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The association between echogenicity and progression of Dupuytren's disease (DD): Birth of an imaging biomarker?☆

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Summary *Background:* The shift of focus towards disease-controlling treatments to prevent DD progression at an early stage underlines the need for objective and reliable measurements that can monitor and predict the course of disease. Ultrasound has been studied as a potential tool for this purpose. This study examined to what extent echogenicity of early DD nodules predicts clinical progression.
Methods: Sonographic assessments of Dupuytren's nodules were performed by the same observer on 151 participants as part of an ongoing prospective cohort study on the course of DD. Echogenicity was assessed by determining the greyness of a nodule relative to the surrounding

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tissue, using ImageJ software. Progression of disease was defined as 1) an increase in total passive extension deficit (TPED) of ≥15 degrees and 2) surgical intervention of the examined ray, both occurring after the sonographic assessment. The associations between echogenicity and time to progression were estimated using Cox-regression models.

Results: The association between echogenicity and time to TPED progression showed that for every additional decrease of 1% in relative greyness (darker image) of a nodule, the risk of TPED progression during follow-up increases by 3.4% (hazard ratio [HR] = 0.966, 95% confidence interval [CI]: 0.935-0.966). Similarly, echogenicity was also associated with time to surgical intervention (HR = 0.967, 95% CI: 0.938-0.997), which indicates a higher risk for surgery during follow-up for darker nodules.

Conclusions: These results suggest that echogenicity is predictive of the prognosis of the early stages of DD and might potentially be used as a prognostic imaging biomarker in the future.

The mainstay of Dupuytren's disease (DD) treatment is surgical excision of the diseased tissue.[1,2] However, surgical intervention often does not provide durable results. When repetitive treatment is necessary, surgery may lead to functional impediment and sometimes loss of sensibility or even amputation.[3] Therefore, the focus of DD research and management is shifting towards the prevention of contracture [3,4]. However, to identify patients being at risk for progression, knowledge about the prognosis of DD is essential.

Classically, the pathology of DD is subdivided into three progressive phases: proliferative, involutional, and residual.[5] During the first two phases, Dupuytren's tissue mainly contains myofibroblasts, which produce the abundant extracellular matrix. During the residual phase, cords are formed, consisting largely of acellular and fibrous structures.[6] A higher risk of disease recurrence after surgery has been ascribed to patients in whom DD tissue was excised in the proliferative phase.[6-8]

Dupuytren's diathesis characteristics are also thought to relate to a more aggressive disease course after surgery. These consist of early onset of disease (< 50 years), bilateral involvement, a positive family history, knuckle pads, and male sex.[9,10]

When describing the course of DD, the terms 'progression, 'recurrence' and 'extension' are commonly used. Progression is tissue growth prior to surgery, recurrence is the appearance of new DD tissue in a previously cleared area or the recurrence of contractures after their release, and extension is the appearance of DD tissue outside the operated area where previously no disease was detected.[7,11-13] Clinical studies often do not specifically distinguish between progression or extension, but in general, most studies report on recurrence since they report on previously operated patients.[14] The prognosis of early disease related to progression has hardly been studied and it asks for outcome measures that can predict clinical progression before surgery is needed.

For this purpose, ultrasound may be used, which enables measurement of nodules size and echogenicity.[15,16] Ultrasonography uses soundwaves that pass through and reflect body tissue, creating an image. The matter of reflection depends on resistance to the dispersion of soundwaves and varies according to the density of the tissue.[17] DD tissue is hypoechogenic (dark) at ultrasound examination during the proliferative and involutional phases, because of the high density of myofibroblasts.[18] Under the assumption that a higher myofibroblast load is associated with a higher chance of progression, echogenicity may be used as a prognostic imaging biomarker that can predict the course of disease.[19]

In this study, we aimed to examine to what extent echogenicity of nodules predicts progression of total passive extension deficit (TPED) during a 5-years follow-up study. Secondarily, we studied to what extent ultrasound can predict clinical progression of DD in terms of surgery and the additional predictive value of echogenicity on TPED progression in addition to the Dupuytren's diathesis characteristics.

