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TITLE PAGE

PAPER TITLE

Volumetric versus single slice measurements of core abdominal muscle for sarcopenia.

SHORT TITLE

Measurements of core abdominal muscle for sarcopenia.

TYPE OF MANUSCRIPT

Full paper.

AUTHORS

Mohammed A Waduud^{1*} MRCS MSc, P Adusumilli² MBChB BSc, Michael Drozd³ MBChB BSc, MA Bailey³ MRCS PhD, G Cuthbert¹ MRCS, C Hammond² FRCR MRCS MA, DJA Scott¹ FRCS MD. On behalf of the Vascular Surgeons and Interventional Radiologists at the Leeds Vascular Institute.

NOTE: qualifications are reported as highest clinical followed by highest academic qualification.

*corresponding author: m.a.waduud@leeds.ac.uk.

MAW, PA contributed equally.

1. Leeds Vascular Institute, Leeds General Infirmary, Leeds, LS1 3EX, UK.2.

2. Department of Radiology, Leeds General Infirmary, Leeds, LS1 3EX, UK.

3. Leeds Institute for Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, LS1 9JT, UK.

WORD COUNT

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1 **ABSTRACT**

3 **Objectives**

4 We investigated whether total psoas muscle area (TPMA) was representative of the total psoas
5 muscle volume (TPMV). Secondly, we assessed whether there was a relationship between the
6 two commonly used single slice measurements of sarcopenia, TPMA and total abdominal
7 muscle area (TAMA).

9 **Methods**

10 Pre-operative CT imaging of 110 patients undergoing elective endovascular aneurysm repair
11 were analysed by two trained independent observers. TPMA was measured at individual
12 vertebral levels between the second lumbar vertebrae and sacrum. TPMV was also estimated
13 between the second lumbar vertebrae and sacrum. TAMA was measured at the third lumbar
14 vertebrae (L3). Observer differences were assessed using Bland-Altman plots. Associations
15 between the different measures were assessed using linear regression and Pearson's correlation.

17 **Results**

18 We found single slice measurements of the TPMA to be representative of the TPMV at
19 individual levels between L2 to the sacrum. The strongest association was seen at L3 (adjusted
20 regression coefficient 16.7, 95% CI 12.1 to 21.4, $p < 0.001$). There was no association between
21 TPMA and TAMA (adjusted regression coefficient -0.7, 95%CI -4.1 to 2.8, $p = 0.710$).

25 **Conclusions**

26 We demonstrate that measurements of the TPMA between L2 to the sacrum are representative
27 of the TPMV, with the greatest association at the third lumbar vertebrae. There was no
28 association between the TPMA and TAMA.

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30 **Advances in knowledge**

31 We demonstrate that a single slice measurement of TPMA at L3 is representative of the muscle
32 volume, contrary to previous criticism. Future sarcopenia studies can continue to measure
33 TPMA which is representative of the TPMV.

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BJR UNCORRECTED PROOFS

35 **MAIN TEXT**

37 **Introduction**

38 Sarcopenia is a condition that is categorised by low skeletal muscle mass and declining function.
39 It is associated with worse patient outcomes and is an increasing problem due to a rapidly
40 ageing population (1, 2). The European Working Group on Sarcopenia in Older People have
41 recognised this and have recommended the routine assessment for sarcopenia in all patients
42 aged above 65 years (2). Therefore, the quantification of core abdominal muscles as a surrogate
43 marker for sarcopenia has become an increasingly popular in clinical research. The total psoas
44 muscle area (TPMA) or the total abdominal muscle area (TAMA) from single slice computed
45 tomography (CT) imaging at the endplates of the third or fourth lumbar vertebrae are the two
46 commonest methods of quantifying sarcopenia (1). However, at present the optimum vertebral
47 level to measure the TPMA is yet to be validated.

49 As muscles are complex three-dimensional structures, the use of single slice two-dimensional
50 measurements of these may be criticised as being a poor representation to assess sarcopenia.
51 The association between single slice TAMA and volumetric measurements of total abdominal
52 muscle on CT imaging has been previously described and validated (3-5). Furthermore gender-
53 specific cut-off values for TAMA have also been proposed which have been demonstrated to
54 correlate with mortality (6). The assessment of the patients muscle volume using an automated
55 quantification method with specialist software has been shown to be a better prognostic marker
56 than area alone (7). However similar correlations are yet to be validated between single slice
57 measurement of TPMA and three dimensional volumetric assessment of the psoas muscle (6).

59 The heterogeneity of the different methods of quantifying sarcopenia, TPMA and TAMA,
60 currently make it difficult to compare and derive cut-of values for sarcopenia from single slice
61 imaging. Measuring TAMA is more time consuming and often requires the use of specialist
62 software. However, we have previously demonstrated that the TPMA can be easily and
63 consistently measured on any picture archiving communications system (PACS) viewer (8).
64 The identification of an interchangeable relationship between TPMA and TAMA may facilitate
65 comparative analysis of previously reported outcomes and derive clinically uniform cut-off
66 values defining sarcopenia applicable to the general patient population (1).

