

Title page

The propagation display method improves the reproducibility of pancreatic shear wave elastography

Kiyotaka Hashizume¹, Yoshiki Hirooka², Hiroki Kawashima¹, Eizaburo Ohno¹, Takuya Ishikawa¹, Manabu Kawai¹, Hiroki Suhara¹, Tomoaki Takeyama¹, Toshinari Koya¹, Hiroyuki Tanaka¹, Daisuke Sakai¹, Takeshi Yamamura², Kazuhiro Furukawa², Kohei Funasaka¹, Masanao Nakamura¹, Ryoji Miyahara¹, Osamu Watanabe¹, Masatoshi Ishigami¹, Takamichi Kuwahara³, Senju Hashimoto⁴, Hidemi Goto¹

¹ Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Tsuruma-Cho, Showa-ku, Nagoya City, 466-8550, Japan

² Department of Endoscopy, Nagoya University Hospital, Nagoya, Japan

Tsuruma-Cho, Showa-ku, Nagoya City, 466-8550, Japan

³ Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan

Kanokoden, Chikusa-ku, Nagoya City, 464-8681, Japan

⁴ Department of Liver, Biliary Tract and Pancreas Diseases, Fujita Health University,

Toyoake, Japan

Dengakugakubo, Kutsukake, Toyoake City, 470-1192, Japan

Correspondence to: Yoshiki Hirooka, Department of Endoscopy, Nagoya University Hospital, Nagoya, Japan Tsuruma-Cho, Showa-ku, Nagoya City, 466-8550, Japan

Phone: +81(52)-735-8806, Fax: +81(52)-744-2180

E-mail: hirooka@med.nagoya-u.ac.jp

1 ABSTRACT

2 Evaluation of the pancreatic elastic modulus (PEM) using shear wave elastography (SWE)
3 requires at least 5 measurements to ensure reproducibility. The aim of this study was to
4 evaluate improvement in reproducibility of SWE using the propagation display method in
5 normal pancreas (NP) (phase 1) and to examine differences in PEM between NP and chronic
6 pancreatitis (CP), intraductal papillary mucinous neoplasm (IPMN), and autoimmune
7 pancreatitis (AIP) (phase 2).

8

9 In phase 1, the measurement success rate, median PEM in repeated measurements, and
10 appropriate number of SWE measurements were determined in 109 cases with NP. In phase 2,
11 PEM was measured in CP (n=10), IPMN (n=31), and AIP (n=5) using the required number of
12 SWE measurements determined in phase 1.

13

14 In phase 1, the measurement success rate was 93.9% (92/109 cases). The median PEM for
15 NP was 14.6 kPa and the appropriate number of SWE measurements was at least 3. In phase
16 2, the median PEMs in CP, IPMN, and AIP were 19.6, 18.1, and 17.2 kPa, respectively, with
17 significant differences between NP and CP ($P=0.0133$), and NP and IPMN ($P=0.0436$).

18

19 Use of the propagation display method in SWE improves the reproducibility of
20 measurement of PEM.

21

22 Keywords: shear wave elastography; pancreas; chronic pancreatitis; propagation display
23 method

24

25 **Introduction**

26 Ultrasound elastography is a useful technique for measurement of tissue elasticity (Shiina
27 2013; Hirooka et al. 2015). Tissue is generally elastic and Young's modulus can be used for
28 evaluating elasticity (Ferraioli et al, 2012). There are two types of ultrasound elastography:
29 strain elastography and shear wave elastography (SWE). Strain elastography uses hand
30 pressure and pulsation of the heart and aorta beat, and measures the target tissue elasticity
31 with the strain generated, whereas SWE generates strain by a push pulse from a probe,
32 measures the propagation velocity, and obtains the tissue elasticity. Strain elastography may
33 be affected by the skill of the operator and the site chosen for measuring the tissue elasticity,
34 whereas in SWE the difference between examiners is small, but the elastic modulus can
35 change due to inflammation (Arena et al. 2008), jaundice (Millonig et al 2008), or blood
36 congestion (Colli et al. 2010). Elastography can be performed using endoscopic
37 ultrasonography (EUS), but transabdominal ultrasonography is superior to EUS in that it is a
38 non-invasive and simple procedure (Hirooka et al. 2015).

39 The speed at which a shear wave propagates in a material has a positive correlation with
40 the elastic modulus of the substance: the faster the propagation speed, the harder the material.
41 This principle is used in SWE to determine the elastic modulus of tissue in a noninvasive and
42 simple manner, including measurement of the pancreatic elastic modulus (PEM) (Hirooka et
43 al. 2015).