Methods

Study design, setting, and sample

We used ultrasound data, patient characteristics and diathesis characteristics, physical examination measurements, and data on surgical treatment from an ongoing prospective cohort on the course of DD.[20] Participants with an ultrasound measurement in the study between 2016 and 2021 were included in this analysis.

Participants

Participants were originally recruited from two sources: 1) a prevalence study among a random age-stratified sample of the general population of a city in the northern region of the Netherlands,[21] and 2) DD patients who consulted the outpatient clinic of the Department of Plastic Surgery of an academic medical centre in the northern region of the Netherlands between 2012 and 2014. DD was diagnosed when a palpable palmar or digital nodule or cord, skin tethering, or pitting was present, either with or without digital contractures. The diagnosis was set by physical examination by 1) a clinically qualified researcher, trained

in the physical examination of DD, or 2) a medical doctor from the Plastic Surgery department of the institution.

Because DD nodules form along the longitudinal lines of the palmar fascia into cords that produce the contracture deformities[9], tissue growth often occurs in the same ray. Participants included in the current analysis had DD nodules without extension deficits in the visualised ray. One nodule of a hand was chosen per participant for ultrasound visualisation. We selected nodules that were either isolated or easy to distinguish from a cord by means of physical examination.

Participants with nodules that gave unclear ultrasound visuals (no visible anatomical landmarks or no visible nodules), were excluded (n = 37). Participants who had a surgical intervention such as percutaneous needle fasciotomy, limited fasciectomy, or collagenase injection of the investigated ray prior to ultrasound imaging, were also excluded (n = 4).

For the primary analysis of the time between ultrasound examination and progression of the TPED, participants with nodules in the thumb (n = 8) or in a webspace (n = 6) were excluded. We excluded nodules in the thumb, because contractures of the thumb's interphalangeal joint are relatively rare. Nodules in a webspace were excluded, because these cords often lead to adduction deficits instead of metacarpophalangeal and/or interphalangeal joint contractures, which we did not measure.

Participants with no follow-up of TPED measurements were also excluded for the primary analysis (n = 12). All participants gave written informed consent.

Outcomes

The primary outcome for clinical progression was the progression of the TPED of the visualised ray and time to TPED progression. The three secondary outcomes were time between ultrasound examination and:

1) surgical treatment (yes/no) of the visualised ray,
2) surgical treatment of the ray examined by ultrasound and/or of an adjacent ray,
3) surgical treatment of the investigated hand.

The passive extension deficit of all three finger joints per ray was assessed using a finger goniometer at baseline and at follow-up twice (until 2018) or once (2018 and onwards) per year, by one of two trained researchers. Censoring occurred after the last follow-up appointment in 2021. The extension deficits were summed to obtain TPED per ray.[22] If surgical intervention occurred, the last known preoperative TPED measurement was retrieved from the medical files. Progression of TPED (yes/no) was defined as an increase between baseline and follow-up, larger than the measurement error of 15 degrees.[23] Whether and when a patient had been surgically treated during follow-up was assessed using case record forms, including files on surgical treatments from other hospitals and electronic patient files. Participants who did not undergo surgery were censored at the end of the follow-up.

Echogenicity

For ultrasound, the Esaote MyLab one device (Genova, Italy) was used, with an 18 MHz probe and the following settings: depth 2 cm, focus 0.5 cm, X-view 1, greymap 2, ambient light 3, dynamic range 8, colourise blue line 3, sharpness 4, persistence 4.

The ultrasound examination was done at baseline by one trained researcher to avoid inter-individual differences.[15,20] A previous study reported good intra-observer reliability for the circumference and area measurement of a nodule in the transversal and sagittal plane.[15] Our measurements included a transverse and sagittal image of the selected nodule. To assess echogenicity, the grey-value of the nodule was determined for each image using ImageJ software. [24]. First, we encircled the nodule by drawing a line on the outer border of the nodule. The grey-value of a nodule was then defined as the grey-value mode (most frequent value). Because of inter-individual differences in the overall echogenicity of the images, we divided the grey-value mode of the nodule by the grey-value mode of the subcutaneous tissue of that same image, using it as a reference (Figure 1).