67
68 In this study, we investigated whether there was a relationship between total psoas muscle
69 volume (TPMV) and TPMA, and identify the vertebral level at which the TPMA is most
70 representative of the muscle volume. Secondly, we investigated the relationship between single
71 slice measurements at the third lumbar vertebrae of TPMA and TAMA.

74 **Methods**

75 We analysed prospectively collected data from patients who have had an elective endovascular
76 aneurysm repair (EVAR) for an abdominal aortic aneurysm (AAA).

78 ***Study population***

79 We randomly selected pre-operative abdominal CT angiogram (CTA) scans routinely
80 performed as part of the assessment for intervention. All scans were performed in the supine
81 position with a breath-hold to minimise motion artefact. Patients were all identified from the
82 Health Quality Improvement Partnership National Vascular Registry (NVR), a prospectively
83 maintained database, from January 2008 and December 2014 (9). Inclusion into the study

84 required the patient to have an abdominal CT with the psoas muscle clearly identifiable from
85 the second lumbar vertebrae to the sacrum. Patients were excluded if they had incomplete
86 imaging with missing portions. Ethical approval was granted by the local radiology research
87 authorisation group and Health Research Authority (IRAS project ID, 228484).

88

89 *Covariate assessment*

90 Data were reviewed from the NVR for baseline age, gender, height and weight. These are all
91 parameters that are routinely collected, however, medical records were also reviewed to ensure
92 all data collected was accurate.

93

94 *Image analysis*

95 Imaging was performed using a Siemens Somatom Definition AS CT scanner with the patient
96 in the supine position with a breath-hold to minimise motion artefact. Slice thicknesses were
97 between 1mm - 2.5mm. Scans were assessed for inclusion by a single investigator, who did not
98 participate in any images analysis, using the picture archiving and communications system
99 (PACS) viewer IMPAX (AGFA-Gevaert Group, Mortsel, Belgium) and ImageJ (National
100 Institute of Health, Bethesda). Two independent observers (Rater 1 [R1] and Rater 2 [R2])
101 were trained by an investigator with prior expertise. R1 was a clinician with two years
102 postgraduate clinical experience and R2 was a postgraduate research fellow with 3 years
103 postgraduate clinical experience. The trainer was a surgical fellow with five years postgraduate
104 clinical experience.

105

106 TPMA was measured by manually tracing around the area of the left and right psoas muscle at
107 each vertebral level of the transverse processes from L2 to the sacrum (figure 1). TPMV was
108 calculated by multiplying each individual TPMA by the distance between the corresponding

109 vertebral levels. TAMA was measured using a fully automated technique. In brief, single slice
110 images at the third lumbar vertebrae were downloaded in the digital imaging and
111 communications in medicine (DICOM) format with preservation of actual dimensions to avoid
112 magnification indices and scales. Analysis was subsequently performed using ImageJ
113 (National Institute of Health, Bethesda) by setting the Hounsfield unit (HU) range between -30
114 to 130 (8). TAMA was calculated by measuring all the abdominal muscles, namely: psoas,
115 erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique's,
116 and rectus abdominis muscles based on the total pixel densities (figure 2). We acknowledge
117 that there are a variety of other software packages and methods that may also be used.

119 *Statistical analysis*

120 Measurements were made in centimetres (cm). TPMA and TAMA are reported as an area (cm²)
121 and TPMV as a volume (cm³). Statistical analyses were performed using Minitab 17 (Minitab
122 Inc., Pennsylvania) (10). Continuous variables were checked for normality and reported as a
123 mean and SD or 95% confidence interval (CI). Non-parametric data was reported as a median
124 and interquartile range (IQR). Categorical variable are reported as absolute numbers (n) and
125 percentages (%), and were compared using the chi-square test. Statistical significance was
126 defined as a two-tailed p-value <0.05.

127
128 Fifty images were analysed by two trained independent investigators (R1 and R2) to measure
129 the TPMA, TAMA and TPMV. Repeat measurements of all images were made by Rater 1 (for
130 example, R1a and R1b). Intra-observer and inter-observer differences were evaluated using
131 Bland-Altman plots and differences in measurements evaluated using student's t-test. The
132 limits of agreement were calculated as two standard deviations (SD) from the mean difference
133 calculated between observer measurements.

134

135 We calculated that we would require at least 85 patients in this study in order to assess for a
136 correlation of greater than 0.7 with 95% significance at 80% power. All images were analysed
137 by R1. Comparisons between the individual methods of assessing core muscle were evaluated
138 using measurements recorded by Rater 1 as single observer measurements are likely to
139 represent clinical practice. The relationship between TPMV and TPMA: at the second lumbar
140 vertebrae (L2), third lumbar vertebrae (L3), fourth lumbar vertebrae (L4), fifth lumbar
141 vertebrae (L5) and sacrum were assessed using Pearson's correlation and linear regression
142 analysis. Similarly, the relationship between TPMA versus TAMA were assessed using
143 Pearson's correlation and linear regression analysis. All regression analyses were adjusted for
144 age and sex.