44 SWE permits measurement of the PEM, but there are errors in the measurement. One
45 problem is setting the correct region of interest (ROI). If the ROI contains tissues other than
46 pancreatic parenchyma, such as the extended main pancreatic duct and blood vessels, or the
47 aorta or intestinal tract is close to the ROI, it becomes difficult to evaluate the PEM
48 (Ichikawa et al. 2012). Thus, we found that obtaining a reproducible median PEM from SWE
49 performed at an arbitrary part of pancreatic parenchyma required at least 5 measurements
50 (Kuwahara et al. 2016).

51 The “propagation display method” in SWE was developed in 2014 to confirm the tissue
52 arrival time of the shear wave using contour lines (Iijima 2014). Using this indication of the
53 timing of SWE, it is possible to visualize the shear wave propagating in the target tissue
54 before measurement. That is, since the tissue elasticity can be measured within the range
55 where the shear wave is well propagated (Iijima reported that in areas where the contour lines
56 are parallel, the shear waves propagate properly and the reliability of the obtained data is
57 high.), more reliable measurements can be made, which may lead to improvement of SWE
58 reproducibility. In this study, SWE with propagation display method was applied to a normal
59 pancreas and improvement of PEM reproducibility was evaluated. The relationship of PEM
60 for the normal pancreas with PEMs for chronic pancreatitis (CP), intraductal papillary
61 mucinous neoplasm (IPMN), and autoimmune pancreatitis (AIP) was then examined using
62 the same SWE method.

63

64 **Materials and methods**

65 *Phase 1*

66 Phase 1: A total of 109 cases with a normal pancreas (NP) were included in this phase of
67 the study. Cases with NP were defined as patients with no apparent pancreatic diseases such
68 as tumors, cysts, or a dilated main pancreatic duct, no history of alcohol consumption >80 g
69 per day, and normal serum levels of amylase and lipase. The mean age was 62.6 ± 13.8 years
70 (range 29-85 years) and the male/female ratio was 46/63 (Table 1) (Kuwahara et al. 2016).

71

72 *Phase 2*

73 Phase 2: Cases with CP (n=10), IPMN (n=31), and AIP (n=5) that underwent SWE with
74 propagation display method were included in this phase of the study (Table 1). In the CP,
75 IPMN, and AIP cases, the mean ages were 53.7 ± 18.2 (30-79), 67.6 ± 7.4 (51-81), and $71.8 \pm$
76 8.3 (61-82) years, respectively, and the male/female ratios were 6/4, 11/20, and 4/1,

77 respectively (Table 1). CP, IPMN, and AIP were diagnosed using Japanese Clinical
78 Diagnostic Criteria for Chronic Pancreatitis 2009 (Shimosegawa et al. 2010), International
79 Consensus Guidelines 2012 for Management of IPMN and MCN of the Pancreas (Tanaka et
80 al. 2012), and Clinical Diagnostic Criteria for Autoimmune Pancreatitis 2011 (The Japan
81 Pancreas Society 2012), respectively.

82 In both phases, consecutive patients were recruited from March 2015 to May 2016 at
83 Nagoya University Hospital and all provided informed consent before the examination.
84 Patients for whom it was difficult to perform an examination because of severe complications
85 or mental disorder were excluded. The study was approved by the Institutional Review Board
86 of Nagoya University Hospital, performed according to the Declaration of Helsinki, and
87 registered in UMIN-CTR (registration ID 000016497).

88

89 *Shear wave elastography*

90 In all cases, SWE was performed using an Aplio 500 ultrasound system (Toshiba Medical
91 Systems, Otawara, Japan) with a 5-MHz convex probe (PVT-375BT). SWE detects the speed
92 at which the shear wave caused by a push pulse from the probe propagates through the tissue
93 and evaluates the tissue elasticity. The shear wave has constant velocity in the same elastic
94 materials, and is fast in hard material and slow in soft material. In soft tissues such as in vivo,
95 it is possible to assume that the difference in tissue density is small, so it is possible to
96 estimate Young's modulus(E) from shear wave velocity(v_s). From this fact, the shear wave
97 velocity is expressed in kilopascals(kPa) or m/s through $E = 3(v_s^2 \rho)$, where ρ is the tissue
98 density (Ferraioli et al, 2012).