Each reference frame was identical in size and placed on subcutaneous tissue next to the nodule. After defining the proportional grey-value mode of both the transverse and the sagittal image, the mean of both grey-value mode proportions was calculated and multiplied by 100 for better interpretability. We define this as the 'mean grey-value' (Figure 2).

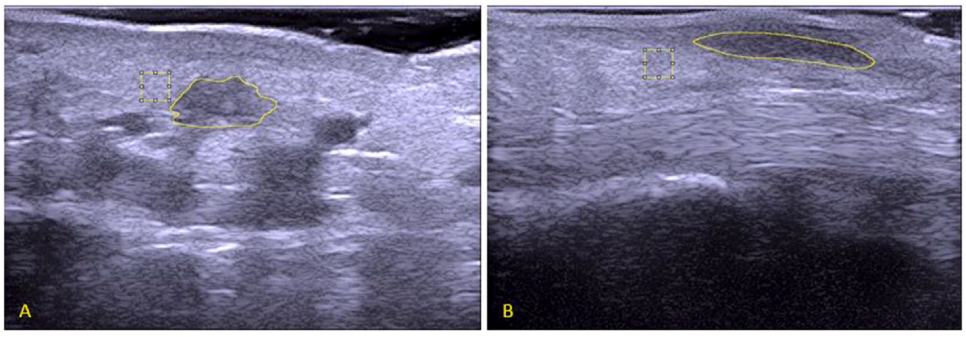

Figure 1 Ultrasound images on which the outer border of a nodule is indicated, as well as the reference frame (square). A) Transversal plane and B) sagittal plane.

$$mean\ grey-value = \left(\frac{\left(\frac{grey-value\ image\ sagittal}{grey-value\ reference\ sagittal}\right) + \left(\frac{grey-value\ image\ transverse}{grey-value\ reference\ transverse}\right)}{2} \right) * 100$$

Figure 2 Definition of mean grey-value.

Patient characteristics

Patient characteristics and other prognostic factors were assessed by history and physical examination at baseline. These included age of onset (< 50 years yes/no), sex (male/female), family history of DD (yes/no), bilateral disease (yes/no), and knuckle pads (yes/no).

Statistical analyses

Descriptive statistics of the baseline assessments were presented by number, percentages, mean and standard deviation (SD), or median and interquartile range (IQR). The variability in mean grey-values for TPED progression and surgical treatment of the visualised ray was shown in boxplots with individual data points.

To determine the association between the echogenicity of a DD nodule and the time to TPED progression, we used a Cox-regression model, with time to TPED progression as dependent variable and the mean greyness as independent variable. Prior to analysis, we visually inspected the Kaplan-Meier curve to check the proportional hazard assumption, which showed no evidence of violation of the assumption for any of the analyses. We also checked the analyses for linearity by assessing the regression coefficient trend for quartiles of echogenicity.

To evaluate the influence of outliers, we also performed a sensitivity analysis excluding outliers in mean grey-value with a value below 30%. We used a cut-off of 1.5*IQR to define outliers.

To analyse the association between echogenicity with the time to surgical treatment we also used a Cox-regression model, with a similar methodology as described above. Results are presented as hazard ratios (HR) and 95% confidence intervals (CI).

To assess the predictive value of echogenicity in addition to diathesis factors[10] we aimed to add age of onset < 50, male sex, knuckle pads, family history and bilateral disease as variables in the models described above.

Statistical analyses were calculated using SPSS software package 23VA (SPSS Inc., Chicago, IL).

Results

A total of 125 participants were included for the TPED progression analysis and 151 participants were included in the surgical intervention analysis (Figure 3).