145

146

147 **Results**

148

149 *Patient characteristics*

150 In total, CT scans from 110 consecutive patients were analysed in this study. Scans were
151 performed between October 2008 and July 2014. The median age of patients was 77.5years
152 (IQR 71.3 - 81.0) and there were 96 (87.3%) men. The median height was 174.0cm (IQR 165.5
153 - 179.0) and the medium weight was 77.0kg (IQR 69.0 - 95.0).

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155 *Intra-observer and inter-observer differences*

156 Intra- and inter observer difference are shown in figure 3. No significant differences in
157 measurements were identified between observers (table 1). Single observer variation (R1) was

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158 lowest with TAMA (mean $309.1 \text{ cm}^2 \pm 0.1$ [0.03%]), followed by TPMA (mean $8.8 \text{ cm}^2 \pm 0.3$
159 [3.7%]) and then TPMV (mean $337.4 \text{ cm}^3 \pm 13.6$ [4.0%]).

161 *Comparative analysis*

162 Measurements of TPMV, TPMA and TAMA were all normally distributed. Mean
163 measurements of the TPMA at each vertebral level, L2 to the sacrum, are highlighted in table
164 2. As anticipated, men had larger psoas muscle size than women (table 2). The mean TPMV
165 was $334.0 \pm 101.6 \text{ cm}^3$ and the mean TAMA was $303.7 \pm 62.2 \text{ cm}^2$. The mean distance between
166 measurements at the: sacrum and L5 was $4.9 \pm 1.0 \text{ cm}$, L5 to L4 was $4.5 \pm 0.9 \text{ cm}$, L4 to L3 was
167 $4.3 \pm 0.8 \text{ cm}$, L3 to L2 was $3.3 \pm 0.9 \text{ cm}$ and L2 to first lumbar vertebrae was $3.2 \pm 0.9 \text{ cm}$.

169 Significant positive correlations were observed between measurements of TPMV and TPMA
170 at all levels, L2 to sacrum (figure 4). Regression analysis highlighted significant associations
171 between measurements of the TPMA, from L2 to the sacrum, with TPMV (table 3). The
172 greatest association between single slice measurements and volumetric analysis was seen at L3
173 (unadjusted regression coefficient 20.1, 95% CI 15.4 to 24.9, $p < 0.001$, adjusted regression
174 coefficient 16.7, 95% CI 12.1 to 21.4, $p < 0.001$).

176 There was no significant correlation between TPMA and TAMA (figure 5). No association was
177 evident when comparing measurements of TPMA and TAMA (unadjusted regression
178 coefficient 2.9, 95%CI -0.8 to 6.6, $p = 0.126$ and adjusted regression coefficient -0.7, 95%CI -
179 4.1 to 2.8, $p = 0.710$).

182 **Discussion**

183 In this study, we demonstrate single slice measurements of the TPMA to be representative of
184 the TPMV on CT imaging. Measurements of the TPMA at any vertebral level between L2 to
185 the sacrum were found to be significantly representative of the TPMV. Therefore, it may be
186 plausible to use measurements of TPMA at any of these levels when limited by the images
187 available from routine imaging. This is important as it may not always be possible to measure
188 the TPMA at the L3 vertebrae if the CT sequence has not captured this section. However, it is
189 important to appreciate that the observed regression coefficients and confidence interval were
190 almost identical for TPMA measurements at L3 and L4 therefore utilisation of measurements
191 at either level is acceptable.

192
193 Our research adds to the growing body of evidence utilising the measurements of core
194 abdominal muscles from imaging as a surrogate marker for sarcopenia. Shen *et al* previously
195 demonstrated the association between measurements of the TAMA 5cm above the L4-L5
196 junction to be associated with volumetric measurements of the abdominal muscle volume on
197 CT imaging in a healthy cohort of patients (3). These findings were confirmed by Mourtzakis
198 *et al* who demonstrated the relationship between single slice imaging of fat free mass to whole
199 body fat free mass (4). However, it must be noted that these measures were validated on either
200 a normal cohort of people or cancer patients. Despite the correlation between single slice
201 TAMA and abdominal muscle volume, few studies have demonstrated the correlation between
202 single slice measurements of the TPMA and the TPMV. In this study, we have demonstrated a
203 relationship between TPMA and TPMV, and have identified that the measurement of TPMA
204 at L3 (the most widely used level) is most representative of the TPMV. Our group has
205 previously shown that the measurement of TPMA is reproducible and independent of observer
206 bias (8).

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208 Similar to the findings of Rutten *et al*, we demonstrate no correlation between single slice
209 measurements of TPMA and TAMA (11). Therefore, studies evaluating outcomes in relation
210 to sarcopenia utilising these different measures cannot be reliably compared. We have
211 previously reported that measurements of the TPMA may be easily performed by manually
212 tracing around the psoas muscle at the third lumbar vertebrae without the need for specialist
213 software or clinical experience (8). Therefore, we would recommend the routine measurement
214 of the TPMA for the quantification of sarcopenia as it may be easily utilised in clinical practice.

