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Factors Related to the Skin Thickness of Cardiovascular Implantable Electronic Device Pockets

Short title: Skin Thickness of CIEDs Pockets

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36

Abstract

Background: The skin overlying cardiovascular implantable electronic devices (CIEDs) sometimes becomes very thin after implantations, which could cause a device erosion. The factors related to the skin thickness of device pockets have not been elucidated.

Objective: This study aimed to evaluate the skin thickness of CIED pockets and search for the factors associated with the thickness.

Methods: Seventeen skin thickness points around the CIED pocket were measured through ultrasonography in each patient.

Results: A total of 101 patients (76 ± 11 years, 26 female) was enrolled. The median duration from the implantation to the examination was 95 months (quartile: 52.5~147.5). The median skin thickness overlying the device was 4.1 mm (3.3~5.9). Patients with heart failure and malignancy had thinner skin overlying the CIED than those without. A significant correlation existed between skin thickness and body mass index (BMI), hemoglobin, serum creatinine, estimated glomerular filtration rate (eGFR), and left ventricular ejection fraction. In contrast, the age, gender, and device size did not exhibit a significant correlation with the skin thickness. A multivariate logistic regression analysis

revealed that chronic heart failure and a decrease in the eGFR and BMI were independent predictive factors of “very thin (≤ 3.3 mm)” skin of the CIED pocket late after an implantation.

Conclusion: Aside from a low BMI, the comorbidities (low hemoglobin, heart failure, and renal dysfunction) had a stronger impact on the skin thickness overlying the device than the device size. A careful observation of the device pocket should be performed in patients with those risk factors.

Key words

cardiovascular implantable electronic devices, skin thickness, device pocket, device erosion, device infection

Introduction

With the aging society, the number of patients requiring pacemakers due to sick sinus syndrome or atrioventricular block has been increasing.^{1,2} In addition, implantable cardioverter defibrillators (ICD) have been shown to prevent sudden cardiac death, and cardiac resynchronization therapy (CRT) has been shown to improve the prognosis in patients with severe heart failure. While expanding the clinical indications for these devices, the number of device implantations has been growing.

On the other hand, one of the most serious complications in patients with CIEDs is device-related infections. Multiple factors associated with the risk of device infections have been reported. Skin disorders are considered to be one of the factors related to device infections.³ In a previous study, one-third of the patients with device infections were associated with a device pocket erosion.⁴ The skin thinning of the CIED pocket following a device implantation is not only a cosmetic problem for the patients, but is also a possible risk of a device erosion and infection. However, the factors related to the skin thickness of CIED pockets have not been studied. The aim of this study was to investigate the skin thickness overlying CIEDs and search for the factors associated with “very thin” skin late

after an implantation.

Methods

Study Design

A total of 101 consecutive patients who underwent a CIED implantation and were followed-up at Kobe University Hospital was prospectively enrolled in this study between June 2020 and June 2021. The exclusion criteria were as follows: 1) patients under 20 years old and 2) being within 1 year of the device implantation or battery change. The patient data including the blood tests, comorbidities, and information on the implanted CIED were reviewed during the first implantation and the time of the enrollment in the study. This study was approved by the local ethics committee of Kobe university hospital (Protocol ID: B200054).

Consent

Written informed consent was obtained from all patients.

Appearance of the CIED pocket

The appearance of the device pocket was classified into three grades. Grade 1: the outline of the device could hardly be seen. Grade 2: the outline of the device was partially seen. Grade 3: the entire outline of the device was fully seen.

Measurement of the Skin Thickness

The skin thickness was measured at 17 points around the CIED pocket (**Figure 1A**) using ultrasound (LOGIQ eV2VA scanner, GE Healthcare Japan, Tokyo, Japan) and a linear probe (12L RS, 6-13 MHz) in the supine position (**Figure 1B**). The CIED generator was implanted under the pectoralis fascia, and the device pocket was closed by separate stitches (usually 2-3 layers) in all patients at Kobe University Hospital. At the points on the device (points ① to ⑨ in **Figure 1A**), the skin thickness was measured as the distance from the skin surface to the device surface. The echo probe was placed perpendicular to the skin to measure the distance. At the points around the device (points ⑩ to ⑬ in **Figure 1A**), the skin thickness was measured from the skin surface to the surface of the pectoralis major. We also measured the skin thickness on the other side of the device implantation (points ⑭ to ⑰ in **Figure 1A**). In the present study, the skin thickness of the CIED pocket was defined as the mean skin thickness of 5 points on the device (points ① to ⑤).

Patient Characteristics and the Device Information

The patient data analyzed included the age, sex, body weight, body mass index (BMI), left ventricular ejection fraction (LVEF), and blood test results at the time of the device implantation and at the time of the study enrollment. The

comorbidities and past medical history were also examined. Congestive heart failure was defined as chronic heart disease with an NYHA class I-IV. Chronic kidney disease was defined as an eGFR (estimated glomerular filtration rate) < 60 mL/min/1.73m². The device type (pacemaker, ICD, CRT), weight of the device, thickness of the device, volume of the device, number of leads, and implantation side (right or left anterior chest) were examined.

“Very Thin” skin of the CIED pocket

The definition of “very thin” skin of the CIED pocket in the present study was patients whose mean skin thickness on the device was in the lowest quartile in all patients.

Statistical analysis

Continuous variables are presented as the mean value and standard deviation for normally distributed data and as the median (interquartile range) for non-normally distributed data. If those data followed a normal distribution, they were tested with an unpaired t-test or Welch test. If not, they were tested with a Mann - Whitney test. A Kruskal-Wallis test was used to compare three groups. The Spearman's correlation coefficient for revealing the degree of the association between the skin thickness and each continuous variable was performed.