Baseline characteristics

The characteristics of the participants are shown in Table 1. The mean age was 67.8 years (SD: 10.6) and 108 participants were male (71.5%). For 11 participants (7.3%) all 5 diathesis factors were present.

The mean grey-value had a median of 70% (IQR 64-78). Participants with TPED progression of the visualised ray during follow-up had a mean grey-value median of 66% (IQR 59-73) and participants without TPED progression of the visualised ray had a median of 72% (IQR 65-79). The mean grey-value medians were 64% (IQR 55-69) and 71% (IQR 65-79) for participants with and without surgical intervention of the visualised ray, respectively. Figures 4 and 5 not only show the difference in median between these groups, but also that the dispersion is greater in those without TPED progression or who did not undergo surgery than in those with TPED progression or who did undergo surgery.

The association between echogenicity and time to TPED progression

Median follow-up time was 36.8 months, (IQR 26.5-60.9). During follow-up, 14 participants developed an extension deficit of more than 15 degrees. The median time to TPED progression was 37.3 months (IQR 31.2-61.1).

Our results indicate that for every increase of 1% in the mean grey-value (more hyper-echogenic) of a nodule, the risk of an increased extension deficit of the assessed ray at every time point during follow-up decreases by 3.4% (HR = 0.97; 95% CI: 0.94-1.00, Table 2). So the risk of TPED progression increases when the nodule is more hypoechogenic. The results of the sensitivity analysis (outliers excluded) were similar (Table 2).

The association between echogenicity and time to surgical intervention

The median follow-up time was 35.1 months (IQR 32.4-59.1). During follow-up, 24 participants underwent surgical intervention on the assessed hand of which 11 participants had surgery on the assessed ray and 7 participants had surgery on the neighbouring ray.

The median time to surgery was 17.4 months (IQR 11.8-38.6).

Our results show that for every additional increase of 1% in the mean grey-value of a nodule, the risk of surgery of the assessed ray at every time point during follow-up decreases by 3.3% (HR = 0.97) (95% CI: 0.938 and 0.997, see Table 2). The relation between the mean grey-value and time to surgery was attenuated when the operated area was defined less specifically (e.g. event same hand). After exclusion of outliers, these results were similar.

The additional predictive value of echogenicity for TPED progression over other potential prognostic factors

Due to the small number of participants with TPED progression, we were not able to conduct the planned analysis.