215
216 Similar to previous studies, we demonstrate that women have lower measurements of the psoas
217 muscle in comparison to men. The number of women in our study were too few to allow for
218 assessment of whether these relationships identified by gender were statistically relevant.
219 However it is important to acknowledge that the study was powered to detect the associations
220 between TPMA and TPMV as well as TPMA and TAMA.

221
222 However, measurements of TPMA had the lowest variation when compared to TPMV as
223 demonstrated by percentage variation of the standard deviation against the mean intra-observer
224 measurements. This finding is expected as due to the compounding effect of errors
225 accumulating at each level analysed. The utilisation of the TPMA as an assessment tool for
226 sarcopenia instead of TPMV may also facilitate and reduce the numbers needed for patient
227 recruitment when powering future prospective studies. Although TAMA had the least variation,
228 this was primarily due to a completely autonomous method of measurement which may not be
229 routinely applicable out of the research setting.

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231 It is important to acknowledge that our study estimates the TPMV as we did not utilise
232 specialist software as described in previous studies (12). The TPMV was calculated as blocks

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233 based on two-dimensional assessment of the psoas muscle at each vertebral level and then
234 multiplying the area by the distance between vertebral levels. This was intentional as we
235 wanted to replicate the potential real-life application of risk stratification using the psoas
236 muscle as not all clinicians in the National Health Service in the United Kingdom have access
237 to specialist software for this type of image analysis. We acknowledge that this might be a
238 crude measurement given the large interslice distances.

239

240

241 **Conclusions**

242 In conclusion, we demonstrate an association between measurements of TPMA and TPMV.
243 Measurements of TPMA may be made at any vertebral level between the sacrum and L2 and
244 be reflective of the TPMV, with the greatest association at L3. We also demonstrate the absence
245 of any association between TAMA and TPMA therefore outcomes reported with either
246 measure cannot be reliably compared and results translated.

247

248 **FIGURES AND TABLES**

249

250 **Figure 1.** Illustration of TPMV calculated from L2 to sacrum. Red line shows manual tracing
251 of TPMA. Example shows TPMA at L2 (4.2cm²), L3 (10.0cm²), L4 (16.8cm²), L5 (22.4cm²),
252 Sacrum (23.1cm²). Distances: 2.9cm between L1 and L2, 3.1cm between L2 and L3, 4.4cm
253 between L3 and L4, 5.0cm between L4 and L5, 5.3cm between L5 and sacrum. Therefore, the
254 TPMV calculated is 351.5cm³.

256 **Figure 2.** TAMA measurement using the automated technique. Red highlights tissue matching
257 pixel density with HU between -30 to 130.

259 **Figure 3.** Bland-Altman plots showing intra- and inter- observer differences in measurements
260 of TPMA, TAMA and TPMV.

262 **Figure 4.** Scatter graph illustrating relationship between TPMV and single slice TPMA
263 measurements at: (a) L2, (b) L3, (c) L4, (d) L5 and (e) sacrum.

265 **Figure 5.** Scatter graph demonstrating the relationship between TPMA and TAMA.

271 Table 1. Observer measurements of TPMA, TAMA and TPMV.

272

Measurement	R1a Mean (SD)	R1b Mean (SD)	R2 Mean (SD)	Intra-observer differences		Inter-observer differences	
				Mean (SD)	p-value	Mean (SD)	p-value
TPMV [cm ³]	337.6 (105.3)	337.1 (101.0)	338.8 (106.6)	0.5 (13.6)	0.981	-1.1 (11.8)	0.957
TPMA [cm ²]	8.8 (3.5)	8.9 (3.6)	8.8 (3.4)	-0.03 (0.3)	0.963	0.03 (0.3)	0.924
TAMA [cm ²]	309.1 (66.8)	309.0 (66.7)	309.1 (66.8)	0.1 (0.1)	0.997	-0.003 (0.01)	1.000

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274

275 Table 2. Measurements of TPMA from L2 to the sacrum by gender.

276

Spinal level	TPMA			
	Male (N=96)	Female (N=14)	p-value	Overall
L2 [cm ²]	2.6 ± 1.8	1.7 ± 1.4	0.058	2.5 ± 1.8
L3 [cm ²]	9.4 ± 3.1	6.3 ± 2.4	<0.001	9.0 ± 3.2
L4 [cm ²]	16.9 ± 4.2	12.2 ± 3.7	<0.001	16.3 ± 4.4
L5 [cm ²]	23.8 ± 5.2	17.0 ± 4.5	<0.001	22.9 ± 5.6
Sacrum [cm ²]	25.6 ± 5.7	18.5 ± 5.3	<0.001	24.7 ± 6.1

277

278 Table 3. Linear regression analysis comparing measurements of TPMA from L2 to sacrum in
 279 relation to TPMV.

280

Spinal level	Unadjusted			Adjusted		
	Regression coefficient	95% CI	p-value	Regression coefficient	95% CI	p-value
L2	16.7	6.2 – 27.2	0.002	12.1	2.6 – 21.5	0.013
L3	20.1	15.4 – 24.9	<0.001	16.7	12.1 – 21.4	<0.001
L4	17.7	14.9 – 20.6	<0.001	15.6	12.5 – 18.7	<0.001
L5	14.1	12.0 – 16.3	<0.001	12.9	10.3 – 15.5	<0.001
Sacrum	11.8	9.5 – 14.0	<0.001	10.3	7.6 – 12.9	<0.001

281 *Adjusted for age and sex.

