheumatology, Immunology, Nephrology, Hamburg, Germany), Dr Giovanna Cuomo (UOC Medicina Interna, Università della Campania, Napoli, Italy), Dr Francis Gaches (Médecine Interne, Centre de Compétence Maladies Lysosomales, Hôpital Joseph Ducuing, Toulouse, France), Dr Laura Belloli (S.C. Reumatologia, A.O. Ospedale Niguarda Cà Granda, Milano, Italy), Prof. Petros Sfikakis (Rheumatology Unit, First Propaedeutic and Internal Medicine, Athens University Medical School, Goudi, Athens), Prof. Daniel Furst (Arthritis Association of Southern California, Los Angeles, CA, USA), Dr Ana-Maria Ramazan (Rheumatology Department, Spitalul Clinic Judetean de Urgenta, 'Sf Apostol Andrei', Constanta, Romania), Dr H. U. Scherer and Dr Tom W. J. Huizinga (Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands), Dr Marie-Elise Truchetet (Rheumatology Department, CHU de Bordeaux, Bordeaux, France), Dr Alain Lescoat (Service de Médecine Interne Hôpital Sud, Rennes, France), Dr Giacomo De Luca and Dr Corrado Campochiaro (Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR) San Raffaele Hospital—Vita-Salute San Raffaele University, Milan, Italy), Dr J. M. van Laar (University Medical Center Utrecht, Utrecht, The Netherlands), Dr Lidia Rudnicka (Department of Dermatology, Medical University of Warsaw, Warsaw, Poland), Dr Susana Oliveira (Systemic

Immunomediated Diseases Unit, Department of Medicine IV, Fernando Fonseca Hospital, Amadora, Portugal), Dr Fabiola Atzeni (Rheumatology Unit, University of Messina, Messina, Italy), Prof. Masataka Kuwana (Nippon Medical School Hospital Sendagi, Tokyo, Japan), Dr Arsene Mekinian (Internal Medicine Saint Antoine, Paris, France), Cédric Landron, Mathieu Puyade and Pascal Roblot (Department of Internal Medicine, Poitiers University Hospital, Poitiers, France), Dr Satoshi Kubo and Dr Yasuyuki Todoroki (University of Occupational and Environmental Health, Kitakyushu, Japan).

Funding: 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.