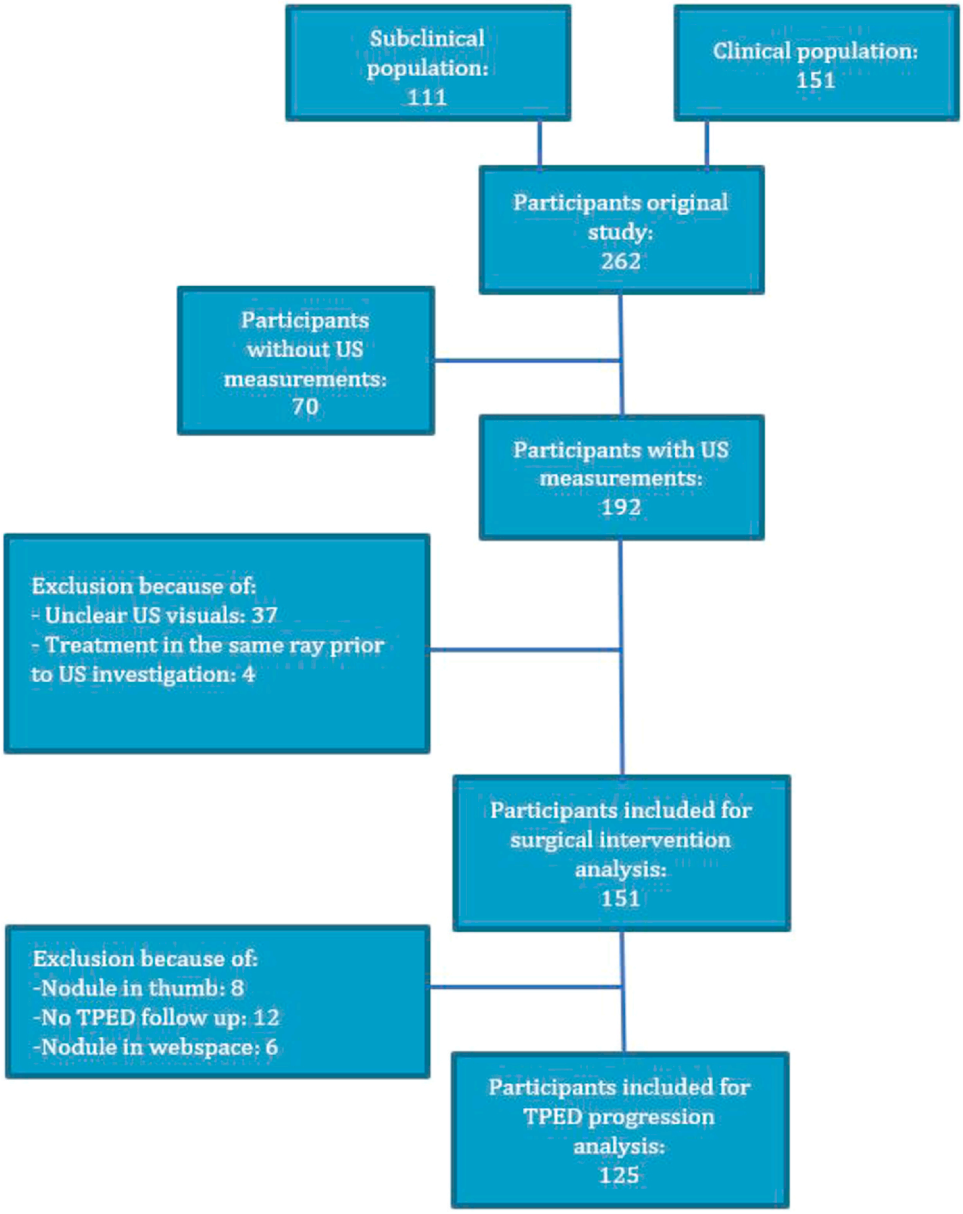

Figure 3 Flowchart of participants.

Discussion

The aim of this study was to evaluate the association between echogenicity and progression of early DD in 151 participants with a median follow-up time of 3 years. Although there was an overlap in mean grey-values between participants with and without TPED progression and those who did and did not undergo surgery, our results suggest that hypoechogenicity is associated with an increased risk of earlier TPED progression and surgical intervention. This adds to the finding that echogenicity is associated with the histological phase[18] and is further substantiated by the observation that the association between echogenicity and time to surgery was weaker when the outcome was less specifically defined.

Many histological studies have determined the relationship between tissue cellularity and the prognosis [5,12,25,26] and it has been reported that the removed DD tissue in the proliferative phase has a higher recurrence rate compared to that when removed in the residual phase.[7,8] Our results suggest that hypoechogenicity is also related to progression, meaning that echogenicity might be a potentially useful indicator of prognosis in general in the future.

Results of a previous study using partly the same data showed that echogenicity was not related to nodule growth in terms of surface area during a follow-up of one year.[20] This was probably caused by the relatively short follow-up. In addition, nodules that were surgically excised during follow-up could not be included in the analysis. This might have caused an underestimation of the predictive value of echogenicity in this earlier study.

Our study population consisted of participants with nodules without contractures and prior surgery. We found that 16% of the study population had surgery within a median

Table 1 Patient characteristics.