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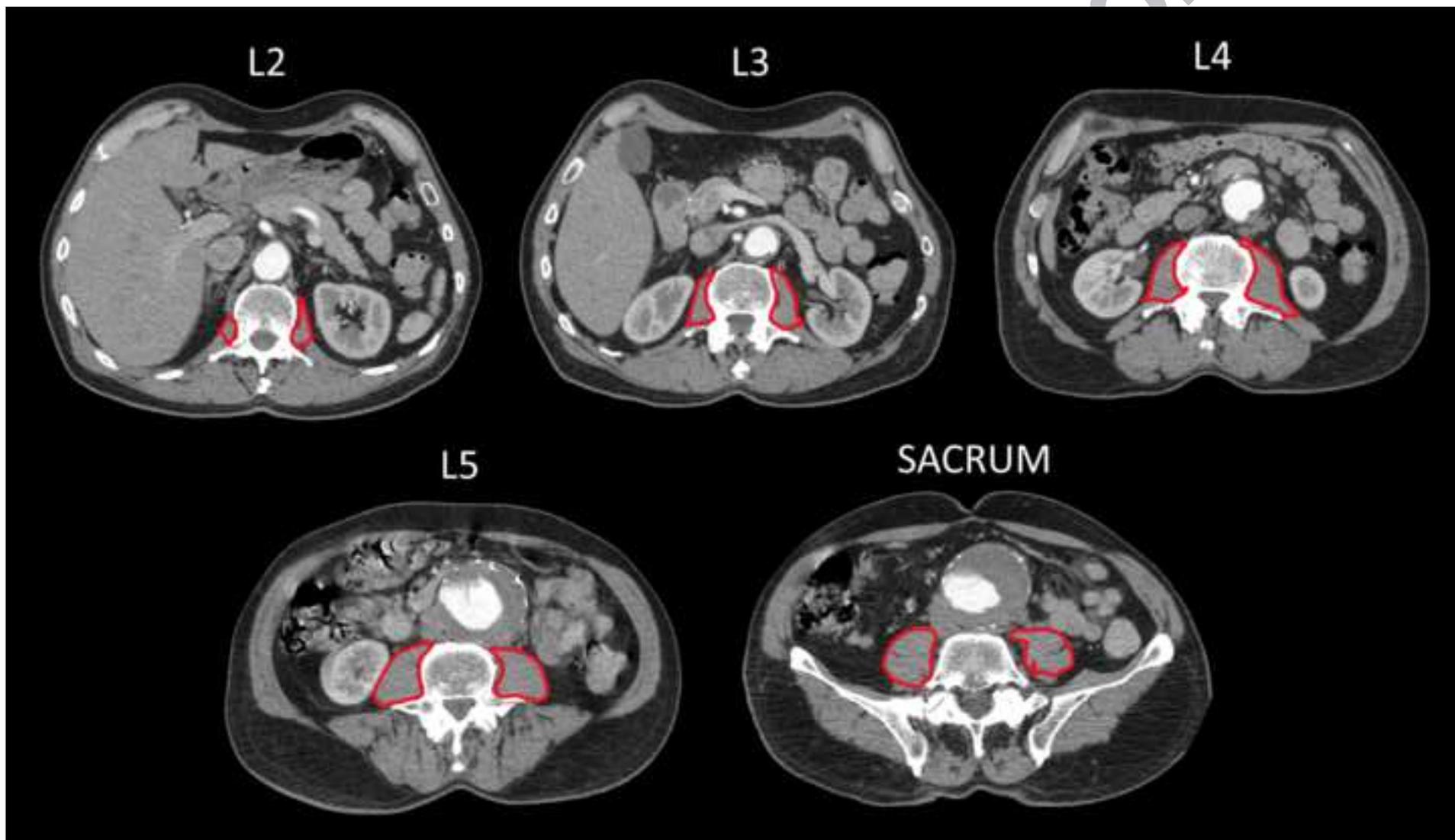
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