Disclosure statement: C.M. reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events (MEDtalks Switzerland and Mepha); support for attending meetings and/or travel (Roche and Boehringer Ingelheim); and participation on a Data Safety Monitoring Board or Advisory Board (Boehringer Ingelheim, Janssen). R.D. reports grants from Articulum Fellowship, sponsored by Pfizer (2013–2014), grants from Actelion, personal fees from Actelion and Boehringer-Ingelheim, outside the submitted work. C.B. has received grants or contracts (Gruppo Italiano Lotta alla Sclerodermia, European Scleroderma Trials and Research Group, Scleroderma Clinical Trials Consortium, AbbVie); and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events (Eli-Lilly, Actelion, Boehringer-Ingelheim). J.H. has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events (Boehringer-Ingelheim, BMS, GSK, Roche/Chugai, ABBVIE, Pfizer, Novartis, Janssen-Cilag, UCB); support for attending meetings and/or travel (Boehringer-Ingelhelm, UCB); and participation on a Data Safety Monitoring Board or Advisory Board (Boehringer-Ingelhelm, Janssen-Cilag). J.deV.-B. reports research grants from Roche, Galapagos and Janssen; consulting fees from Janssen and Boehringer Ingelheim; payment for presentations and educational events by Boehringer Ingelheim and Janssen; advisory board Abbvie; chair of national working group on systemic sclerosis. V.S. has received grant/research support from the Research Foundation Flanders (FWO), the Belgian Fund for Scientific Research in Rheumatic Diseases (FWRO), Boehringer-Ingelheim Pharma GmbH&Co and Janssen-Cilag NV; consulting fees were provided by Boehringer-Ingelheim GmbH&Co and Janssen-Cilag NV; speaker fees were provided by UCB Biopharma Sprl, Boehringer-Ingelheim GmbH&Co, Janssen-Cilag NV and Accord Healthcare; support for attending meetings and/or travel from Celgene and Boehringer-Ingelheim; board, society, committee or advocacy group, paid or unpaid at EULAR Study group on Microcirculation in Rheumatic Diseases, ACR Study Group on Microcirculation, SCTC working group on capillaroscopy, ERN-ReCONNET. Y.A. reports grants or contracts from Boehringer Ingelheim, Amiculum, MediTech Media, Alpine Immunosciences, OSE Immunotherapeutics, MedsenicBoehringer; consulting fees (Boehringer, Bayer, Astra-Zeneca, Prometheus, Sanofi, Genentech/Roche); payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events (Boehringer, Abbvie); participation on a Data Safety Monitoring Board or Advisory Board (Boehringer, Bayer, Astra-Zeneca, Prometheus, Sanofi, Genentech/Roche). B.A. is President of Croatian Society for Rheumatology. O.K.-B. reports Grants or contracts from CSL Behringhas, consulting fees and/or congress support from Boehringer Ingelheim Health Care system Navigator; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Boehringer Ingelheim, Gilead, Janssen-Cilag, Medac, MSD, Novartis, Pfizer, Sandoz; support for attending meetings and/or travel (Abbvie, Boehringer Ingelheim, Medac, Roche); participation on a Data Safety Monitoring Board or Advisory Board (Boehringer Ingelheim, CSL Behring, MSD, Novartis); leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid (Regional consultant in rheumatology in Podlasie district, Member of the Polish Coordinating Committee for biological treatments in rheumatic diseases, Chairman of the Regional, Bialystok Branch of the Polish Society of Rheumatology, Chairman of the Ethics Committee at the Medical University in Balystok, Member of the EULAR task force for the update of EULAR treatment recommendations in systemic sclerosis). Y.T. reports grants or contracts from Asahi-Kasei, Abbvie, Chugai, Mitsubishi-Tanabe, Eisai, Takeda, Corrona, Daiichi-Sankyo, Kowa, Behringer-Ingelheim; consulting fees from Eli Lilly, Daiichi-Sankyo, Taisho, Ayumi, Sanofi, GSK, Abbvie; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events (Gilead, Abbvie, Behringer-Ingelheim, Eli Lilly, Mitsubishi-Tanabe, Chugai, Amgen, YL Biologics, Eisai, Astellas, Bristol-Myers, Astra-Zeneca). A.M.H.-V. reports grants or contracts from Boehringer Ingelheim; Consulting fees from Actelion, Boehringer Ingelheim, Jansen, Roche, Merck Sharp & Dohme, ARXX Therapeutics, Lilly and Medscape; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Actelion, Boehringer Ingelheim, Jansen, Roche, Merck Sharp & Dohme, ARXX Therapeutics, Lilly and Medscape; support for attending meetings and/or travel from Actelion, Jansen, BI, Roche; and leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid (EUSTAR, EULAR, ACR, ERS). O.D. reports grants or contracts from Kymera and Mitsubishi Tanabe; consulting fees from Abbvie, Acceleron, Alcimed, Amgen, AnaMar, Arxx, AstraZeneca, Baecon, Blade, Bayer, Boehringer Ingelheim, ChemomAb, Corbus, CSL Behring, Galapagos, Glenmark, GSK, Horizon, Inventiva, iQvia, Kymera, Lupin, Medac, Medscape, Miltenyi Biotec, Mitsubishi Tanabe, MSD, Prometheus Biosences, Roche, Roivant, Topadur and UBC; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Bayer, Boehringer Ingelheim, Medscape, Novartis,

Roche, Pfizer, Roche und Sanofi; Issued patent ('mir-29 for the treatment of systemic sclerosis'); and leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: ERS/EULAR Guidelines, EUSTAR, Pfizer, SCQM (Swiss Clinical Quality Management in Rheumatic Diseases), SAMW, Hartmann Müller Foundation. M.O.B. has received personal fees from Amgen and Bayer, outside the submitted work. The other authors have declared no conflicts of interest.