Categorical variables were presented as frequencies and percentages. Categorical variables were analyzed with the chi-squared test. An initial univariate logistic regression analysis was used to identify any univariate factors to identify the thin skinned group, and it was followed by a multivariate analysis using a stepwise selection, with the p levels for entry into the model set at <0.10. A value of $p < 0.05$ was considered statistically significant. All statistics were performed using SPSS Statistic version 28.0 software (SPSS, Chicago, IL).

Results

Patient characteristics

Table 1 shows the baseline characteristics (76 ± 11 years, 26 female) of the 101 patients. The median duration from the first implantation to the study enrollment was 95 months (interquartile range: 53~148). The mean BMI was 22 ± 4 and half (50%) of the patients had defibrillators. The major comorbidities were chronic heart failure (67%), chronic kidney disease (59%), atrial fibrillation (45%), and hypertension (44%).

Skin thickness overlying the CIED

Figure 2 shows that the skin thickness at 17 points around the device pocket in

all patients. The skin thickness overlying the device (mean thickness of points ① to ⑤) was 4.1 mm (3.3~5.9). The skin at the edge of the device (points ⑥, ⑦, ⑧, and ⑨) was relatively thin. Also, the skin on the superior edge of the device was significantly thinner than that on the inferior edge of the device (1.8 mm [1.1~2.7] at point ⑥ vs. 2.8 mm [1.5~4.2] at point ⑧, $p<0.001$; 1.9 mm [1.2~2.7] at point ⑦ vs. 2.4 mm [1.4~3.7] at point ⑨, $p<0.001$).

Appearance of the pocket and skin thickness

Figure 3 shows the representative appearance of the CIED pocket classified into Grade 1 (n=20), Grade 2 (n=58), and Grade 3 (n=23). The skin thickness overlying the device was 6.6 mm (6.1~7.4) for Grade 1, 4.4 mm (3.6~5.5) for Grade 2, and 3.1 mm (2.4~3.8) for Grade 3 ($p<0.001$).

Correlation with the skin thickness

Figure 4 and Figure 5 show the comparison of the mean skin thickness for the nominal variables. The gender, device type (pacemaker or ICD, CRT or non-CRT), number of leads, and number of device exchanges did not have any significant differences for the skin thickness (**Figure 4**). However, the skin thickness in the patients with a malignancy or chronic heart failure was significantly thinner than that in those without (malignancy: yes 3.9 mm [2.6~4.7] vs. no 4.3 mm [3.6~6.2],

p=0.016. chronic heart failure: yes 3.8 mm [3.0~5.1] vs. no 5.2 mm [4.1~6.6],
p=0.030) (**Figure 5**).

Figure 6 shows the correlation between the mean skin thickness overlying the device and continuous variables. A significant correlation existed between the skin thickness and BMI, LVEF, hemoglobin, creatinine, and eGFR, respectively (BMI: p=0.001, r=0.38; LVEF: p=0.001, r=0.34; hemoglobin: p=0.004, r=0.36; creatinine: p=0.025, r=-0.27, eGFR: p=0.043, r=0.242). Also, the skin thickness on the other side had a good correlation with the skin thickness overlying the device (p=0.001, r=0.615). In contrast, the age, duration from the first implantation to the examination, device volume, device thickness, and device weight did not have a significant correlation with the skin thickness.

A comparison of the skin thickness between the three age groups (≤ 65 years, 66-80 years, and ≥ 81 years) did not reveal any significant differences (age ≤ 65 years [n = 11]: 3.9 mm [3.0-5.5] vs. age 66-80 years [n = 56]: 4.6 mm [3.6-6.3] vs. age ≥ 81 years [n = 34]: 3.9 mm [3.0-5.4], p = 0.236). Also the skin thickness was compared between the three groups according to the duration from the first implantation to the examination (≤ 5 years, 6-10 years, and ≥ 11 years). No significant difference was found among the three groups (duration ≤ 5 years [n

= 29]: 4.3 [3.1-5.7] mm vs. 6-10 years [n = 35]: 3.9 [3.4-5.0] mm vs. \geq 11 years [n = 37]: 4.6 [3.3-6.4] mm, p=0.499).

Predictors of “very thin” skin of CIED pockets

Those with a mean skin thickness of less than or equal to 3.3 mm (lowest quartile) were defined as the “very thin” skin group (n=26). **Table 2** shows the univariate and multivariate analyses for predicting a CIED pocket with “very thin” skin. In the multivariate logistic regression analysis, patients with chronic heart failure (odds ratio [OR] 6.74 [95% confidence interval (CI); 1.41-32.14], p=0.017), changes in the eGFR (Δ eGFR) from the first implantation to the study enrollment (OR 0.97 [95% CI; 0.94-1.00], p=0.037), and changes in the BMI (Δ BMI) (OR 0.80 [95% CI; 0.65-0.98], p=0.031) were independent determining characteristics of a “very thin” skin CIED pocket.

Discussion

The novel findings of this study were 1) the skin thickness overlying the CIEDs was able to be evaluated by ultrasound echography, which exhibited a good correlation to the appearance of the CIED pocket. 2) The skin thickness of the CIEDs had a significant correlation to not only the BMI, but also the hemoglobin, kidney function, LVEF, and skin thickness on the other side. 3) The device volume,

weight, thickness, and number of leads did not have any correlation to the skin thickness.

Factors related to the skin thickness

1) BMI, hemoglobin, and malignancy

Ludescher et al.⁵ reported that there are significant correlations between the local thicknesses of the subcutaneous adipose tissue and the BMI. Other studies have shown that an increasing BMI is associated with an increase in the skin (epidermis-dermis) thickness.⁶ Therefore, patients with a greater BMI have thicker skin over the device.