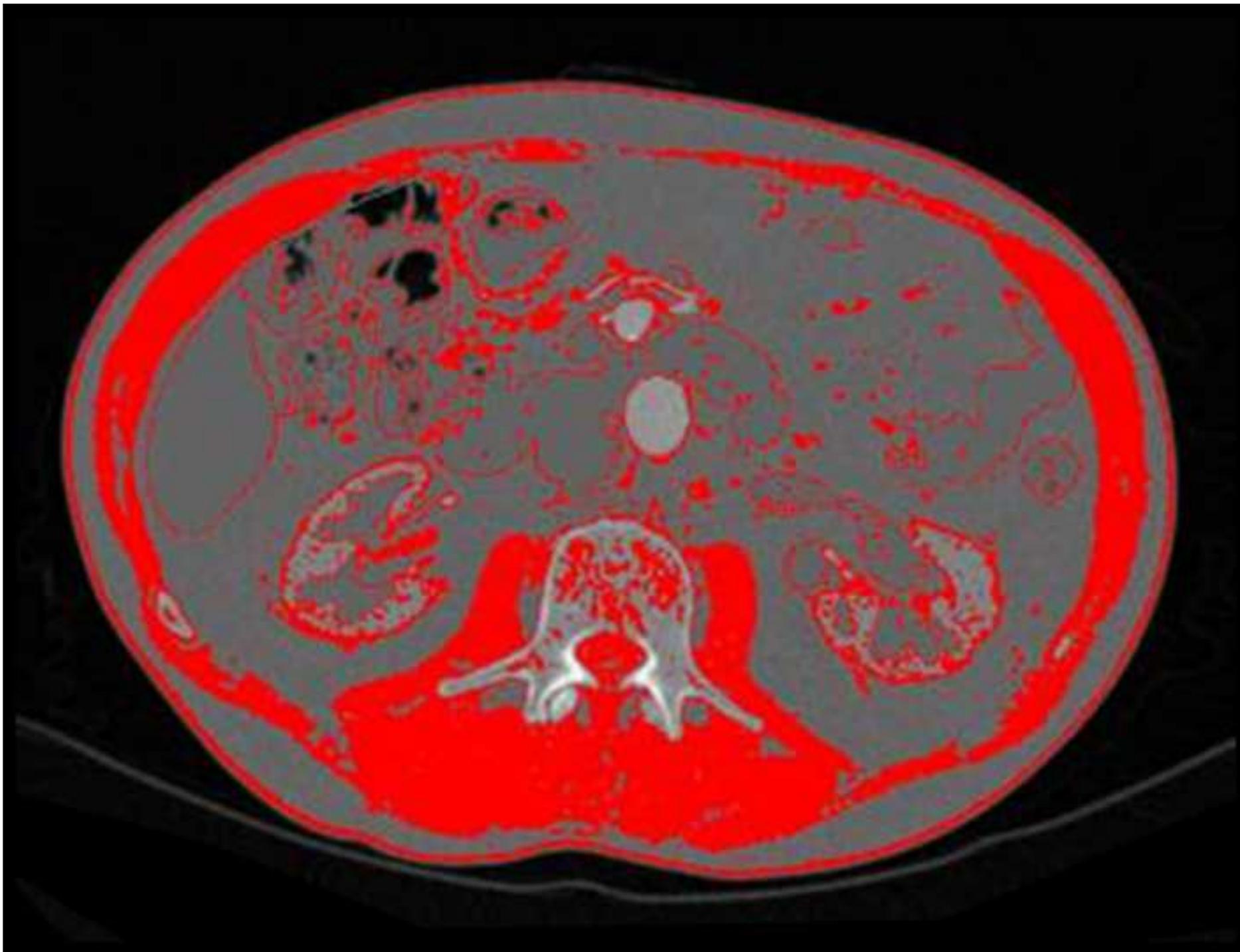
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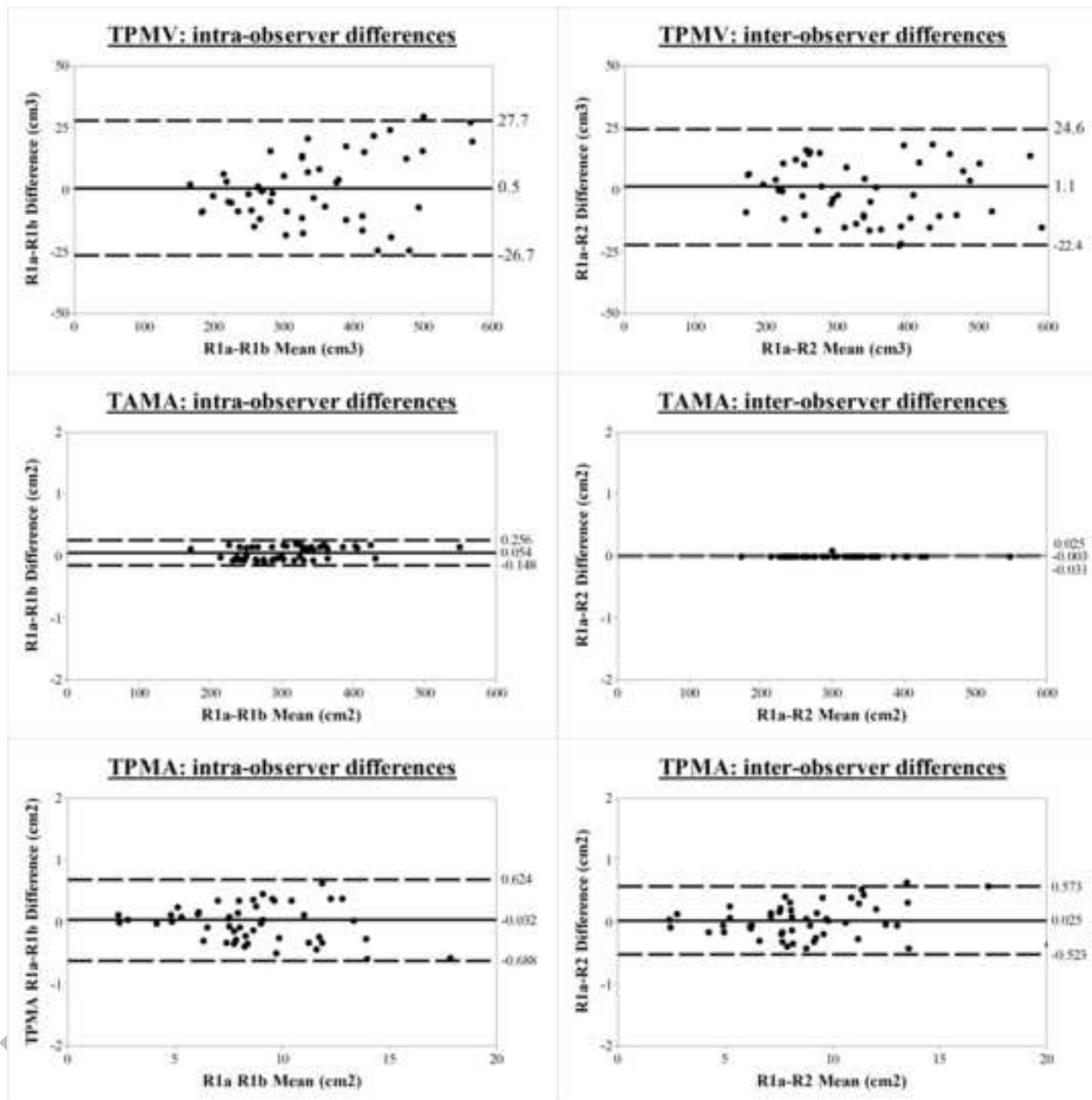