	No surgery (n = 127, %)	Surgery (n = 24, %)
Diathesis characteristics:		
Male sex (*n* = 108, 71.5%)	91 (71.7)	17 (70.8)
Age of onset < 50 years (mean 67.8 SD 10.6))	29 (22.8)	11 (45.8)
Bilateral disease (*n* = 142, 94%))	127 (93.7)	23 (95.8)
Knuckle pads (*n* = 75, 49.7%)	58 (45.7)	17 (70.8)
Positive family history (*n* = 72, 47.7%)	57 (44.9)	15 (62.5)
Right hand evaluated hand (*n* = 76, 50.3%)	67 (52.8)	9 (37.5)
Ray:		
Thumb	5 (3.9)	1 (4.2)
1st webspace	1 (0.8)	1 (4.2)
Index	7 (5.5)	2 (4.4)
2nd webspace	2 (1.6)	0
Middle finger	42 (33)	10 (41.6)
3rd webspace	2 (1.6)	0
Ring finger	45 (35.4)	4 (16.7)
4th webspace	2 (1.6)	1 (4.2)
Little finger	24 (18.3)	5 (21.9)

follow-up time of 2.9 years. The progression of disease in a population with early-stage DD, without prior surgery, has not been studied often. One population-based cohort study on the prevalence of surgical intervention in early-stage DD reported that 35% underwent primary surgery during 18 years of follow-up.[27] Note, however, that these authors evaluated the progression per participant whereas we evaluated progression per hand. Notwithstanding, results from both studies provide first insights into the short and long-term progression in patients with early-stage DD.

We defined our main outcome as the time from ultrasound examination to TPED progression. However, contractures occur relatively late in the disease course, whereas our study population consists of participants without contractures in the included ray at baseline. TPED has a maximum standard error of measurement of 15 degrees for inter- and intra-observer agreement, meaning that changes in TPED can only be measured reliably if a difference of ≥15 degrees occurs.[22] Therefore, all changes < 15 degrees were not defined as progression. This may have caused an underestimation of the relation between echogenicity and time to TPED progression.

The use of TPED as outcome measure could be discussed. It is possible that a PIP-joint contracture occurs, separated from the nodule. However, even if this occurred, there is no reason to assume it occurred more often with hyper-echogenic nodules compared to hypo-echogenic nodules. Therefore, we think there is no reason to assume this would have biased our results in a specific direction.

Our secondary outcome was time to surgical intervention (or censoring). The timing of surgical intervention, may not be solely related to progression of disease but also to the impact DD has on daily functioning of the patient; a patient that experiences many functional problems, will probably choose surgery sooner than a patient with comparable symptoms but less impact on daily functioning. This may cause an underestimation of the relation between echogenicity and objective progression of disease, but in our view captures an important aspect of progression, not captured by TPED progression, in terms of experienced functional limitations.

A strength of our study is that we analysed a well-documented cohort of 151 patients who were structurally followed for a period of up to 5 years. We included a population in an early stage of DD. Most studies on prognosis