The hemoglobin level also exhibited a good correlation with the skin thickness. In other words, patients with anemia had a tendency of skin thinning on the device pocket. Anemia could occur due to an iron deficiency or malignancy. An iron deficiency affects the epithelial cells with a rapid turnover, causing dryness and roughness of the skin.⁷ Malignancies cause an appetite loss, cachexia, and malnutrition, which would also cause a decrease in the subcutaneous fat tissue. These factors would affect the skin thickness for CIEDs.

2) Cardiac and Renal function

Heart failure and chronic kidney disease induce chronic inflammation and

oxidative stress associated with frailty.^{8 9} The chronic inflammation accelerates the aging process in the skin. As skin ages, the vasculature progressively atrophies, and the dermis also deteriorates, with collagen and elastin fibers becoming sparse and increasingly disordered.¹⁰ These changes can lead to dry skin, a lowered barrier function, and atrophy. Iizuka et al.¹¹ reported that frail older adults had a significantly decreased skin elasticity and thickness. In addition, there is a thinning of the adipose tissue with age due to a decrease in the white adipose tissue.¹⁰ Therefore, heart and renal failure accelerate skin aging and thinning through a frailty-sarcopenia-malnutrition cycle.

3) Device factors

The impact of CIED implantations on the surrounding tissue in the human body is known as the foreign body response to the device.¹² A foreign body response is a natural defense mechanism of the body that initiates an acute inflammatory response to the implanted device. This is followed by chronic inflammation and remodeling with infiltration of monocytes, lymphocytes, and leukocytes, and replacement of the damaged tissue with granulation.¹² The intercellular matrix is replaced by collagen, and eventually, the cell-rich granulation tissue is gradually transformed into scar tissue and a fibrotic capsule.¹³ This fibrotic capsule is

associated with a reduced vascularization of the pocket. In some cases, chronic inflammation has been observed even more than 5 years after the implantation.¹² This chronic inflammation and the fibrotic changes might lead to skin aging and subsequent skin thinning. Recently, it has been reported that wrapping the device with a small intestinal submucosa extracellular matrix envelope, which would reduce the inflammation, facilitate angiogenesis, promote remodeling of healthy tissue, and stabilize the device.^{14 15}

In the present study, however, the device volume, weight, thickness, and number of leads did not have any correlation with the skin thickness of the CIED. The following points could be given as the reason. 1) We implanted the CIED generator under the pectoral fascia in all patients, which would have reduced the impact of the device size on the skin thickness. 2) The skin thickness on the other side of the device pocket had a strong correlation with the skin thickness of the CIED pocket. That meant that the thickness of the skin overlying the CIED would be greatly affected by the patient's general condition or the comorbidities rather than the device size. 3) The selection of the device was at the discretion of the operator, and therefore, the selection bias of the device size may have affected the results (e.g. physicians choose a small device for the small or skinny patients).

Clinical Implications

Patients with chronic heart failure, chronic kidney disease, a low hemoglobin level, low BMI, and malignancy have a risk of the advancement of the skin thinning of CIED pockets. Therefore, implanting the CIED generator under the pectoralis major muscle might be an optional strategy during the CIED implantation in these patients.

The present study did not focus on the direct relationship between the skin thickness and device infection. However, the risk factors reported as device infections in the previous studies³ overlapped with the factors related to the skin thickness in this study. Therefore, a careful observation of the device pocket should be performed in the outpatient clinic in patients who have risk factors for skin thinning of the CIED pocket.

Limitations

This study had several limitations. First, in this study, we did not use high-frequency ultrasound (>20 MHz)¹⁶ but instead utilized the commonly used linear ultrasound probes (6-13 MHz), so we could not evaluate the skin and subcutaneous tissue separately. Second, this was a retrospective study, the thickness of the skin at the time of the implantation was unknown, and time-

dependent changes could not be assessed. Third, this study population consisted of Japanese patients. There is a possibility that the racial differences in the physiques and BMI could affect the skin thickness of the CIED pocket. **Fourth, there were no cases with skin erosions or device pocket infections in this cohort. The number of the patients in this study was too small to discuss the direct relationship between the skin thickness and the erosions and device infections. A further continuation of this study in a large multicenter cohort will be needed.**

Conclusion

Not only the BMI, but a low hemoglobin level, malignancy, chronic heart failure, and a lower renal function were found to be associated with the skin thickness overlying the CIED. In contrast, the device size did not affect the skin thickness. Those findings would be useful information during device implantations and follow-up at the outpatient clinic.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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365 **Table 1.** Patient characteristics

	Total (n = 101)
Age, years†	76 ± 11
Female gender, n (%)	26 (26)
Bodyweight, kg†	57 ± 12
BMI†	22 ± 4
Duration from the first implantation to the examination, month‡	95 (53~148)
Weight change from the first implantation, kg‡	0 (-3.0~1.0)
BMI change from the first implantation, kg‡	0 (-1.3~0.3)
Number of device exchanges‡	0 (0~1)
Pacemaker, n (%)	50 (50)
Implantable cardioverter-defibrillator, n (%)	51 (50)
Comorbidities	
Hypertension, n (%)	44 (44)
Diabetes mellitus, n (%)	20 (20)
Chronic obstructive pulmonary disease, n (%)	7 (7)
Chronic heart failure, n (%)	67 (67)
Chronic kidney disease, n (%)	59 (59)
Hemodialysis, n (%)	4 (4)
Atrial fibrillation, n (%)	45 (45)
Coronary artery disease, n (%)	22 (22)
Malignancy, n (%)	21 (21)
Oral corticosteroid use, n (%)	8 (8)
Blood Test, Echocardiography	
Hemoglobin, g/dL‡	12.4 (10.7~14.0)
Albumin, g/dL‡	3.7 (3.5~4.2)
Cholinesterase, U/L‡	247 (224~298)
BNP, pg/mL‡	129 (58~239)
Creatinine, mg/dL‡	0.90 (0.75~1.26)
Urea nitrogen, mg/dL‡	18.0 (14.0~27.2)
eGFR, mL/min/1.73m ² ‡	58.2 (42.8~73.0)
LVEF, %‡	50.0 (34.0~61.5)