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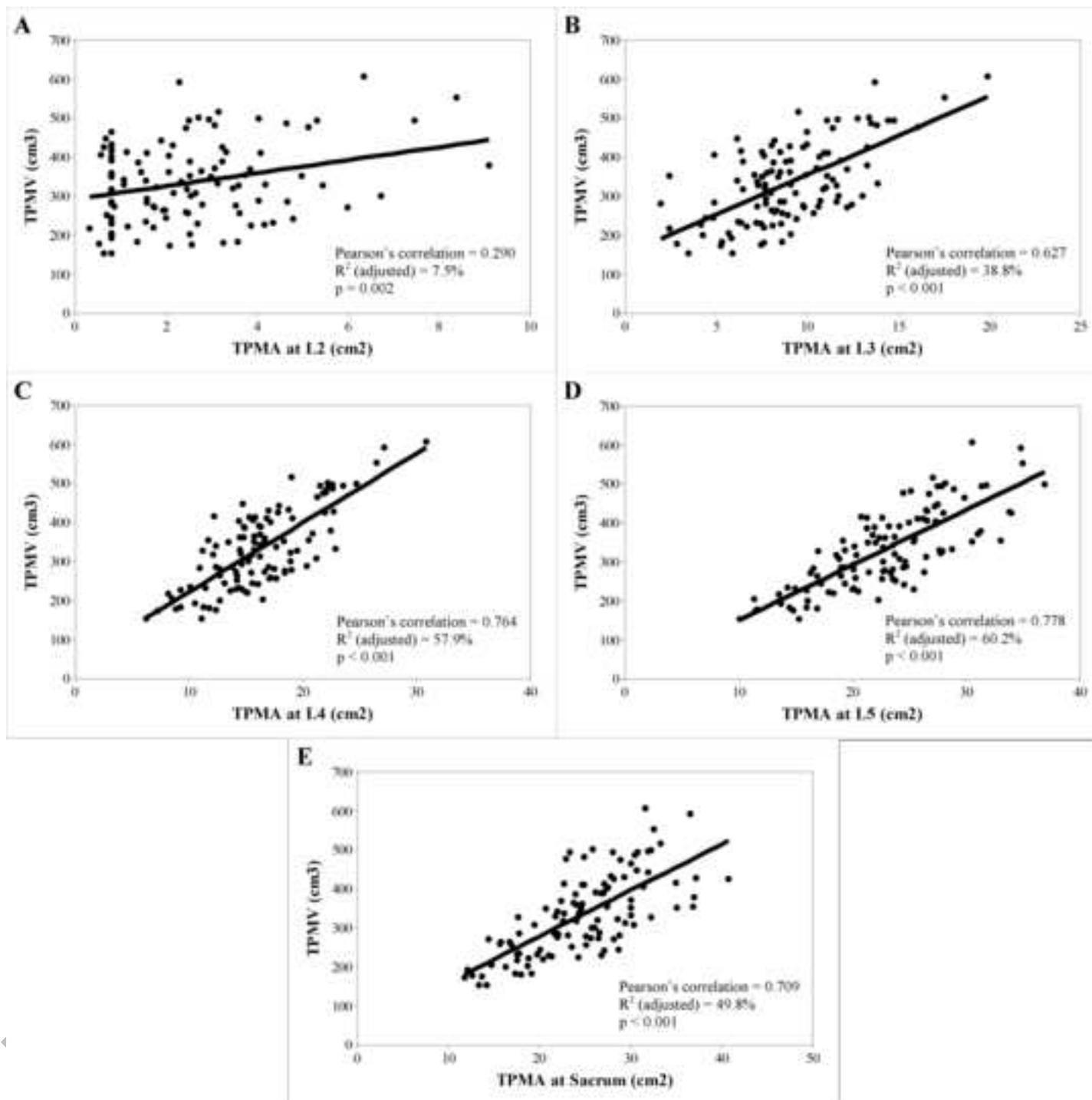