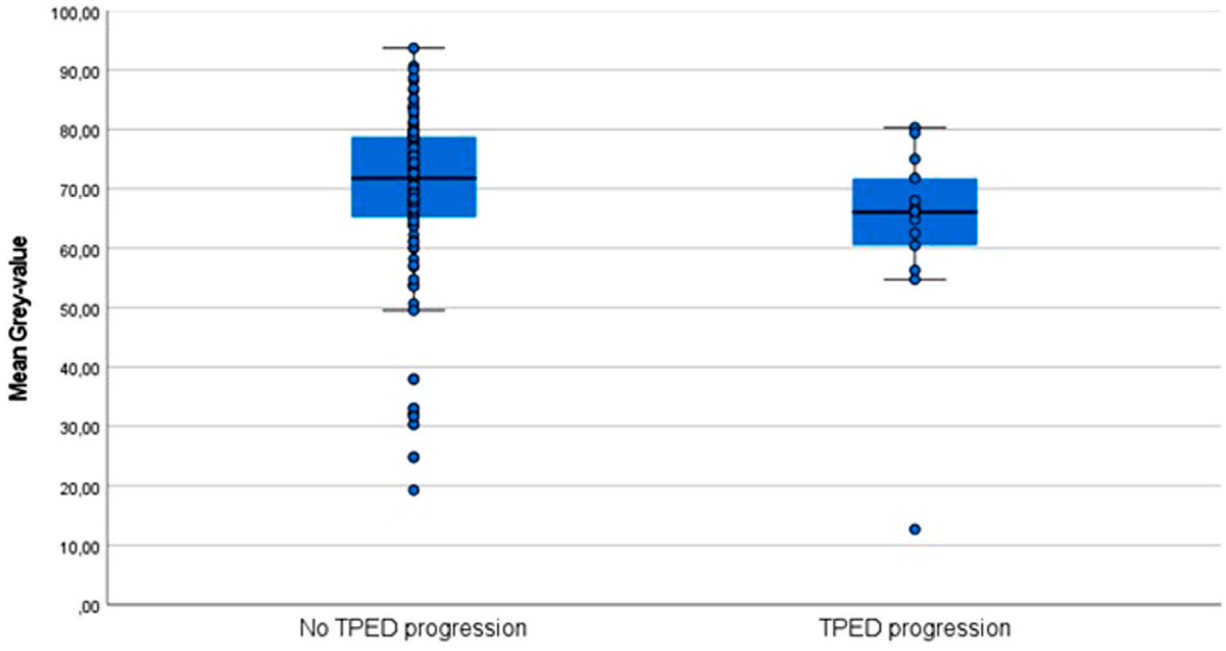

Figure 4 Boxplot of mean grey-value by TPED progression (yes/no) of the visualised ray.

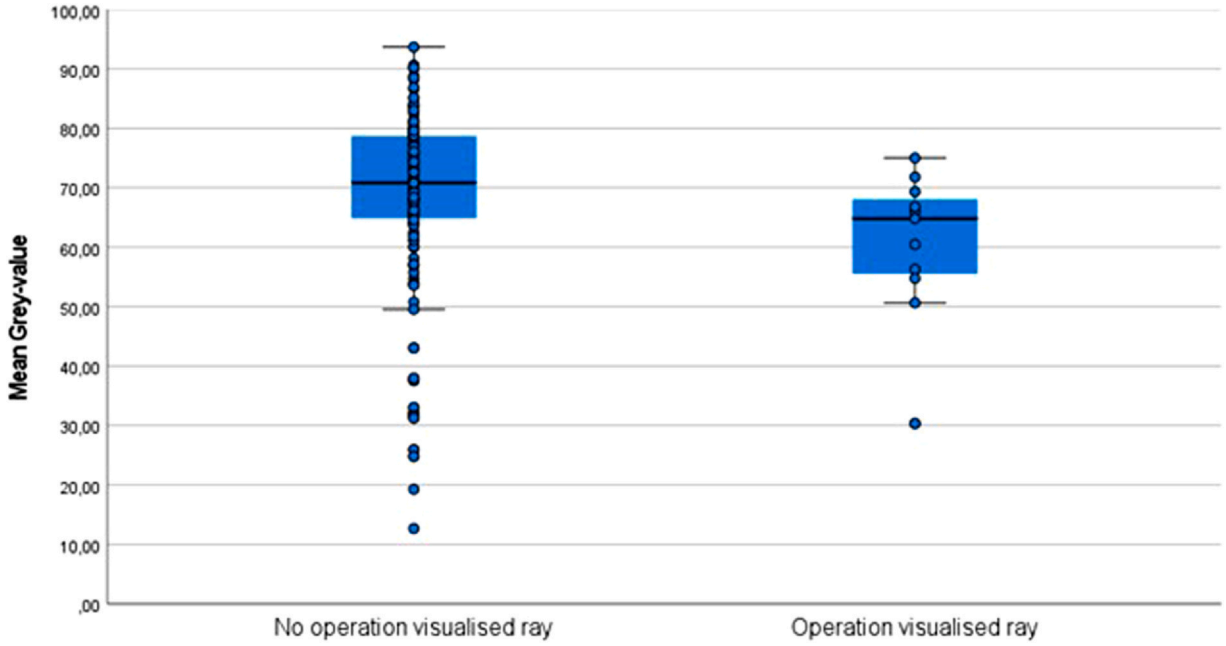

Figure 5 Boxplot of mean grey-value by surgical treatment (yes/no) of the visualised ray.