99

100 *Propagation display method*

101 A feature of the Aplio 500 used in this study is the propagation display method mounted on
102 the shear wave. The propagation display method allows the arrival site of the shear wave to

103 be visualized by contour lines at regular time intervals by utilizing the difference in
104 propagation speed of the shear wave. The intervals between the displayed contour lines are
105 wider in hard tissues and narrower in soft tissues. In a homogeneous elastic tissue, since the
106 velocity of the shear wave is constant, the widths of the contour lines are equal and parallel.
107 Parallel contour lines mean that the shear wave has propagated properly and the data are
108 highly reliable, whereas distorted or non-parallel contour lines indicate that the reliability of
109 the data is low(Iijima 2014) (Fig. 1).

110

111 *Elastography*

112 SWE measurements were performed from the epigastric fossa in the supine position and
113 the measurement site was defined as the parenchyma of the pancreatic body. The transducer
114 was repositioned for each acquisition. In the measurement of PEM by SWE, a so-called
115 “evaluation ROI” was first established as the target and the “measurement ROI” was set as
116 wide as possible for the part where the width of the contour line was equal and parallel. The
117 ROI is the recommended measurement range up to 5 cm from the probe. Measurements were
118 evaluated by a doctor and an ultrasonic specialist.

119 In the phase 1 study, SWE using the propagation display method was performed 5 times
120 for NP cases (Kuwahara et al. 2016). Contour lines from the propagation display method that
121 were visually recognized were defined as a valid measurement. It was defined as invalid
122 measurement when the ROI did not reach, when the patients could not hold their breath, and
123 when it was difficult to visualize the pancreas due to the influence of intestinal gas. Valid
124 measurements were judged to be successful when the contour lines were equal in width and
125 equilibrium (Fig. 1). The measurement success rate was calculated as the average of the
126 number of valid measurements/total measurements $\times 100$ in each case (Castera et al. 2012).
127 ICC(1,1) was obtained from valid measured values, and the appropriate number of
128 measurements (k) was obtained from the equation $k = \rho_2(1-\rho_1)/\rho_1(1-\rho_2)$, where ρ_1 is

129 ICC(1,1) and ρ^2 is the target coefficient value (0.9).

130 In the phase 2 study, PEM measurements for CP, IPMN, and AIP were performed using the
131 required number of measurements (k) found in phase 1, and PEM for each disorder was
132 compared with PEM for NP. For cases of IPMN, the measurement ROI did not cover the
133 cystic lesion or extended main pancreatic duct. In CP, a case in which the pancreas was
134 thinned and the pancreas itself was difficult to visualize was excluded as unmeasurable.

135

136 *Statistical analysis*

137 Statistical analyses of recorded data were performed using an Excel-based program
138 (BellCurve for Excel for Windows, Social Survey Research Information Co.). All tests were
139 2-tailed and $P < 0.05$ was considered significant. Continuous variables are expressed as mean
140 \pm SD or median and interquartile range (IQR), where indicated. A Steel-Dwass test was used
141 for continuous variables. The ICC was used to assess the intra-rater reproducibility of the
142 PEM of NP in SWE. ICC values were defined as indicating slight ($\rho < 0.2$), fair ($\rho = 0.2-0.4$),
143 moderate ($\rho = 0.4-0.6$), substantial ($\rho = 0.6-0.8$), and almost perfect ($\rho = 0.8-1.0$) reproducibility
144 (Landis et al.1977).

145

146 **Results**

147 *Pancreatic elasticity modulus and measurement success rate for NP using SWE*

148 SWE with propagation display method was performed 5 times for 109 NP cases. Seventeen
149 cases were excluded as unmeasurable due to a deep location of the pancreas (n=4), failed
150 breathholding (n=4), and difficulty with pancreatic visualization due to intestinal gas (n=9)
151 (Fig. 2). In SWE using propagation display method in the 92 measurable cases, the
152 measurement success rate was $93.9 \pm 11.0\%$ and the median PEM (IQR) was 14.6 (12.3-17.3)
153 kPa (Fig. 3).

154

155 *Appropriate number of SWE measurements*

156 The ICC (1, 1) for SWE performed for NP was 0.7629 and the appropriate number of
157 measurements obtained from this value was 2.7970. This indicates that an appropriate value
158 can be obtained from three or more measurements, which is fewer than the 5 measurements
159 required using the conventional method.