Data availability statement

Data are available on reasonable request. On request, and subject to review by the EUSTAR committee, access can be granted to the anonymized raw data and the R code. Deidentified data will be made available via secure data transfer. Data requests may be sent to the corresponding author. Email: mikeoliver.becker@usz.ch.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Walker UA, Tyndall A, Czirják L *et al.* Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis 2007;66:754–63.

2 Kowal-Bielecka O, Fransen J, Avouac J *et al.*; EUSTAR Coauthors. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 2017;76:1327–39.

3 Friedrich S, Lüders S, Klotsche J *et al.* The first composite score predicting Digital Ulcers in systemic sclerosis patients using Clinical data, Imaging and Patient history—CIP-DUS. Arthritis Res Ther 2020;22:144.

4 Sebastiani M, Manfredi A, Lo Monaco A *et al.* Capillaroscopic Skin Ulcers Risk Index (CSURI) calculated with different videocapillaroscopy devices: how its predictive values change. Clin Exp Rheumatol 2013;31:115–7.

5 van den Hoogen F, Khanna D, Fransen J *et al.* 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2013;72:1747–55.

6 Silva I, Almeida J, Vasconcelos C. A PRISMA-driven systematic review for predictive risk factors of digital ulcers in systemic sclerosis patients. Autoimmun Rev 2015;14:140–52.

7 Tiev KP, Diot E, Clerson P *et al.* Clinical features of scleroderma patients with or without prior or current ischemic digital ulcers: post-hoc analysis of a nationwide multicenter cohort (ItinérAIR-Sclérodermie). J Rheumatol 2009;36:1470–6.

8 Hachulla E, Clerson P, Launay D *et al.* Natural history of ischemic digital ulcers in systemic sclerosis: single-center retrospective longitudinal study. J Rheumatol 2007;34:2423–30.

9 Caramaschi P, Martinelli N, Volpe A *et al.* A score of risk factors associated with ischemic digital ulcers in patients affected by systemic sclerosis treated with iloprost. Clin Rheumatol 2009;28:807–13.

10 Riley RD, Ensor J, Snell KIE *et al.* Calculating the sample size required for developing a clinical prediction model. BMJ 2020;368:m441.

11 Riley RD, Debray TPA, Collins GS *et al.* Minimum sample size for external validation of a clinical prediction model with a binary outcome. Stat Med 2021;40:4230–51.

12 Royston P, Moons KGM, Altman DG, Vergouwe Y. Prognosis and prognostic research: developing a prognostic model. BMJ 2009;338:b604.

13 Altman DG, Vergouwe Y, Royston P, Moons KGM. Prognosis and prognostic research: validating a prognostic model. BMJ 2009;338:b605.

14 Steyerberg EW, Pencina MJ, Lingsma HF *et al.* Assessing the incremental value of diagnostic and prognostic markers: a review and illustration. Eur J Clin Invest 2012;42:216–28.

15 Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med 2015;162:55–63.

16 Wigley FM, Wise RA, Seibold JR *et al.* Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. Ann Intern Med 1994;120:199–206.

17 Hachulla E, Hatron PY, Carpentier P *et al.*; SEDUCE study group. Efficacy of sildenafil on ischaemic digital ulcer healing in systemic sclerosis: the placebo-controlled SEDUCE study. Ann Rheum Dis 2016;75:1009–15.

18 Korn JH, Mayes M, Matucci Cerinic M *et al.* Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. Arthritis Rheum 2004;50:3985–93.

19 Matucci-Cerinic M, Denton CP, Furst DE, Mayes MD *et al.* Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. Ann Rheum Dis 2011;70:32–8.

20 Khanna D, Denton CP, Merkel PA *et al.*; DUAL-2 Investigators. Effect of macitentan on the development of new ischemic digital ulcers in patients with systemic sclerosis: DUAL-1 and DUAL-2 randomized clinical trials. JAMA 2016;315:1975–88.