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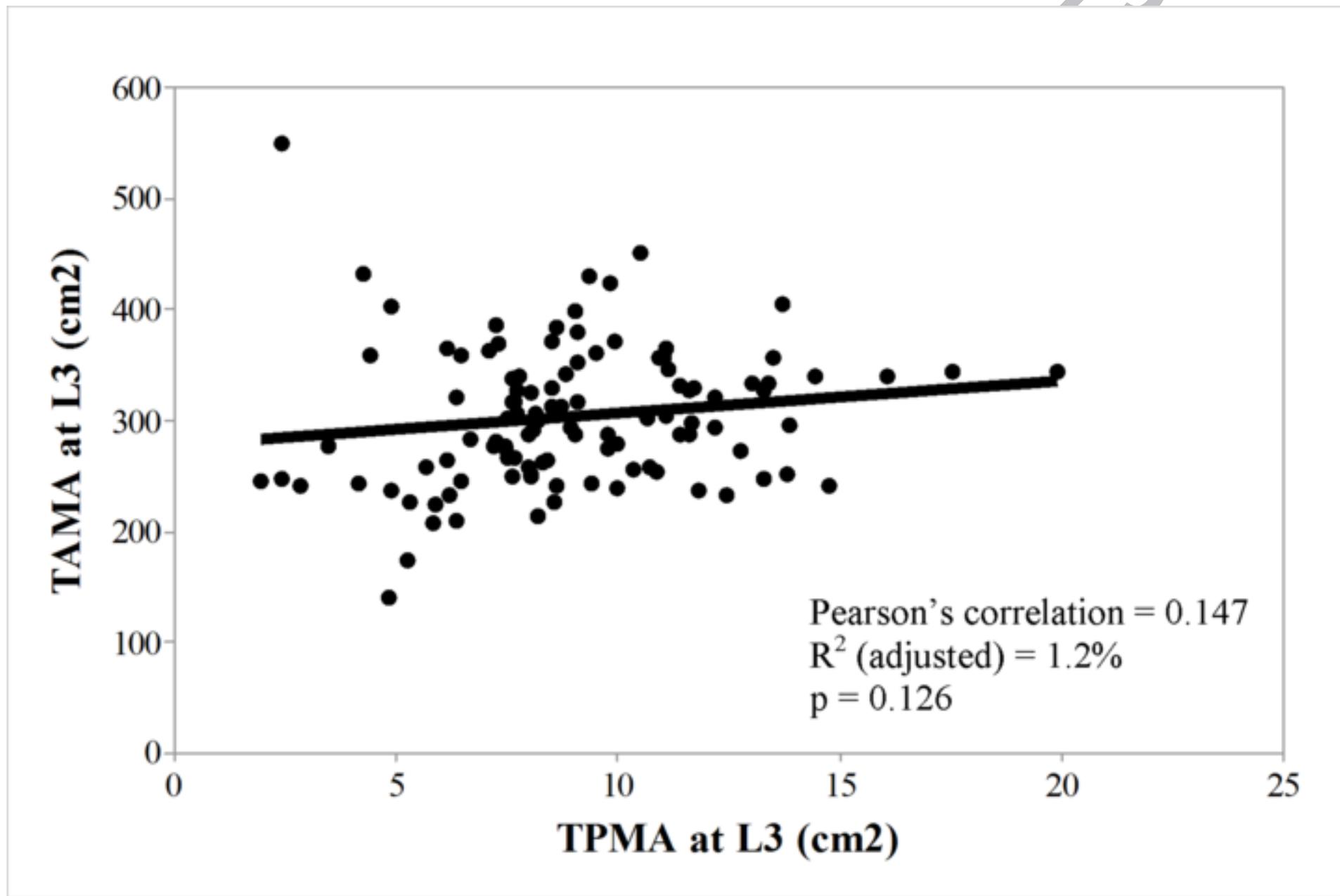
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