160

161 *Comparison between NP and other pancreatic diseases*

162 The median (IQR) PEMs for SWE performed three times for CP (n=10), IPMN (n=31) ,
163 and AIP (n=5) cases were 19.6 (15.6-22.4), 18.1 (13.3-20.9), 17.2 (15.6-40.4), respectively.
164 PEMs for CP and IPMN were significantly higher than PEM for NP ($P=0.0133$, $P=0.0436$).
165 There was no significant difference between PEMs for NP and AIP ($P=0.1809$) (Fig. 4).

166

167 **Discussion**

168 In the current study, we examined improvement of SWE reproducibility using the
169 propagation display method, and further examined PEM for several pancreatic disorders.
170 When SWE was measured, good reproducibility is required to get the reliable data on the
171 elasticity of a target tissue. Therefore, we examined whether reproducibility is improved
172 using the propagation display method in SWE. The propagation display method can display
173 and visualize the propagation of the shear wave in the target tissue. Measurements using this
174 method indicated that reliable data can be obtained by measuring only three times, which is
175 less than the number of measurements required for reproducibility of SWE using the
176 conventional method (Kuwahara et al. 2016).

177 Comparison of PEM values between NP and pancreatic diseases (CP, IPMN, AIP) showed
178 that CP and IPMN had significantly higher elasticity than NP. CP has a high elastic modulus
179 due to chronic inflammation and accompanying fibrosis. A relationship between fibrosis and
180 elastography has been reported in liver diseases (Castera 2008; Friedrich 2009; Cassinotto

181 2013; Ogawa 2016; Sande 2017; Ferraioli 2012). Ferraioli et al. described the relationship
182 between liver fibrosis and SWE measurements (Ferraioli et al. 2012), and this relationship
183 was confirmed between SWE and fibrosis in pancreatic parenchyma by Kuwahara et al.
184 (2016) and Harada et al. (2014). Using acoustic radiation force impulse (ARFI) elastography,
185 Yashima et al. found that the shear wave velocity in CP was higher in the pancreatic head,
186 body, and tail, compared with NP (Yashima et al. 2012). The shear wave velocity in the
187 pancreatic body in Yashima et al. was 2.09 ± 1.03 m/s, which is similar to the value in the
188 present study (19.6 (15.6-22.4) kPa, which converts to 2.54 (2.28-2.73) m/s). In IPMN, the
189 higher PEM compared to NP is due to mucus produced by IPMN, which exerts pressure on
190 the pancreatic duct. This leads to the pathology of chronic obstructive pancreatitis in the
191 pancreatic parenchyma, and resulting chronic inflammation causes a high PEM (Rickaert
192 1991; Zapiach 2004; Venkatesh 2011; Pelletier 2010).

193 This study has several limitations. First, because the number of cases with a diseased
194 pancreas was small, we could not conclude the comparison of PEM among pancreatic
195 diseases in this study. Second, histopathological evidence was not obtained for the elasticity
196 modulus. Third, the results were taken from examples that were valid in the propagation
197 display method, and invalid or unmeasurable cases could not be evaluated. Fourth, in SWE
198 for the pancreas, there is a difference in the distance from the body surface to the pancreas in
199 each individual, and this may alter the elastic modulus (Wang et al. 2014). Fifth, the viscosity
200 of the target tissue is not considered in this study. Given these limitations, the results of the
201 study are not conclusive and further data are required from more disease cases. However, we
202 showed that PEM measurements in SWE using propagation display method are reproducible
203 from as few as three measurements, and this suggests that this method may be viable for
204 clinical application in pancreatic disease.

205

206 **Conclusion**

207 Shear wave elastography using propagation display method improves the reproducibility of
208 measurement of PEM.

209

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214 employment, consultancy, patents, products in development, or marketed products, do not
215 exist regarding this manuscript.

216

217 **Conflict of Interest**

218 Hashizume K declares no conflict of interest.

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233 **Table list**

234 Table 1. Patient characteristics

| Characteristic | | | |
|----------------------|--|------------|------------------|
| Pancreatic diagnosis | Number of cases | Age(years) | Sex(Male/Female) |
| NP | 109 | 62.6±13.8 | 46/63 |
| CP | 10 | 53.7±18.2 | 6/4 |
| IPMN | 31 | 67.6±7.4 | 11/20 |
| AIP | 5 | 71.8±8.3 | 4/1 |
| NP | nomal pancreas | | |
| CP | chronic pancreatitis | | |
| IPMN | intraductal papillary mucinous neoplasms | | |
| AIP | autoimmune pancreatitis | | |

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253 named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria
254 for authorship for this manuscript, take responsibility for the integrity of the work as a whole,
255 and have given final approval to the version to be published.