†Mean±SD, ‡Median(quartile), BMI=body mass index; BNP=B-type natriuretic peptide; eGFR= estimated glomerular filtration rate; LVEF=left ventricular ejection fraction

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367 **Table 2.** Predictors of “very thin” skin (≤ 3.3 mm)

	≤ 3.3 mm (n = 26)	> 3.3 mm (n = 75)	Univariate analysis P value	Multivariate analysis		
				OR	95% CI	p value
Age, years†	77 \pm 12	76 \pm 10	0.562			
Female gender, n (%)	7 (27)	19 (25)	0.873			
Duration from first implantation to examination, month‡	95.0 (41.5~224.6)	95.0 (58.0~148.0)	0.938			
Number of device exchange	0 (0~1)	0 (0~1)				
Implantation side, n (%)	Left : 24 (92.3)	Left : 67 (89.3)	1.000			
Number of leads‡	2 (1~2)	2 (1~2)				
ICD, n (%)	ICD : 14 (53.8)	ICD : 38 (50.7)	0.780			
Hypertension, n (%)	8 (30.8)	35 (46.7)	0.158			
Diabetes mellitus, n (%)	7 (26.9)	13 (17.3)	0.290			
Chronic obstructive pulmonary disease, n (%)	2 (7.7)	5 (6.7)	1.000			
Chronic liver disease, n (%)	3 (11.5)	0 (0)	0.016			
Chronic heart failure, n (%)	24 (92.3)	46 (61.3)	0.003	6.740	1.41-32.14	0.017
Chronic kidney disease, n (%)	20 (76.9)	39 (52.0)	0.026			
Hemodialysis, n (%)	1 (3.8)	3 (4.0)	1.000			
Atrial fibrillation, n (%)	15 (57.7)	30 (40.0)	0.118			
Coronary artery disease, n (%)	5 (19.2)	17 (22.7)	0.715			
Malignancy, n (%)	9 (34.6)	12 (16.0)	0.044			
Skin disease, n (%)	1 (3.8)	3 (4.0)	0.972			
Oral corticosteroid use, n (%)	2 (7.7)	6 (8.0)	1.000			

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	≤ 3.3 mm (n = 26)	> 3.3 mm (n = 75)	Univariate analysis P value	Multivariate analysis		
				OR	95% CI	p value
Creatinine, mg/dL‡	1.4 (1.0~2.5)	1.1 (0.8~1.2)	0.030			
Urea nitrogen, mg/dL‡	32.0 (17.5~64.0)	18.0 (14.6~23.7)	<0.001			
eGFR, mL/min/1.73m ² ‡	36.9 (19.9~57.2)	52.3 (37.4~64.8)	0.013			
Δ eGFR, mL/min/1.73m ² ‡	-14.1 (-30.5~-0.2)	-6.1 (-15.8~-1.0)	0.085	0.97	0.94-1.00	0.037
BNP, pg/mL‡	311 (134~780)	140 (64~384)	0.009			
LVEF, %‡	37.5 (25.3~56.0)	56.0 (40.8~63.8)	0.025			
BW, kg‡	52.5 (43.0~60.5)	58.0 (51.0~68.0)	0.010			
Δ BW, kg‡	-2.0 (-8.50~0.0)	0.0 (-1.0~0.0)	0.005			
BMI‡	20.4 (18.2~21.6)	23.2 (19.5~24.6)	<0.001			
Δ BMI‡	-0.83 (-3.68~0.0)	0.0 (-0.96~0.37)	0.006	0.80	0.646-0.979	0.031
Hemoglobin, g/dL‡	10.6 (9.7~11.8)	13.0 (11.9~14.5)	<0.001			
Albumin, g/dL‡	3.6 (3.2~4.0)	3.8 (3.6~4.1)	0.024			
Cholinesterase, U/L‡	204.0 (166.5~257.0)	248.5 (213.0~290.0)	0.062			
Mean thickness of the skin on the opposite side, mm‡	3.8 (3.3~5.5)	5.9 (4.9~8.1)	<0.001			

‡Mean±SD, ‡Median(quartile), ICD=implantable cardioverter defibrillator; eGFR=estimated glomerular filtration rate; BNP=B-type natriuretic peptide; LVEF=left ventricular ejection fraction; BW=body weight; BMI=body mass index, Δ=(data at examination) – (data at implantation)

Figure Legends

Figure 1. Measurement of the skin thickness

(A) The skin thickness was measured at 17 points around the CIED pocket: Five points on the plane of the device (① to ⑤), four points on the device corners (⑥ to ⑨), four points around the device (⑩ to ⑬), and four points on the other side of the device implantation (⑭ to ⑰). (B) The echo probe was placed perpendicular to the skin to measure the distance. The tissue components overlying the device are the epidermis, dermis, hypodermis, and pectoral fascia (left panel). The right panel shows a representative case of the tissue components. The green arrow indicates the skin thickness from the epidermis to the device surface.

Figure 2. Skin thickness around the device pocket

Each box plot shows the skin thickness at each point (① to ⑰)

Figure 3. Appearance of the pocket and skin thickness

(A) The appearance of the CIED pocket was classified into 3 grades. Grade 1: the outline of the device could hardly be seen. Grade 2: the outline of the device was partially seen. Grade 3: the outline of the device was fully seen. The white arrows indicate the outline of the device. The skin thickness is shown by the green arrows.

(B) The box plots indicate the median skin thickness on the device for each grade.

