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Concise report

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

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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: 77.9%, 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

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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 administered 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 ≥ 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 (± 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 17212 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-ScI-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)

^aDefinitions 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.

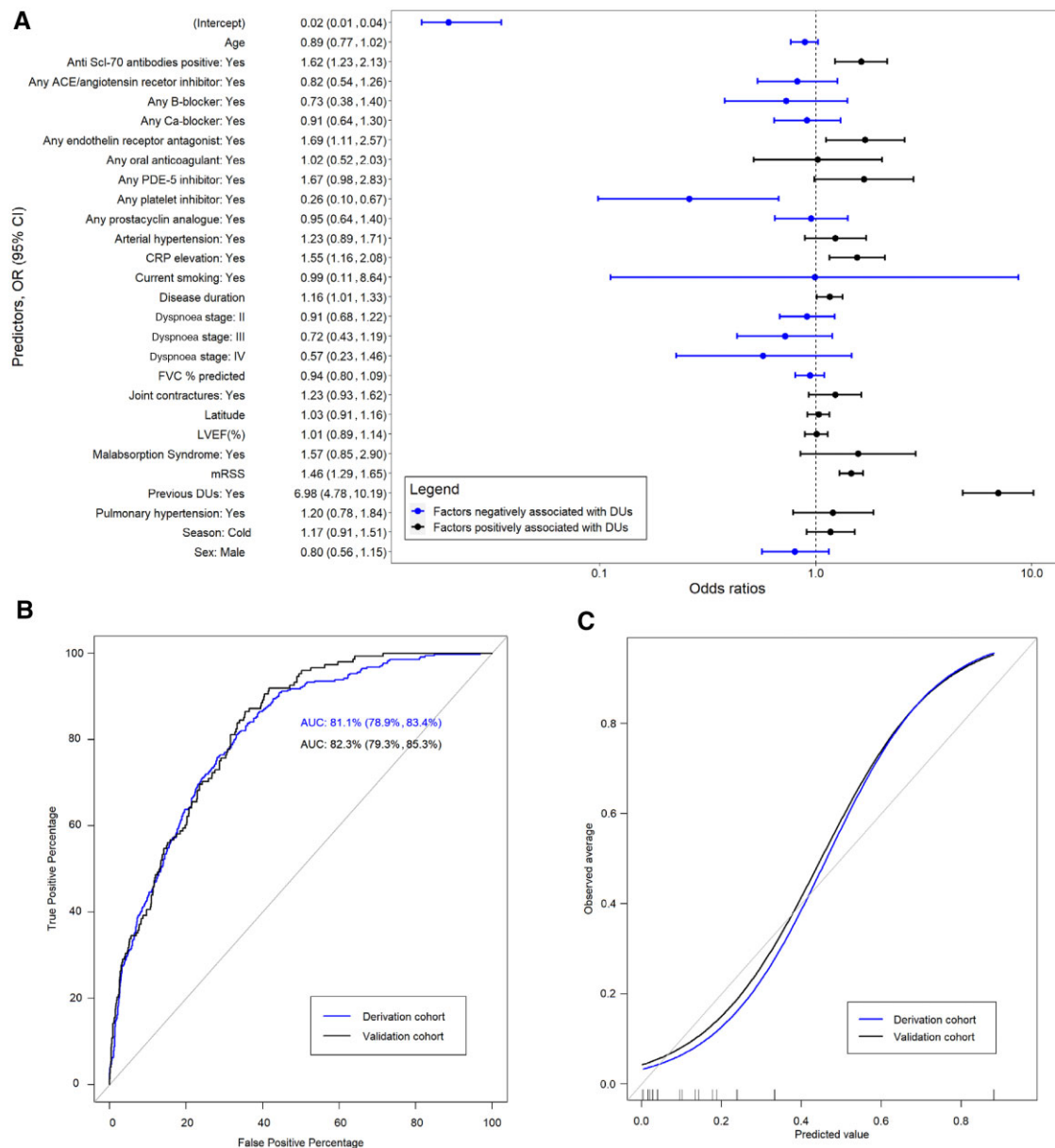
Incremental value of the PIs as predictor

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.

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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: mikeliver.becker@usz.ch.

Supplementary data

[Supplementary data](#) are available at *Rheumatology* online.

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