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407 **Figure Captions list**

408 Fig. 1. Shear wave elastography using the propagation display method in the pancreas.

409 (a) Images showing measurement success have equal width balance. (b) Images showing
410 measurement failure have heterogeneous widths.

411

412 Fig. 2. Flowchart of subjects.

413 A total of 109 cases with normal pancreas (NP) were enrolled in the study. Seventeen cases
414 with failed measurements in shear wave elastography were excluded, leaving 92 cases for
415 analysis.

416

417 Fig. 3. Median of the pancreatic elastic modulus (PEM) of the normal pancreas (NP).

418 The median measured in each case five times was taken as the PEM of each case. The median
419 (IQR) of the PEM of 92 normal pancreas cases was 14.6(5.0) kPa.

420

421 Fig. 4. Comparison of PEM values for normal pancreas (NP) and cases of chronic pancreatitis
422 (CP), intraductal papillary mucinous neoplasm (IPMN), and autoimmune pancreatitis (AIP),
423 PEMs for CP and IPMN were significantly higher than that for NP ($P = 0.0133$, $P = 0.0436$).

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Fig.1

a)



b)

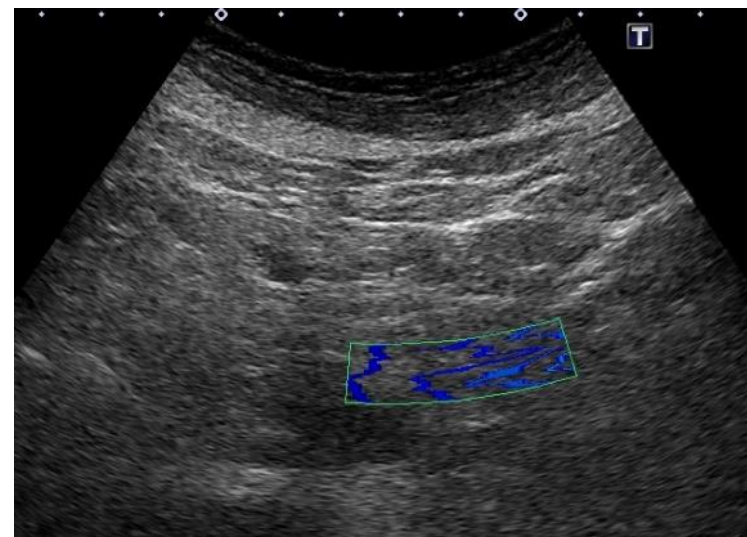


Fig.2

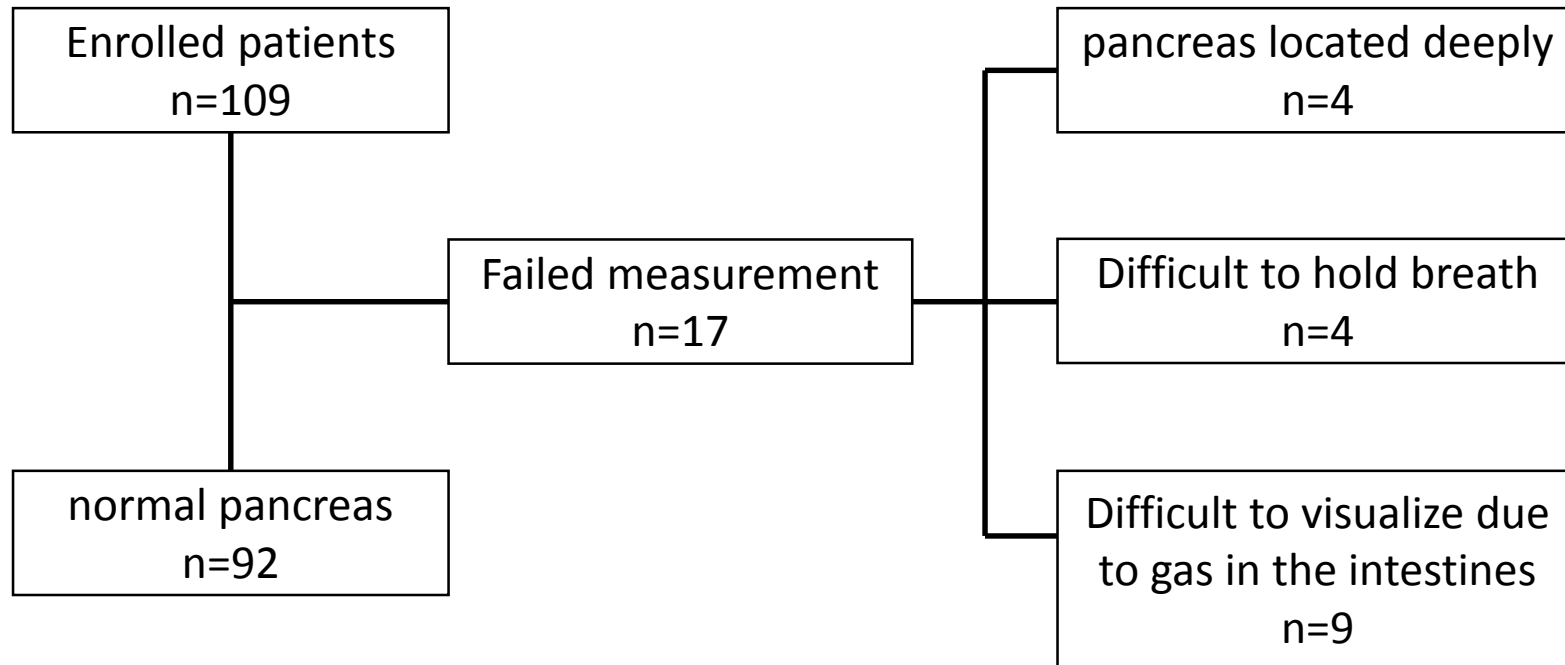


Fig.3

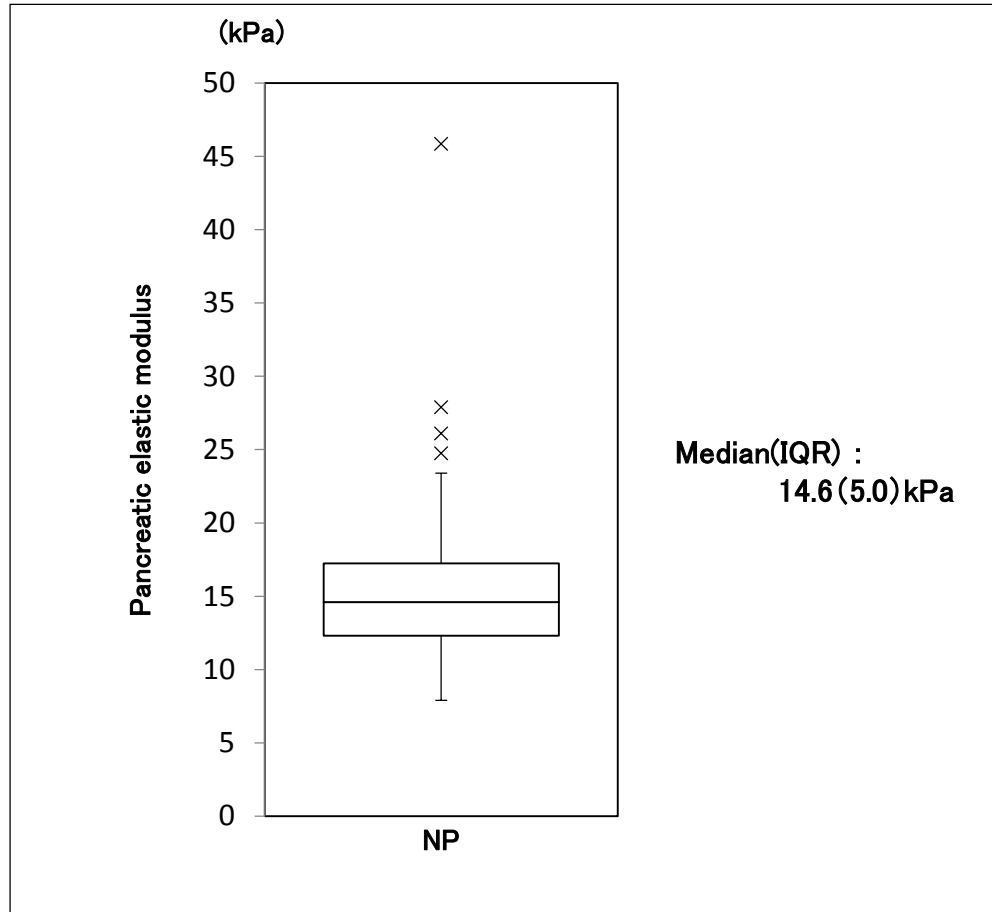


Fig.4