389 **Figure 4.** Comparison of the mean skin thickness for the normal variables (gender and device information)

390 **Figure 5.** Comparison of the mean skin thickness for the normal variables (comorbidities)

391 COPD=chronic obstructive pulmonary disease; CKD=chronic kidney disease.

392 **Figure 6.** Correlation between the skin thickness and continuous variables

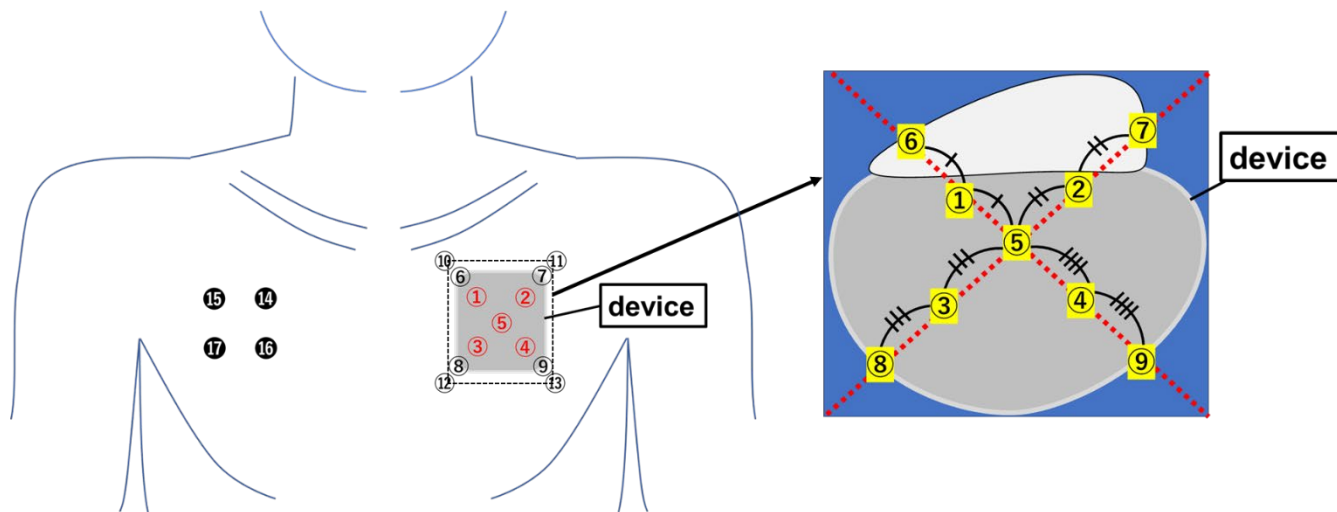
393 BMI=body mass index; LVEF=left ventricular ejection fraction; eGFR=estimated glomerular filtration rate; BNP=B-type

394 natriuretic peptide.