have been performed in operated patients and have measured prognosis as recurrence of disease.[14]

Compared to all other forms of imaging, ultrasonography is the most appealing because it is easily accessible, has no adverse effects, and is the least expensive.[16] In this study ultrasonography was performed by one trained researcher in order to reduce heterogeneity between observers. This might have impacted the generalisability of the results because in daily practice there might be inter-observer heterogeneity.[15]

To study the predictive value of echogenicity, it was necessary to include a follow-up period that was long enough to measure progression. Therefore we chose to include only the echogenicity measurement at baseline. Figures 4 and 5 show that the dispersion of individual grey-values is greater in those without TPED progression than in those with TPED progression, which may lead to individual false-positive findings if we were to use ultrasound as a prognostic marker. A limitation of our study is the low number of events in terms of our primary outcome (TPED progression). This leads to a loss of precision in the estimation of the association between echogenicity and our outcomes. It also precluded the multiple regression analysis meant to answer our last research question about the added predictive value of echogenicity to diathesis factors.

Another limitation is that 19% of the ultrasound measurements in our study gave unclear images and therefore were excluded, which means that our estimates only relate to patients for which clear images can be made.

The association between echogenicity of a DD nodule and progression may allow us to predict a patient's course of disease in the future. If results from our study can be confirmed and strengthened in future studies, patients with more hypoechogenic nodules could be informed of their higher risk of earlier progression, which may inform targeted treatment with disease-controlling interventions.

Several studies evaluating the effect of non-surgical, disease-controlling treatments, such as radiotherapy, intralesional injections with steroids or anti-TNF, show promising results in early-stage DD.[3,4,28] However, the anti-TNF study is the only one of these studies that applied risk stratification for the difference in prognosis of an early-stage DD nodule. The authors included only participants that showed progression, defined as patient-reported increase in nodule size, pain or tenderness, and itching, in the previous 6 months. With ultrasonographic information, it might be possible to apply a more objective form of risk stratification when studying the effect of these treatments. In the end, this may lead to better person-centred treatment decisions.

Table 2 Survival analysis between echogenicity and time to TPED progression/surgical intervention.

	All data				*Outliers excluded*			
	HR	95% CI		P	HR	95% CI		P
TPED progression	0.97	0.94	1.00	0.03	0.95	0.90	1.01	0.11
Surgery same ray	0.97	0.94	1.00	0.03	0.90	0.83	0.97	0.01
Surgery same ray and/or neighbouring ray	0.98	0.95	1.00	0.09	0.95	0.89	1.00	0.05
Surgery same hand	0.99	0.61	1.01	0.26	0.96	0.92	1.01	0.13

Conclusions

In conclusion, our results suggest that echogenicity is predictive of the prognosis of the early stages of DD. It adds to the growing body of evidence that ultrasound could have an important role in the care for DD patients throughout their disease. To build upon our research, we recommend that more studies should be executed in which a larger number of patients with early-stage DD are submitted to ultrasound examination with an extended period of follow-up, and in which the optimal time window between ultrasound assessments is examined. Depending on the results from such studies, echogenicity might be used as a prognostic imaging biomarker in the future.

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Ethical approval

This study was approved by the local medical ethics committee (METc2011/397).

CRediT authorship contribution statement

All authors contributed to the conceptualisation and methodology of the study. DB provided the data collection. The statistical analysis and data interpretation were performed by RS, MB and DB. The manuscript was written by RS and all authors provided feedback and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

The corresponding author should be contacted about this topic.

Declaration of Competing Interest

PW was member of a Safety and Efficacy Review Board of Fidia ltd, Milan, Italy. PW is member of the scientific advisory board of the International Dupuytren Society, and PW and DB are both members of the scientific advisory board of the Dutch Dupuytren Society. These interests are not related to the submitted work. All other authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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