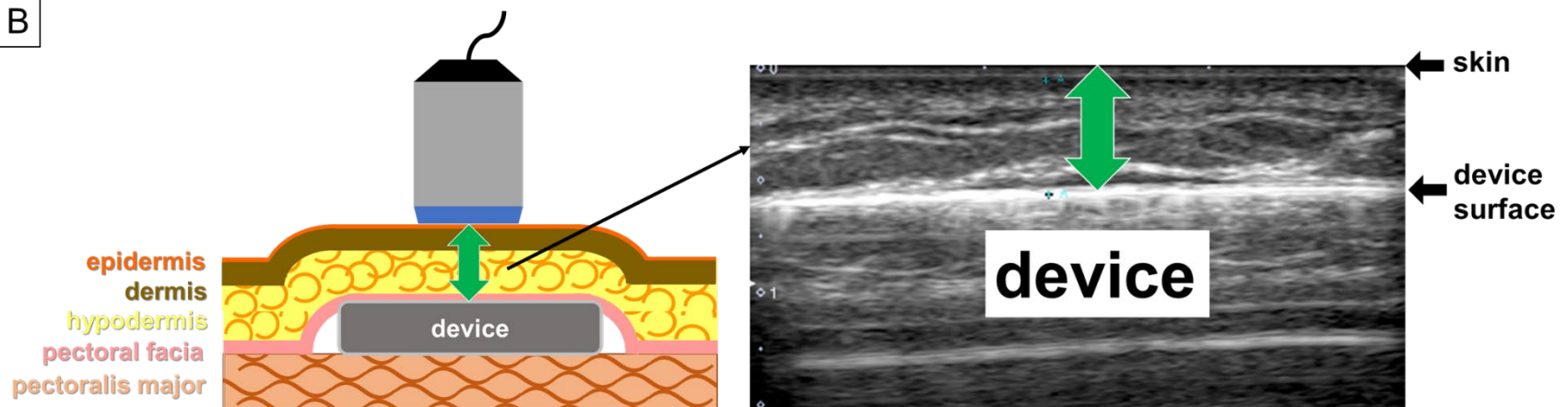
395

396 **Figure 1**

A

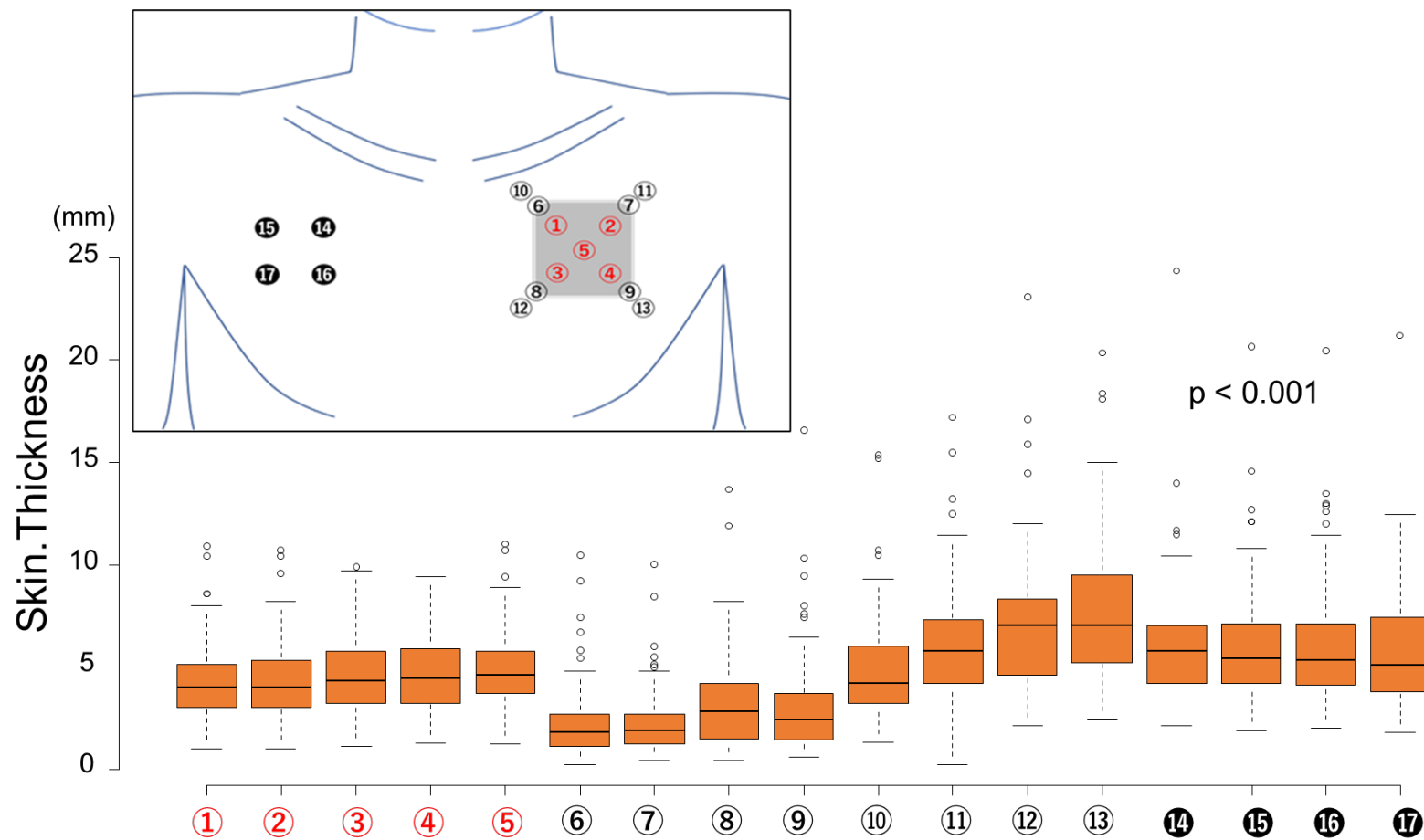


B



397

398 **Figure 2**



399

Figure 3

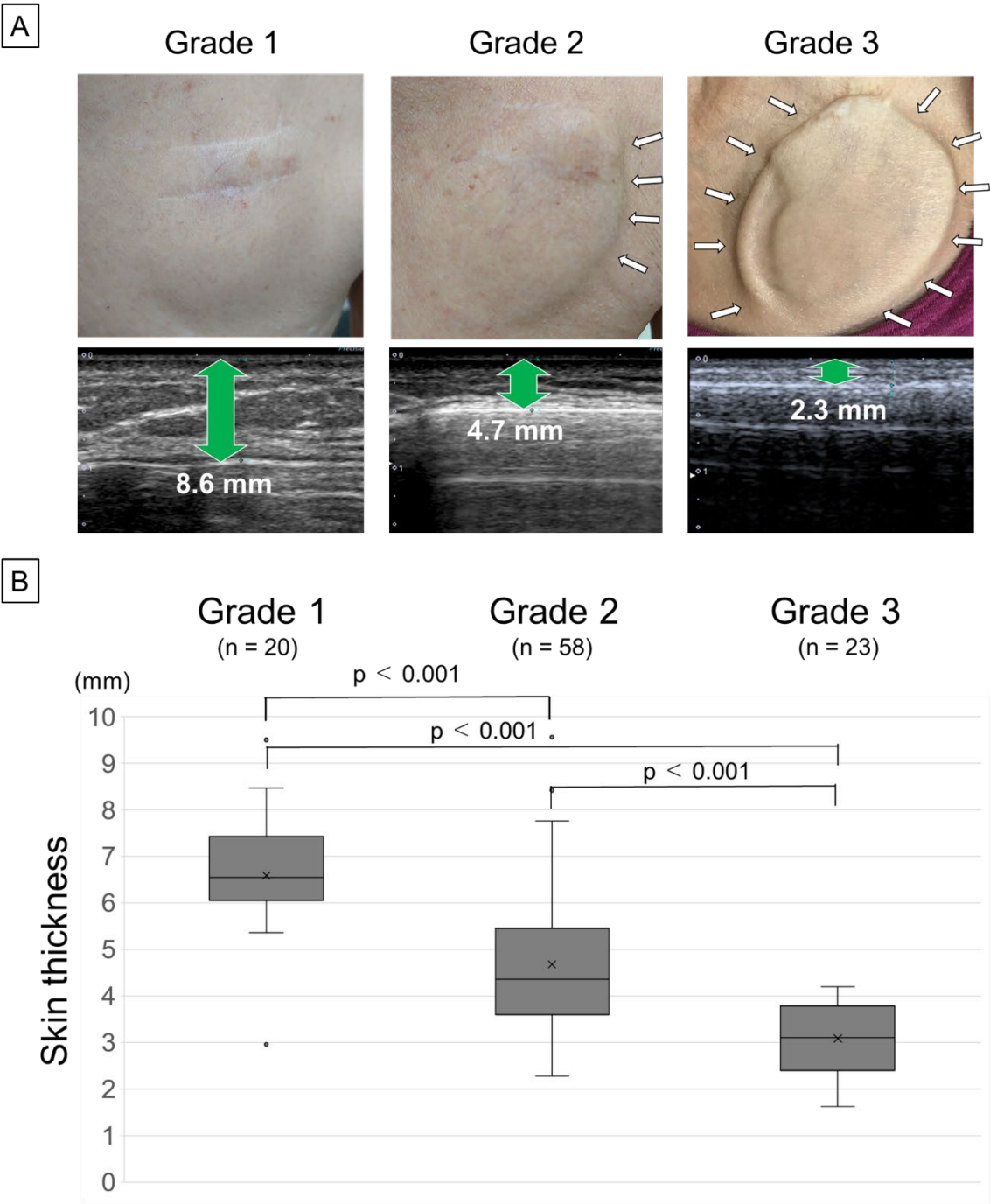


Figure 4

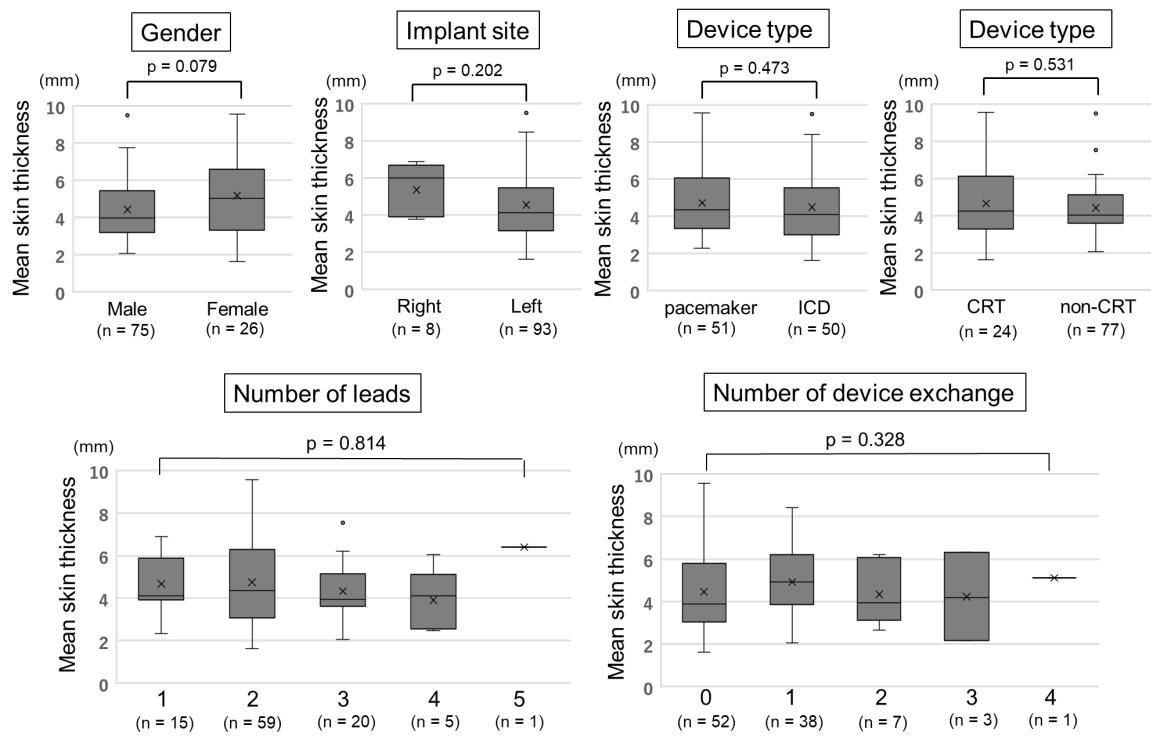
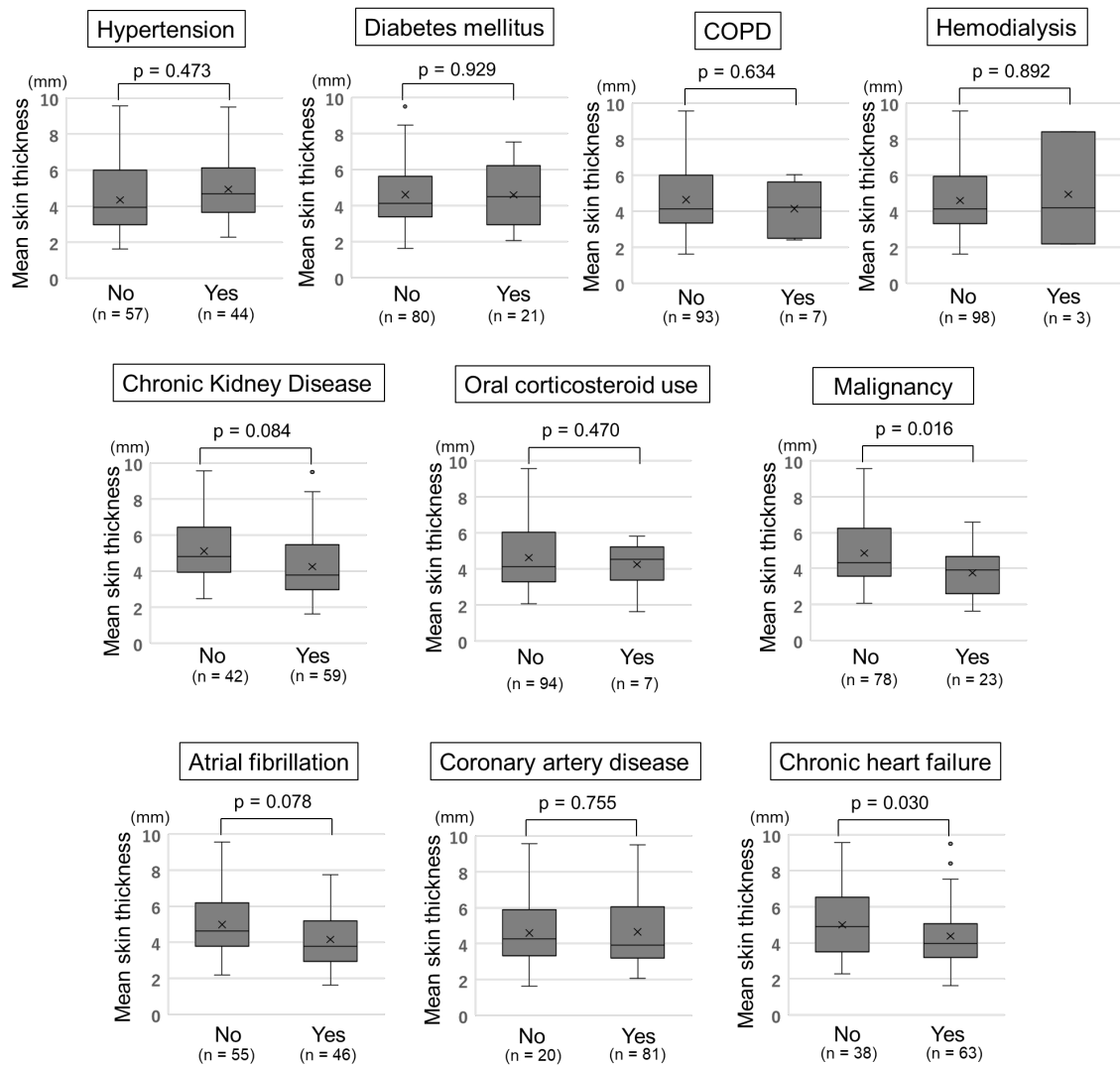
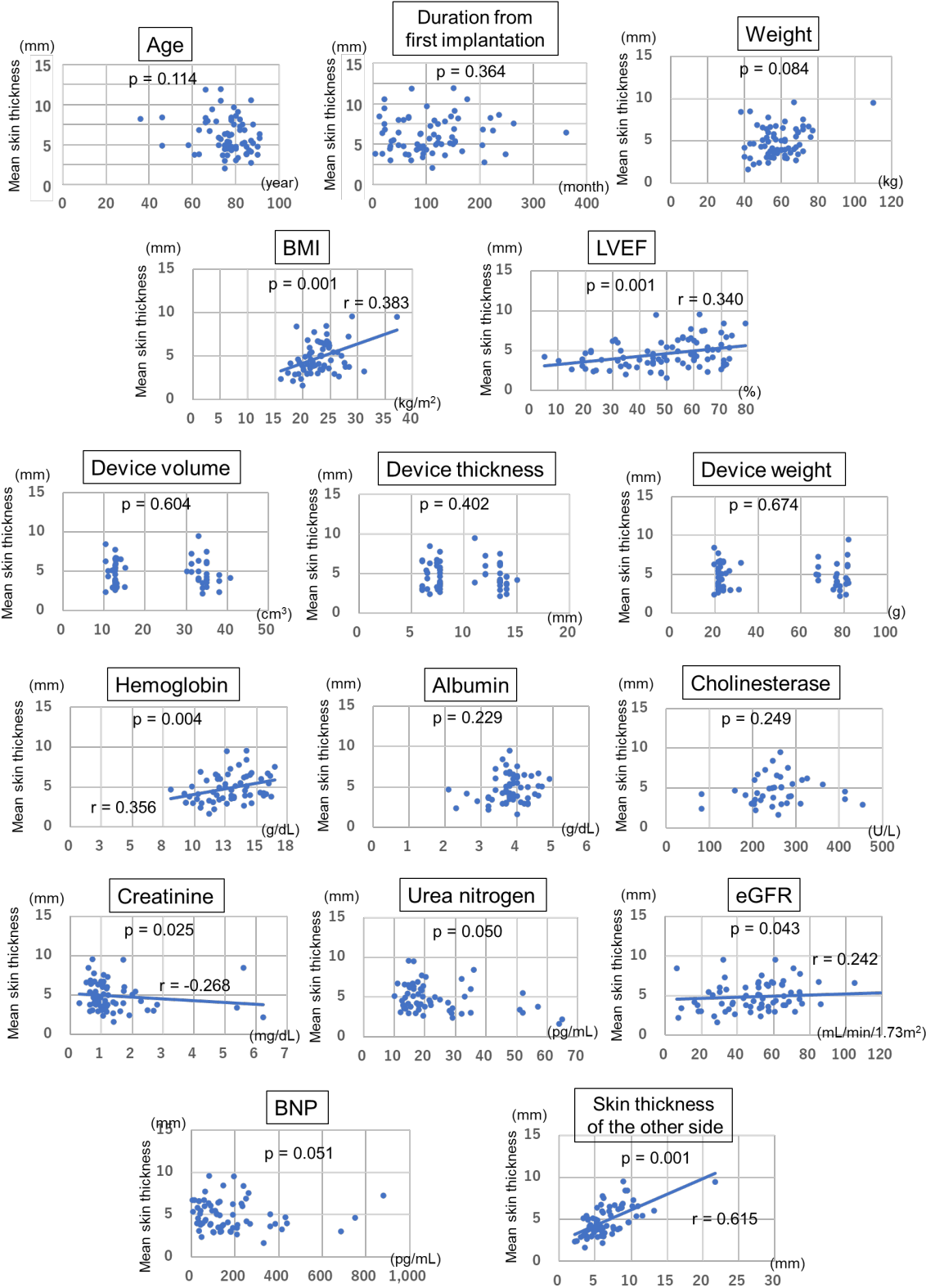


Figure 5



458 **Figure 6**



459
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